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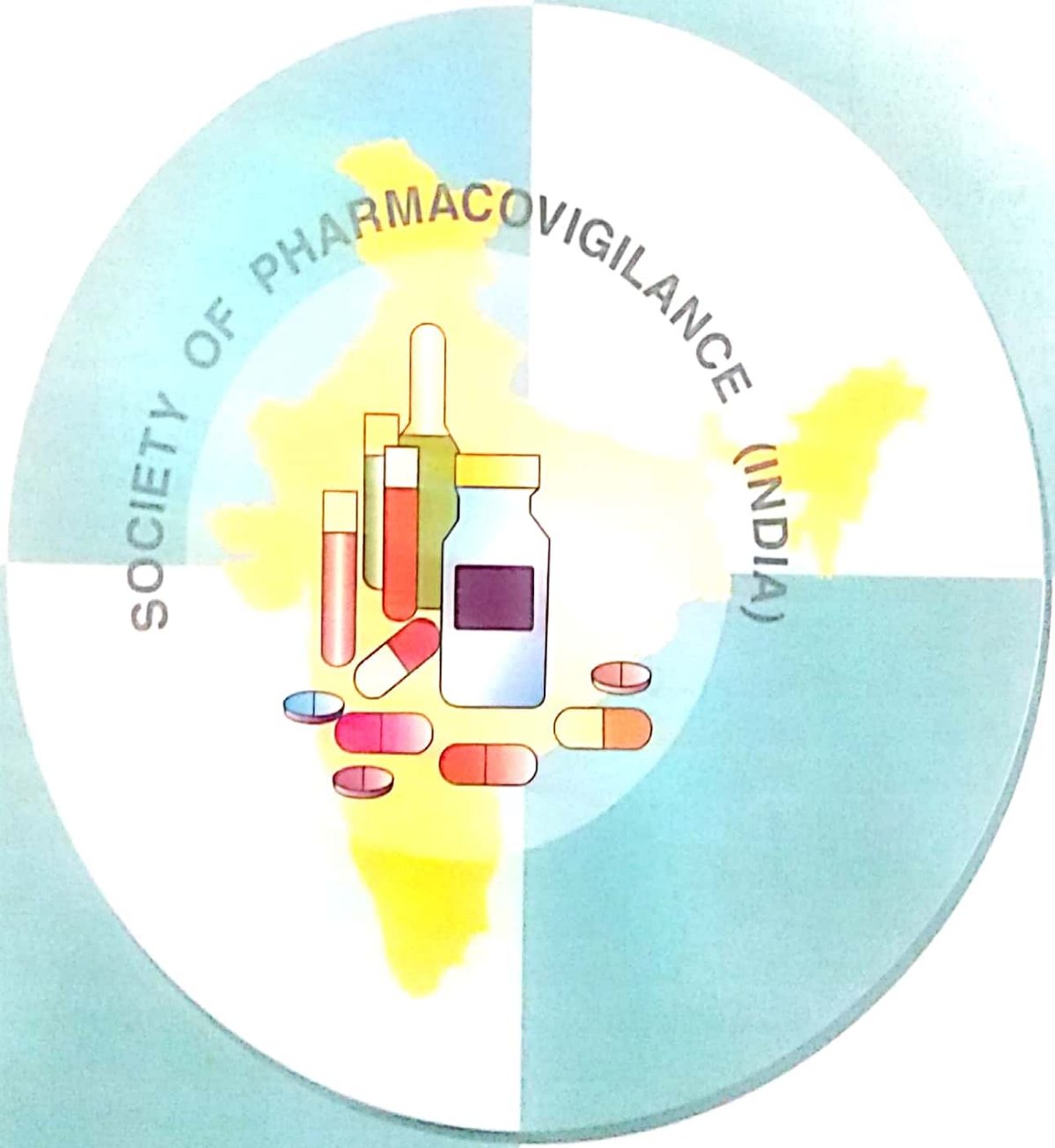

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EDITORIAL...

Recently there has been a boom in pharmaceutical industry with respect to clinical research in India. While there is an encouraging avenue for not only pharmacologists but also clinicians and paramedical science graduates. There are several concerns with respective preparation of medical doctors willing to undertake clinical research. Adverse drug reaction (ADR) monitoring is one of the key issue during a clinical trial and it is necessary to have authentic reporting of ADR. In other words, the concept of pharmacovigilance has still not taken proper seedling, inspite of several developments.

The office of Drug Controller General of India (DCGI) with the help of various agencies had started nodal centers for ADR reporting. There are pharmacovigilance centers across the country. The apex body of health 'Indian Council of Medical Research', New Delhi, has taken several steps with DCGI and Department of Biotechnology to make clinical research more effective. Some institutions have started diploma programmes in pharmacovigilance. There will be a change in DCGI to have drug control authority. Still, it is a long way to go before the pharmacovigilance takes a proper shape.

The articles in this journal are related to pharmacovigilance from various parts of the country. There is an article from SriLanka on pharmacovigilance. There are articles not only related to drugs but also medical devices and injections also. We hope in future the number of articles keep on increasing that the purpose of society of pharmacovigilance is achieved.

Dr. Ramesh K. Goyal
Chief Editor

CONTENTS...

INTERACTIONS OF DRUGS WITH FOOD - AN OVERVIEW

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Modern medicine has given us many useful drugs that not only prolong and save lives, but also improve the quality of our lives. The beneficial effects of the drugs we take, can be affected by the foods in our diet. These food and drug interactions can have dramatic, even dangerous, effects on the way our bodies react to these drugs. Food containing active substances that work against certain medication can produce unexpected or adverse effects. With drugs, the food we eat or the supplements we take, can cause the medication to work incorrectly.[1] Its the impact of food-drug interactions depends upon the dose and dosage form, age, sex, body weight, nutritional status of patient, specific medical condition, time interval between food and drug taken etc. Therefore, these factors should also be taken into account while taking a drug/food. These effects can be reduced by following instructions of the prescriber whether the dosage form should be chewed or crushed or whether the drugs should be taken by empty stomach-(Table-1) 15 min., 30 min. or 1 hr. before meal; with meal or after meal-1 hr 2 hrs or 4hrs after meal; with a glass of water or less water.

Food and drug interactions can be dangerous and in rare cases may be fatal and occur because drugs may interfere with absorption of food speed up or down the actions, vitamins and minerals and vice versa.

Drugs may influence excretion in the body of one or more nutrients. Food and beverages interfere with drug absorption. Drugs may suppress or stimulate appetite.

Certain types of food may alter the chemical structure of the drug, so that it looses its therapeutic effect.

Effect of food on drug absorption: Delay in drug absorption may affect the blood levels of the drug and thus the therapeutic efficacy. Following are some examples of such interactions-

Milk and milk products (Yogurt, Cheese, curd, butter milk, cream etc.), almonds and carich etc., rich in calcium decreases absorption and therefore effectiveness of many drugs, as these drugs chelate with calcium, making an insoluble/ non-absorbable complex in GIT. The antibiotics like tetracyclines, fluroquinolones, estramustine, acromycin, vibramycin, suramycin and bisphosphonates-etidronate, used for osteoporosis, etc. are some examples. Therefore, these food and drugs should not be taken at the same time. Magnesium, calcium, aluminium containing antacids and food, in the same way reduce the absorption of drugs like mycophenolate mofetil, used for prophylaxis of transplant rejection.

If drugs are taken with soda/high acid fruits/ vegetables juice, the pH of gastric fluids will change. This will affect the ionization of drug, and thus the therapeutic effects. Some foods may enhance the absorption of drugs e.g. fatty foods can enhance the absorption of an anti-fungal drug, griseofulvin. Food / drinks containing vitamin C (Ascorbic acid) like oranges, grapefruit juice etc. increases absorption of iron. Therefore, it is beneficial to use.

Effect of food on drug utilization: The therapeutic results may change, if the amount of drug utilized by the body is affected eg.

1. Green leafy vegetables, high in vitamin K contents, can speed the process of coagulation, thus reducing the effect of anti-coagulants.
2. Raspberries contain natural salicylates. Therefore, the effect of salicylates will enhance and patients allergic to salicylates will also be allergic to raspberries.

Effects of drugs on nutritional status:

The drugs may influence the absorption, excretion or may change the nutrients into a form that can not be absorbed. [2] The examples are-

1. Neomycin causes changes in mucosa of GIT and hence reduces the absorption of many substances including nutrients.
2. Liquid paraffin is not absorbed in GIT. Therefore, when given with vitamins or other fat soluble substances, they dissolve in liquid paraffin, thus reducing concentration gradient and are less absorbed, causing the deficiency of fat soluble vitamins.
3. Many drugs are chelated by metal ions. Therefore, the metal ion present in food may be chelated by the drug and hence metal ion can not be absorbed, leading to deficiency of these nutrients.
4. Use of antacids may cause phosphate depletion and can lead to deficiency of vitamin D and osteomalacia due to loss of calcium.

Some examples of food and drug interactions have been discussed below:

Drugs and grapefruit juice: (Table-2) Grapefruit juice inhibits CYP3A4 and therefore can increase plasma levels of drugs, biotransformed through CYP3A4, which is found in the liver and expressed in the gut. Inhibition of CYP3A4 in the gut may lead to maximum absorption of such drugs.[3] However, in contrast, recent researches have demonstrated that grapefruit juice has another mode of action. This juice activates the efflux pump p-glycoprotein, which ejects the drug molecules from the gut wall and back into the intestine thus reducing the absorption of many drugs like HIV protease inhibitors, immuno-suppressants, anticancer drugs etc., which are substrate of both CYP3A4 and p-glycoprotein [6].

Food and Theophyllin: High protein diet may reduce the bioavailability of theophyllin whereas high carbohydrate diet increases the bioavailability of theophyllin. Therefore, major changes in the diet should be avoided during theophyllin therapy [4].

Food and Anti-coagulants: Anti-coagulants like warfarin, dicumarol, phenindiones has narrow therapeutic margin. Therefore, little change in plasma concentration will have impact on therapeutic efficacy. Certain food like green vegetable (Broccoli, Brussels sprouts, spinach, cabbage, kale, ruggola etc.), beef and liver oils contain indoles, which stimulates drug metabolizing enzyme (cytochrome P 450) resulting in increased rate of biotransformation [5].

Faster rate of biotransformation results in lesser bioavailability and hence less anti-coagulant effect.Green vegetables also contain large amount of vitamin K, which has independent effect on the anti-coagulant action of warfarin. As anti-coagulants competes with vitamin K, to affect the coagulation, the change in concentration of vitamin K, can alter the anti-coagulant effect of warfarin.

Food and NSAIDs: Some vegetables and food items like cabbage, cauliflower, kale, brussel sprouts, mustard, soyabeans, turnip, green rutabaga and iodized salt may increase the activity of some oxidative enzymes and thus leads to reduced concentrations of the NSAID. Therefore, this interaction will have impact on the effect of NSAID.

Food and Levo-dopa: Vitamin B_6 counteracts the activity of levo-dopa in relieving symptoms

of parkinsonism as both compete for the same site. Therefore, food rich in vitamin B6 (Beef, pork liver, whole germ yeast) and high protein diet can reduce the concentration of levo-dopa in brain resulting in lesser effect in parkinson's disease.

Alcohol and drugs: Alcoholic beverages tend to increase the depressive effect of drugs like benzodiazipines, anti-histaminics, analgesics, anti-depressants, anti-psychotics, muscle relaxants, corticosteroids, narcotics or any drug with sedative action. Anti-oxidants and beta-carotene intensify the effect of alcohol on the liver.

Other examples : Caffeine may increase the risk of insomnia and cardiac arrythmias in susceptible persons. Therefore, such persons should avoid excessive intake of caffeine.

Tyramine containing food/drink may cause abnormal increase in blood pressure of an hypertensive patient, which may result in hypertensive crisis. These food/drink include cheddar, aged cheese, herring, bananas, avocardo, chicken, liver, non-fresh liver, chocolate, soya sauce, mushrooms, pickles, chianti wine, beer, sherry etc. Therefore, the hypertensive patients should avoid these foods.

However, it is not always true that drugs and food interactions leads to harmful effects. There are good examples that food helps in combating drug induced deficiencies. Some of such examples are given below-

Prolonged use of oral contraceptives may develop deficiency of folic acid and ascorbic acid which can be supplemented by food like spinach, green vegetables, asparagus, broccoli, lima beans, milk & milk products and oranges, grape fruit, lemon, lime, strawberries, potatoes, tomatoes, cabbage and green pepper respectively.

1. Excessive use of diuretics may result in the loss of water and electrolytes, mainly potassium. These patients should eat food like Tomato, orange, cantaloupe, banana, rasin, prunes, potato, sweet potato, which are good source of potassium.
2. Anti-hypertensive drugs, hydrallazine, isoniazid etc may cause deficiency of pyridoxin. Therefore, foods rich in pyridoxin like chicken, fish, liver, whole grain bread, cereals, egg yolk, banana and potato should be advised along with such therapy.
3. Most anti-convulsants can lead to deficiency of folic acid and vitamin D. Such patients can take food rich in folic acid and vitamin D like milk and milk products and other rich source of these vitamins.
4. Several drugs like oral anti-diabetics, colchicines and antimicrobials viz. neomycin etc. can interfere with the absorption of vitamin B_{12} and causes its deficiency. Hence animal products having store of vitamin B_{12}, should be used along with therapy.

CONCLUSIONS

Food and drugs are merely two forms of exogenous chemicals and it is not surprising that they may interact at times as body defenses do not distinguish between them. Avoidance of drug interactions does not necessarily mean avoiding drugs and food. These should simply be taken at different times, rather than eliminating one or the other from diet. Having good information about the medication, one can decide the time for food intake, which will help to avoid drug interactions.

Table 1 : DRUGS USED ON EMPTY STOMACH

Alendronate, aminophylline, ampicillin, astemizole, azithomycin
Benazepril bethanecol,bisacodyl
Calcium channel blockers, calcium folinate, captopril, carbenicillin, cholera vaccine, chrorembucil, ciprofloxacin, cisapride, clofibrate, cloxacilli, co-trimoxazole, coumarin.
Demeclocycline, dicyclomine, didanocine, dipyrimadole, domperidon.
Esomeprazole, etidronic acid, etopside.
Felodipine, floxacollin.
Gemfibrozil, glucomannan
Halofanthrine
Indinavir, iron,iso-mononitrate
Lanzprazole, levo-dopa, lincomycin, lomefloxacin, levo-thyroxin.
Magnesium, melphalan, metaclopamide, mineral oils.
Nalidixic acid, nimodipine, norfloxacin
Ofloxacin, omeprazole
Penicillamine, penicillin G, perindopril, propafenone, pyridostigmine.
Rifampicin, roxithromycin.
Sodium bicarbonate, sotalol, sucralate.
Trioxalen, tetracyclines, typhoid vaccine
Warfarin.
Zafilukast, zalcitabine, zidovudine.

Note : There may be omissions. Absence of a drug does not necessarily indicate that the drug lacks this potential interaction.

POINTS TO REMEMBER-When your doctor prescribes a medicine be sure to mention other drugs that you are taking.

-Be sure when and how the product should be taken (with meal, before meal\after meal or empty stomach).

- Tell your doctor about any change or side effects after using a drug.

- Take drugs with a full glass of water.

- Using over-the counter drugs, always read the level about instructions and warning

Above information about food and drugs will prevent their interactions some of the most commonly used drugs.

Table 2 : DRUGS INTERACTION WITH GRAPE-FRUIT JUICE

Astemizol,alprazolam, amidarone, atorvastatin
Benzodizioines-dizepam, lorazepam, midazolam
Buspiron
Calcium channel blockers-nifedipine, amlodipine, nicardipine, diltizem. etc.
Carbamazepine, carvedilol, cerivastatin, cilostazol, cisapride, clarithomycin, clomipdrmine, cdeine a and cyclosporine
Dapsone, dextrometharphan
Estrogen, erythromycin
Felodipine, fentanyl, finasteride, etc.
Haloperidol
Indinavir
Methadone, midazolam
Lidocaine, lovastatin.
Ondansatron
Paclitol, progesterone, progestrins
Quinidine
Salmaterol, simvastatin
Tacrolimus, trazolam, trazorone
Vicristine
Zaleplon, zolpidem

Table 3 : SOME IMPORTANT HERBS AND THEIR EFFECTS

Herb	Effect	Remark
Apple,apricot and Apricot,cherries, Plums,peaches and Quinces	contains amygdalin (hydrogen cyanide)	large amount may sometimes cyanide poisoning
Hawthorn	lowering cholesterol	digoxin,decrease heart rate and heart failure
Horse raddish	large amount	vomiting,sweating
Ginsen	increase BP	avoid in hypertensives
Ginseng and garlic	increases bleeding disorders	
Goldenseal	increases BP	avoid in hypertensives
Feverfew	increases BP	with other migraine drugs
Guarana		avoid in insomnia, anxiety etc.
Kava		
Potatoes geen tinch	contains solanine	diarrhea,cramps and fatigue
Strawberries, Raspberries, Spinach,Rhubarb	contains oxalic acid	causes kidney \ bladder stones decreases calcium\iran absorption
White willow	stomach ulcers	aspirin etc

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REVIEW ARTICLE

THE RISK OF STENT THROMBOSIS AND ANTIPLATELET THERAPY

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ABSTRACT

Dual antiplatelet therapy reduces ischemic events after percutaneous coronary intervention (PCI) and in patients with acute coronary syndromes. Though, many patients and healthcare providers prematurely discontinue dual antiplatelet therapy, which greatly increases the risk of stent thrombosis, myocardial infarction, and death. The 12 months of dual antiplatelet therapy after placement of a drug-eluting stent and educating the patient and healthcare providers about hazards of premature discontinuation. It also recommends postponing elective surgery for 1 year, and if surgery cannot be delayed, considering the continuation of aspirin during the perioperative period in high-risk patients with drug-eluting stents.

INTRODUCTION

With increased use of percutaneous coronary intervention (PCI) as a revascularization strategy and implantation of stents in coronary arteries with a small diameter, it is anticipated that the number of patients at risk for stent thrombosis may increase. It is therefore important to construct pharmacological regimens that minimize its occurrence. Several risk factors for stent thrombosis may be patient- and/or lesion-specific characteristics or procedure-related. After placement of a bare-metal stent, thienopyridines (clopidogrel or ticlopidine), in combination with aspirin have been shown to dramatically reduce the incidence of early major adverse cardiac events compared with aspirin alone or in combination with warfarin [1]. In addition, the use of thienopyridine therapy in combination with aspirin for 1 year after non–ST-segment elevation acute coronary syndromes is known to decrease the incidence of ischemic cardiovascular events and is recommended in the American College of Cardiology/American Heart Association practice guidelines for the treatment of patients undergoing percutaneous coronary intervention and for the medical treatment of patients with non–ST-segment–elevation acute coronary syndromes [2–4]. Despite these benefits, Antiplatelet therapy is sometimes prematurely discontinued within the first year after stent implantation, either by the patient or by a healthcare provider who may not realize these benefits or the potentially severe consequences of antiplatelet therapy cessation. The leading adverse event associated with early Antiplatelet discontinuation is stent thrombosis, and the majority of these events lead to acute myocardial infarction (MI) or death. Therefore, the American Heart Association, working with the American College of Cardiology, the Society for Cardiovascular Angiography and Interventions, the American College of Physicians, the American College of Surgeons, and the American Dental Association, commissioned this advisory to emphasize the potential complications of premature discontinuation of thienopyridine therapy and to address potential strategies to minimize this occurrence.

Platelet activation associated with coronary intervention

Platelets are integrally involved in the thrombotic complications of atherosclerosis. Atherosclerotic plaque disruption results in exposure of the subendothelial matrix and its constituent platelet-adhesive proteins (von Willebrand factor, collagen and thrombospondin) to circulating blood [5-7]. Platelets are attracted to the site of vascular injury and adhere to the exposed subendothelium, where they are activated by locally generated thrombin, collagen, epinephrine and adenosine diphosphate (ADP). Platelet activation in turn triggers changes in platelet morphology, platelet degranulation and the release of various agonists (ADP, thromboxane A2 and platelet activating factor) that promote further platelet recruitment (Fig 1) [5,8]. The final process of platelet aggregation involves the binding of circulating fibrinogen and von Willebrand factor to the glycoprotein (GP) IIb/IIIa receptor on the platelet surface, leading to cross-linkage of adjacent platelets into a platelet-rich thrombus.[9]

In addition to promoting platelet aggregation and thrombus formation, platelet activation may contribute to the chronic inflammatory and fibroproliferative response that is central to atherosclerosis. Activated platelets bind to leukocytes via surface receptor-ligand interactions to cause the release of proinflammatory cytokines such as tissue necrosis factor-a, monocyte-chemotactic factor-1 and CD-40 ligand [10]. These platelet-leukocyte interactions may be relevant to the development of the late ischemic complications and vessel restenosis that follow angioplasty [11, 12]

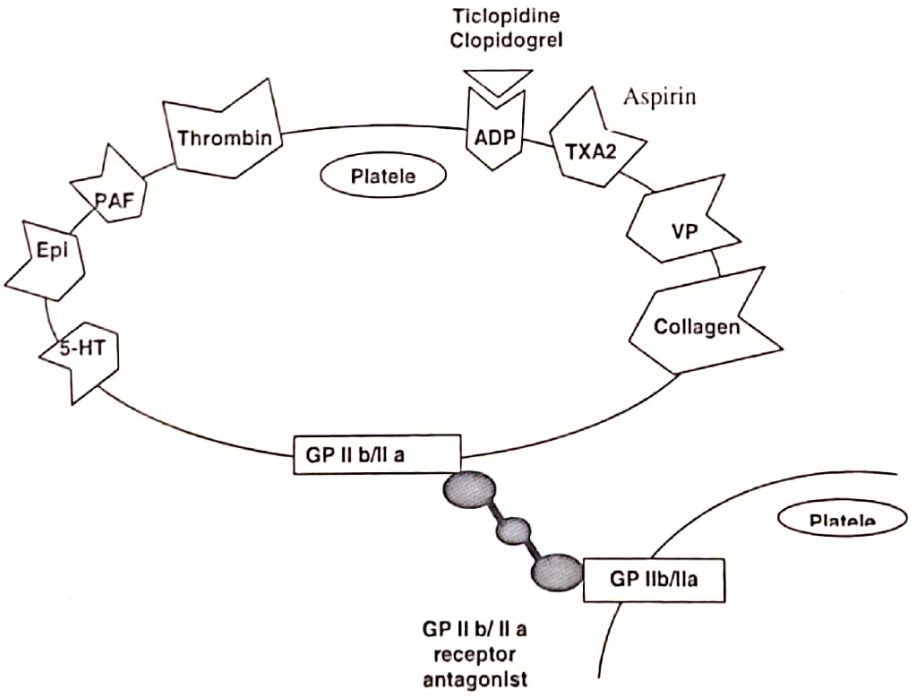

Fig. 1 Platelet activation associated with coronary intervention

Procedure-related platelet activation and its complications

Percutaneous coronary revascularization causes mechanical laceration and fracture of atherosclerotic plaque, frequently extending through the internal elastic lamina into the media, and denudation of the arterial endothelium [13]. The platelet appears to be a pivotal mediator of the ensuing pathophysiological response to vascular injury:

the physical insult triggers thrombin generation, platelet deposition, mural thrombosis and (through the release of platelet-derived cytokines and growth factors) smooth muscle cell proliferation and neointimal hyperplasia [14–16]. The degree of platelet deposition and thrombosis is governed by the extent of arterial wall injury and by local shear forces caused by the stenosis [17, 18] The platelet-rich mural thrombus initially acts as a haemostatic plug, sealing the vascular injury site; the subsequent healing process involves intense cellular (monocyte/macrophage) infiltration of the thrombus, resulting in its gradual resorption and replacement by neointimal tissue [19].

Balloon dilatation of the coronary artery produces transient (~48 hours) local platelet activation [20–24] which forms part of a broader systemic inflammatory response characterized by leukocyte and platelet activation and elevation of C-reactive protein levels [25, 26]. Coronary stenting amplifies platelet activation compared to angioplasty alone [27, 28] presumably on account of the heightened vessel trauma associated with stent placement and the added presence of thrombogenic surfaces (*i.e.*, bare metal struts). Platelet-rich thrombi appear on stent struts within the first 3 days of stenting, and peak in number during the following week [13]. Despite the use of intensive anticoagulant therapy (aspirin, heparin and phenprocoumon), coronary stenting results in sustained platelet activation, as indicated by increased surface expression of activated fibrinogen receptors and P-selectin, with the effect peaking 3–6 days after stenting [29]. Stent design also appears to be relevant, with an open-cell structure producing more pronounced platelet activation over the first 30 days post-stenting than a closed-cell design [30].

Vascular injury and the accompanying platelet activation contribute to the two major drawbacks of coronary stenting-stent thrombosis and in-stent restenosis. Preprocedural platelet activation, as indicated by enhanced surface expression of the platelet membrane proteins CD62, CD63 and thrombospondin, confers an increased risk of acute ischemic events after balloon angioplasty [31] while platelet fibrinogen receptor expression is an independent predictor of subacute stent thrombosis [32] Subacute thrombotic occlusion of coronary stents, which usually occurs within the first few days to weeks of stent deployment, is a catastrophic complication which manifests itself as acute transmural myocardial infarction in 60% of cases and has a 25% mortality rate [33, 34]. In the present era of dual antiplatelet therapy with aspirin and a thienopyridine, the incidence of subacute thrombosis with bare metal stents ranges from a low of 0.4% with intravascular ultrasound guidance to a high of 2.8% after multivessel stenting, [35] although in the early trials with aspirin and coumadin, it occurred in up to 24% of patients [36].

In-stent restenosis, characterized by neointimal hyperplasia and collagen deposition within the stent struts, affects 15–25% of de novo lesions in large vessels following bare-metal stent placement; this rate easily doubles in diabetic patients, long diffuse lesions and/or small vessels or bifurcations [37]. Restenosis is triggered by mechanical arterial injury and a foreign body response to the device, resulting in acute and chronic inflammation in the arterial wall, platelet activation and proliferation of smooth muscle cells [38-41]. Neointimal hyperplasia peaks during the first three months following stenting [42] and may be distributed either focally within the stent at the proximal and distal margins or diffusely over the entire stent length, occasionally extending beyond the stent margins [43] Animal models of angioplasty have directly implicated the platelet in the intimal proliferation that results from arterial injury: levels of platelet-derived growth factor (PDGF), a potent mitogen and chemoattractant released by activated

platelets, correlate with vascular smooth muscle cell proliferation [44]. Clinical studies indicate that platelet hyperreactivity is an important factor in the development of restenosis [45], and that increased surface GP IIb/IIIa ligand binding increases the likelihood of in-stent restenosis [48].

Disease-related platelet activation

In patients with acute coronary syndromes, the short-term platelet activation associated with PCI occurs against a background of persistent platelet hyperreactivity and thrombin generation [51, 52]. Platelets remain active long after these patients have been stabilized clinically. In the TIMI-12 trial, patients continued to show elevated platelet activity one month after experiencing an acute coronary syndrome, despite receiving continuous oral treatment with a potent GP IIb/IIIa receptor antagonist [53]. This would suggest that the prothrombotic environment is maintained for months (possibly longer) after clinical stabilization, possibly contributing to the recurrence of ischemic events over the long term [54].

Role of Antiplatelet Therapy

Optimal treatment strategies to minimize thrombotic complications following stenting involve aggressive anticoagulation with heparin and combination antiplatelet therapy. Unfractionated heparin is the most widely used antithrombin agent in PCI. Novel alternatives to heparin under clinical investigation include the direct thrombin inhibitors (e.g., bivalirudin), which unlike heparin, have little effect on thrombin generation but are potent inhibitors of preformed thrombin and platelet activation. The thienopyridines (ticlopidine and clopidogrel) exhibit synergistic antiplatelet activity with aspirin and the aspirin-thienopyridine combination shows evidence of being more effective than aspirin alone in reducing recurrent ischemia following PCI [56,57] the potential bleeding risk with this combination can be lessened by reducing the daily aspirin dose to less than 100 mg [58] Periprocedural use of intravenous GP IIb/IIIa receptor antagonists in conjunction with heparin, aspirin and clopidogrel, further reduces thrombotic complications and improves clinical outcomes post-PCI, albeit at the expense of an increased risk of bleeding complications [59]. However, routine use of GP IIb/IIIa receptor antagonists in all stent procedures is questionable, largely because of the associated cost and the lack of a demonstrated efficacy advantage over dual antiplatelet therapy [60].

Summary and Recommendations

To eliminate premature discontinuation of thienopyridine therapy, major all the guidelines gives the following recommendations.

1. Before implantation of a stent, the physician should discuss the need for dual antiplatelet therapy. In patients not expected to comply with 12 months of thienopyridine therapy, whether for economic or other reasons, strong consideration should be given to avoiding a DES.
2. In patients who are undergoing preparation for percutaneous coronary intervention and are likely to require invasive or surgical procedures within the next 12 months, consideration should be given to implantation of a bare-metal stent or performance of balloon angioplasty with provisional stent implantation instead of the routine use of a DES.
3. A greater effort by healthcare professionals must be made before patient discharge to ensure patients are properly and thoroughly educated about the reasons they are prescribed thienopyridines and the significant risks associated with prematurely discontinuing such therapy.
4. Patients should be specifically instructed before hospital discharge to contact their treating cardiologist before stopping any

antiplatelet therapy, even if instructed to stop such therapy by another healthcare provider.

5. Healthcare providers who perform invasive or surgical procedures and are concerned about periprocedural and postprocedural bleeding must be made aware of the potentially catastrophic risks of premature discontinuation of thienopyridine therapy. Such professionals who perform these procedures should contact the patient's cardiologist if issues regarding the patient's antiplatelet therapy are unclear, to discuss optimal patient management strategy.
6. Elective procedures for which there is significant risk of perioperative or postoperative bleeding should be deferred until patients have completed an appropriate course of thienopyridine therapy (12 months after DES implantation if they are not at high risk of bleeding and a minimum of 1 month for bare-metal stent implantation).
7. For patients treated with DES who are to undergo subsequent procedures that mandate discontinuation of thienopyridine therapy, aspirin should be continued if at all possible and the thienopyridine restarted as soon as possible after the procedure because of concerns about late-stent thrombosis.
8. The healthcare industry, insurers, the US Congress, and the pharmaceutical industry should ensure that issues such as drug cost do not cause patients to prematurely discontinue thienopyridine therapy and to thus incur catastrophic cardiovascular complications.

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REVIEW ARTICLE

PRESCRIBING FOR PEDIATRIC PATIENTS

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The prescription is a written order of a registered physician to the pharmacist with direction for preparation of the prescribed drugs & their use by the patient.

The prescription is the focal-point in the physician - patient - pharmacist relationship. It serves as a communication between physician and pharmacist, both of whom share the responsibility of safe guarding the patient. The clear communication of a prescription order to other members of the health-care team and to the patient is a vital step in drug therapy. Ideally, a prescription will be written for an optimal drug product for the specific patient and indications. In pediatric prescriptions even the smallest error can be fatal. Abbreviations in prescription have the advantage of both taking history and for convenience.

The impact of development on the disposition of a given drug is determined to a great degree, by age associated changes in body composition (e.g. body water spaces, circulating plasma protein concentrations) and functions of organs & organ systems (e.g. liver for drug metabolism and kidneys for excretion). The fact that child versus adult differences exist in pharmacotherapy has led to the new discipline of pediatric pharmacology (Neonate = 1 month, Infant = 1-12 month of age; children = 1-11 yrs of age and adolescents = 11-18 yrs. of age).

It is important to recognize that changes in physiology, which characterize development, may not correspond to these age defined "break points". Infact, the most dramatic changes in drug disposition occur during the first 18 months of life where the acquisition of organ function is most dynamic. It is important to note that pharmacokinetics of a given drug may be altered in pediatric patients, consequent to intrinsic (e.g. gender, genotype, ethnicity & inherited disease) and extrinsic (acquired disease state, xenobiotic exposure & diet) factors which may occur during the first two decades of life.

For pediatricians, it is essential to consider the developmental factors including physiological, psychological and pharmacological factors. These factors, along with differences in pharmacodynamic modalities, drug toxicity, effects of disease on drug disposition, can influence drug doses in pediatric patients. It is most useful to conceptualize pediatric pharmacokinetic, by examining the impact of development of those physiological variables that govern drug absorption, distribution, metabolism and excretion.

DRUG ABSORPTION

The rate and extent of gastro intestinal absorption is primarily dependent upon pH passive diffusion and motility of stomach and small intestine, both of which control transit time (Table 1)

Table 1 : DRUG ABSORPTION IN NEONATES, INFANTS AND CHILDREN

	Neonates	Infants	Children
Physiological alteration			
Gastric pH	>5	4-2	Normal(2-3)
Gastric emptying time	Irregular	↑	Slightly ↑
Intestinal motility	↑	↑	Slightly ↓
Intestinal surface area	↓	Near adult	Adult pattern
Microbial colonization	↓	Near adult	Adult pattern
Biliary function	Immature	Near adult	Adult pattern
Muscular blood flow	↓	↑	Adult pattern
Skin permeability	↑	↑	Near Adult pattern
Possible pharmacokinetic consequences			
Oral absorption	Erratic-reduced	↑ rate	Near Adult pattern
I.M. absorption	Variable	↑	Adult pattern
Percutaneous absorption	↑	↑	Near Adult pattern
Rectal absorption	Very efficient	Efficient	Near Adult pattern
Pre-systemic clearance	<Adult	>Adult	>Adult (? Rate)

↑ = Increased; ↓ = Reduced

Differences in the rate of drug absorption in neonates may be due to several factors, the neonate has a relative achlorhydria, longer gastric emptying time, and high level of intestinal Beta-glucouronidase activity (increased enterohepatic recirculation). Other factors which can influence drug absorption in neonates are irregularity of peristalsis with change in transit time of drug more and variable permeability of gastrointestinal mucosa to drug absorption e.g. Oral bioavailability of acid labile compounds (β-lactam antibiotics) is increased while that of weak organic acids (phenobarbitone & phenytion) is decreased. Lipid soluble drugs may be less absorbed in infants.

Bioavailability of many drugs administered by rectal route (e.g. diazepam) may be increased due to translocation across the rectal mucosa and the reduced pre-systemic drug clearance produced by immaturity of drug metabolising enzyme in the liver in early childhood.

There is very little information on hepatic first pass elimination of drugs in infants which can affect bioavailability. Since hepatic microsomol enzymes are ill developed, gastrointestinal disorders and systemic blood flow can also change drug absorption in infants. e.g. gastric emptying time and intestinal peristalsis is increased in diarrhoea, which can reduce drug absorption.

PLASMA PROTEIN BINDING AND DRUG DISTRIBUTION

Drug distribution is affected by increased body water, decreased body fat and reduced plasma protein binding. The reduced plasma protein binding is not related to the levels of plasma albumin, which are similar in infants and adults. In neonates, the free fraction of drugs, which are extensively (i.e.>60%) bound to circulating plasma proteins, is markedly increased, largely due to reduced concentrations of drug binding proteins (i.e. fewer number of binding sites) and reduced binding affinity. We can take the example of phenytoin, which is highly (98%) bound to plasma protein in adults but only 80-85% in neonates.

Poor or incomplete blood brain barrier in the neonates allows many drugs to reach CNS. Some drugs (vit.K, inodomethacin, sulfonamides) displace bilirubin from the albumin binding sites, and therefore much higher amount of bilirubin crosses blood-brain barrier which may cause kernicterus in the neonates.

DRUG METABOLISM

In neonates, liver has less capacity for oxidation and conjugation reactions including glucuronidation. Therefore, in general most of the enzymatic activities of metabolism of drugs are reduced. The best example of it is chloramphenicol toxicity (GRAY BABY SYNDROME) in infants. On the contrary, sulfation reaction is more active in infants and children. This may predispose to drug toxicity e.g. paracetamol, as the hepatic change is induced by the toxic metabolite of paracetamol. Induction of hepatic microsomal enzymes by a variety of drugs is known to occur in infants and children, as in adults. Thus drugs like phenobarbitone, carbamazepine, phenytoin or rifampicin can cause enzyme induction. Placental transfer of enzyme inducers may markedly increase drug metabolism of some drugs, like diazepam in neonates. The plasma esterases are lower in infants, which may prolong duration of action of some drugs e.g succinylcholine (Table 2).

Table 2 : DRUG METABOLISM IN THE NEONATE, INFANT AND CHILD

	Neonate	Infant	Children
Physiological alteration			
Liver body weight ratio	↑	↑	Slightly ↑
Cytochrome P450 activity	↓	↑	Slightly ↑
Blood esterase activity	↓	Normal (by 12 mon.)	Adult Pattern
Hepatic Blood flow	↓	↑	Near Adult Pattern
Phase II enzyme activity	↓	↑	Near Adult Pattern
Possible Pharmacokinetic consequences			
Metabolic rate	↓	↑	Near Adult Pattern
Presystemic clearance	↓	↑	Near Adult Pattern
Total body clearance	↓	↑	Near Adult Pattern

↑ = Increased; ↓ = Reduced

RENAL DRUG EXCRETION

At birth, the kidneys are anatomically and functionally immature. Renal function depends, more than on any other organ, on gestational age and post natal adaptations.

In term neonates and in infants, glomerular filtration rates are increased dramatically during first 2 weeks of post-natal life. This change in function is a direct result of post-natal adaptations in distribution of renal blood flow. But glomerular filtration rate is much lower in neonates than in infants, children and adults therefore, the doses and dose interval of penicillin, aminoglycosides or digoxin are required to be adjusted. The over all effect of immature metabolic and renal clearance processes are reflected as changes in the plasma half life of several drugs.

Similarly, a rapid rate of drug elimination has been noted for some drugs in the pre-pubertal child. Conversely, in neonates a decreased rate of drug elimination has been observed for some drugs like ampicillin, aminoglyscosides, (kanamycin, gentamicin, streptomycin etc) and digoxin. Therefore therapeutic monitoring is required for achieving and maintaining optimum drug concentration.

Guidelines for Prescribing: Based on the different physiological factors discussed above, prescribers are required to be aware of pharmacological profile of drugs they use. In general, paediatrician must determine the most effective drug, the correct dosage form and routes to be used. They also should know adverse effects, side effects, interactions, contraindication cost of therapy, drug compliance of patient for appropriate and correct prescription order the following components should be kept in the mind which will provide a rational approach to prescribing drug therapy in paediatric patients.

(1) **Criteria to initiate therapy:** Proper history of patient about the disease, previous treatment, allergies is required. Selection of the appropriate drug depends upon patient characteristics, sign, symptoms diagnosis and availability of drugs.

(2) **Doses** Represents the average range of quantities suitable for child which is to be administered within 24 hours. It is the responsibility of the prescriber regarding the amount of the drug to be prescribed. The dose is individualized for each patient by considering pharmacokinetic parameters. Dose adjustments may include consideration of body weight, age, surface area, renal and hepatic functions.

There are number of methods by which the dose for a pediatric patient can be calculated from the adult dose.-

(A) BASED ON BODY WEIGHT OF CHILD:

Clark's formula.

$$\text{Child dose} = \text{Adult dose} \times \frac{\text{Weight (kg)}}{70}$$

(B) BASED ON AGE OF CHILD

(a) ***Young's formula:***

$$\text{Child dose} = \frac{\text{Age (yrs)}}{\text{Age (yrs)} + 12} \times \text{Adult dose}$$

(b) ***Fried' s formula:***

$$\text{Infant dose} = \frac{\text{Age (month)}}{150} \times \text{Adult dose}$$

(c) ***Dilling 's formula:***

$$\text{Dose of child} = \frac{\text{Age (in yrs)}}{20} \times \text{Adult dose}$$

(C) BASED ON SURFACE AREA OF CHILD:

Surface area is determined from the body weight and age of child. This is perhaps the most accurate method to calculate the dose for child (Nomogram).

$$\text{Dose} = \text{Adult dose} \times \frac{\text{Surface area } (m^2) \times 60}{100}$$

Some drugs may require a loading dose in order to reach a therapeutic concentration more rapidly. Information on paediatric doses are usually provided by the manufacturer in the package insert.

(3) **Dose Interval:** Dosing interval is basically a function of the half life of drugs. (Table 3)

Table 3 : PLASMA HALF- LIVES (H) OF SOME DRUGS IN NEONATES AND INFANTS

Drugs	Neonate	Infant	Adult
Ampicillin	0.7-4.9 ++	1.6-2.3 +	1.0-1.8
Carbamazepine	8-28 -	14-19 - -	18-55
Carbenicillin	1.5-4.7++	1.6 +	1
Chloramphenicol	8-15+++	4-6+	2.3
Diazepam	25-100 ++	20-65 +	15-42
Digoxin	26-106 +	19-25 -	31-60
Doxycycline	6.9-	3.7-	12-22
Gentamicin	2.3-3.5+	1.7-5.4 ++	1-1.6
Paracetamol	2.2-5.0 +	3.0-4.5+	0.9-2.2
Penicillin	1.4-9.7 +++	0.9-2.2 ++	0.6-0.7
Phenobarbitone	40-500 ++	37-133 (-)	53-140
Phenytoin	17-104 ++	6-18 -	12-29
Salicylate	4.5-11.5 ++	3-6 +	2-4
Theophylline	13-26 +	3-4-	5-10

+ Slight increase **++ Moderate increase**
+++ Marked increase **- Decrease**

(4) Route: The route of administration must be carefully elicited. For orally administered drugs GIT disorders like vomiting, diarrhoea must be considered. Cardio-vascular functions must be assessed, before administering drugs parenterally. Some drugs can be effectively given per rectum in infants. The prescriber must consider the absorption, distribution of drugs in plasma as differences are seen with different available routes. Rapid I/V administration to paediatric patient can result in acute toxicity.

(5) Others:

(A) Drugs with narrow therapeutic index require monitoring e.g aminoglycosides, antiepileptic drugs and digoxin. The paediatric patients are generally incapable of communicating specific complaints, therefore paediatrician have to depend on objective criteria for evaluating efficacy and safety of drugs.certain drugs are better not used in neonates and infants for the reason of safety (Table 4).

Table-4 : DRUGS CONTRAINDICATED/AVOIDED IN NEONATES AND INFANTS

Drugs	Remarks
Anabolic hormones	Contraindicated. Stunted growth
Aminoglycosides (gentamicin, streptomycin, kanamycin, etc.)	Risk of ototoxicity and deafness.
Aspirin	Reye's syndrome. Best avoided
Clindamycin	Severe diarrhoea
Chloramphenicol	Gray baby syndrome
Diazepam (and other BZDs)	Respiratory depression
Dicyclomine	Best avoided. Apnoea
Ethambutol	Best avoided, Visual impairment
Fluoroquinolones	Contraindicated, Arthropathy
Fursemide	Synergistic ototoxicity with aminoglycosides
Glucocorticoids	Avoid, Stunded growth, immunosuppression
Imipramine	Avoid, Increased toxicity
Mefenamic acid	Avoid, Increased toxicity
Nalidixic acid	Avoid, Toxicity resembles fluoroquinolones
Neostigmine	Only under cover of atropine
Nitrofurantion	Avoid, Toxicity
Piroxicam	Avoid, Toxicity
Salbutamol	Avoid slow release preparations
Sulfisoxazole	Kernicterus in prematures
Tetracyclines	Avoid, Toxicity
Rabies vaccine	Not effective below 1 yr. Poor immune response.
pyrazinamide	Avoid if possible. Toxicity
Valproic acid	Avoid Haemopietic toxicity
Verapamil	Avoid Conduction defects

Adverse effects of drugs are peculiar in neonates and infants due to immaturity of organs and enzymes e.g. phenobarbital in an adult patient may cause sedation whereas in pediatric patients this may result in hyperactivity. Polypharmacy is a common problem resulting from inadequate assessment of an adverse effect.

(B) Information on likely drug interactions in infants is sparse. Problems are most likely to occur when there is lack of awareness that an interaction is possible. Occasionally some interactions may be therapeutically beneficial, but mostly may result in adverse effects, For example, Phenytoin, phenobarbital and carbamazepine can interfere with the clinical effect of several drugs in the child. Cisapride and erythromycin administration may lead to severe life threatening cardiac complications. The prescriber should be aware of other drugs that the patient may be taking, including herbal drugs, over the counter drugs, diet etc.

(C) Patients compliance is a major continuing problem in today's society because compliance of both parent and child must be considered. There are some problems involved in drug administration to neonates. Infants and young children e.g. number of drugs taken ,taste, unwillingness, dosing interval,route,food intake, adverse effects,cost, patients or parents educational level (forgetting or discontinuing)

effectiveness of pediatrition or pharmacist communication etc. Compliance remains a important factor and parents need to be taken into confidence and educated on the need for proper drug administration.

Thus pediatric patients can not be treated *at par* with adults in the provision of pharmacotherapy to the population. The application of above steps provides, an important safeguard, especially in pediatric patients for safe administration of drugs. This will benefit healthcare professionals and therefore society at large.

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RESEARCH PAPER

CRITICAL EVALUATION OF PHARMACOVIGILANCE IN SRI LANKA

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ABSTRACT

The present communication is a critical evaluation of the scope and various health care activities conducted in Sri Lanka to achieve the principle goals of Pharmacovigilance, recommended by the World Health Organization (WHO). As a part, Info_vig, the National Adverse Drug Reaction monitoring centre has been constituted by the Government of Sri Lanka. It is playing a leading role in the country for the monitoring of the ADRs. This article is an attempt to focus on the achievements of the centre towards contribution to the ADR database of the WHO programme for international drug monitoring and also to pin point the major limitations and constraining factors for contribution to global pharmacovigilance activities.

INTRODUCTION

The World Health Organization defines pharmacovigilance as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible medicines- related problems[1]. The principal aims of pharmacovigilance programmes put forward by the World Health Organization include [2]

1. to improve patient care and safety in relation to the use of medicines, and all medical and paramedical interventions;
2. to improve public health and safety in relation to the use of medicines;
3. to contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost – effective) use)
4. to promote understanding, education and clinical training in pharmacovigilance and its effective communication to health professionals and the public

However, from the outset it was recognized that the scope and activities of individual pharmacovigilance centre needs to be extended beyond the strict confines of detecting new signals of safety concerns. Quantitative and qualitative international differences in the factors mentioned below have all contributed in determining the scope and activities of an individual pharmacovigilance centre;

1. disease prevalence;
2. genetics;
3. socio cultural aspects;
4. health care systems;
5. health practices;
6. indication for and use of medicines
7. pharmaceutical formulations;
8. medicines monitoring and regulation practices.

The responsibility of determining the major pharmacovigilance activities to suit a country's needs lies with its national centre. The following factors need to be considered in determining the national pharmacovigilance activities;

1. Principal aims of pharmacovigilance recommended by the World Health Organization

2. Factors mentioned above which influence the pattern of utilization of medicines in a country
3. Available resources for pharmacovigilance activities
4. Epidemiology of medicine related problems seen in a particular country
5. Administrative constraints

The development of national pharmacovigilance activities in Sri Lanka were based on the above criteria the next part of this paper gives an outline of the pharmacovigilant activities in Sri Lanka.

Pharmacovigilance in Sri Lanka: The National Adverse drug reaction (ADR) monitoring Centre in Sri Lanka is named as Info_Vig, after combining 'Medicine Information and Pharmacovigilance." Info_Vig was born in 1999 in the Department of Pharmacology, University of Colombo with the assistance of the Ministry of Health. However pharmacovigilance activities by the department predate the official birth of the centre; ADR reports dated as far as 1996 are stored in our database. In the year 2000, Info_Vig was recognized as a member country of the WHO Programme for International Drug Monitoring.

The centre is headed by a senior academic member of the department, and assisted by all other academic and non academic members. This is done as an honorary service in addition to the designated duties of the members such as academic, curriculum, research, clinical service and examination duties. No funds are provided by the Ministry of Health for the pharmacovigilance activities. Our centre also contributes to the activities of many other relevant committees such as Drug Evaluation Sub Committee, Committee to evaluate quality failure of medicines, Cosmetic Evaluation Committee, National Medicinal Drug Policy Committee, Essential Medicines List Committee, and many sub committees of professional bodies.

Our main pharmacovigilance activities focus on:

1. promoting adverse drug reactions reporting, evaluating (root cause analysis), documenting and communicating the outcome of the reported ADRs.
2. contributing to the ADR database of the WHO Programme for International Drug Monitoring.
3. providing technical advice to Ministry of Health on patient safety issues such as quality or therapeutic failure of medicines, medication errors, serious adverse events, and capacity building.
4. providing evidence based information on quality and safety of medicines to the Drug Regulatory Authority of the Ministry of Health for purposes of registration / recall/ withdrawal.
5. collaborating with public health disease control programmes.
6. providing knowledge on medicine and medicine related problems to the general public and answer their queries on these issues.
7. assisting the health professionals by providing reliable, evidence based and balanced information on medicines and therapeutics.
8. contributing to safe use of medicines in children.
9. promoting the cost effective, rational and safe use of medicines.

As one can see, these activities cannot be achieved alone; as suggested by the World Health Organization [2].

"The management of the risks associated with the use of medicines demands close collaboration between the key partners in the field of Pharmacovigilance"

The key partners in our programme include clinical pharmacologists, officials in the Ministry

of Health, health professionals, consumers, hospitals, pharmaceutical industry, patients, medical and pharmaceutical professional bodies, media and World Health Organization.

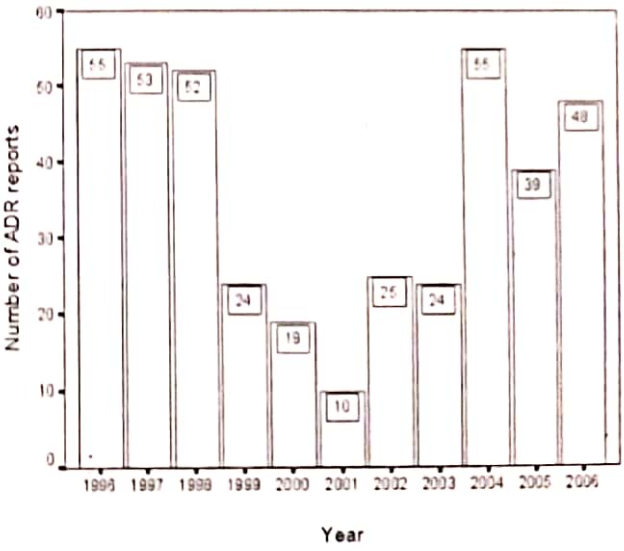
1. Info_ Vig as the National ADR monitoring centre

The primary activity of our centre is to function as the National ADR monitoring centre; the initial objective of Info_ Vig was to receive spontaneous ADR reports from doctors. Now it has expanded to receive reports on medicine safety issues from all healthcare professionals including nurses, pharmacists and consumers; Pharmacists are playing a vital role. The latter scene emerged after two important interventions, (i) a series of workshops organized by the Ministry of Health in 2005 for all the hospital pharmacists where the Info_Vig staff addressed about 650 receptive participants on importance of ADR reporting and (ii) designing a user friendly ADR form for the use of pharmacists.

The ADR forms have been sent to all the hospitals as a Ministry of Health circular in order to give an "official" stamp to the forms and also whenever there is an opportunity the ADR forms are distributed. The ADR reports are usually mailed to the centre; At times when the centre is informed about a suspected ADR (as a medicine query, or as an adverse event) we take measures to "actively" (as opposed to spontaneous) collect the information on the ADR and complete a form. On receipt of an ADR report, it is evaluated by the Info_Vig staff in respect to causality, seriousness, severity, root cause and necessity for any preventive measures. A formal reply with some information on recent literature regarding the event reported (and some times an incentive like a copy of a journal or a booklet) is mailed to the reporter within 7 – 14 days. Subsequently the information on ADR forms are classified according to WHO recommendations coded and entered into a computer programme for future purposes. The hard copies are filed and kept in the centre. The centre regularly forwards the ADR reports to WHO Programme for International Drug Monitoring using an old electronic system called "WINADR".

Since 1996, we have received a total of 404 ADR reports with an annual reporting rate of 36 (range 10-55). The number of reports in the first year (1996) was 55, which gradually dropped to 10 in 2001; however it began to rise in 2002 and reached a figure of 55 in 2004, 39 in 2005 and 48 in the current year until now (Figure 1). Significant proportion of ADR reports (84%, CI 81, 88) was from the doctors; 48 reports (12%, CI 9, 15) were from pharmacists. Interestingly 69% (CI 55, 80) of the ADR reports from the pharmacists were received in 2006 which supports what was mentioned earlier about the interventions carried out in 2005. Analysis of the Info_Vig data was presented in the last year's Sri Lankan Medical Association Annual Sessions as a poster which shows the gradual recognition of pharmacovigilance by professional bodies.

Figure 1: Number of ADR reports received by the Info_ Vig; 1996-2006



2. info_ Vig as a signal generating centre:

We have reported our strengths in the above paragraphs; now we look into our weaknesses

as an ADR reporting centre.

Signal refers to "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously"[3].

Even though a signal can be generated for both new chemical entities (NCE) and established medicines, documenting safety record of the former is very important. Our experience over the last decade indicate that we are making important inroads nationally especially in decision making on patient safety issues together with the Ministry of Health, but our contribution to the international arena on safety of NCE is still in its infancy and needs strengthening.

When we analyse our database it is evident that the ADR reports on NCE are relatively low. Of the total 404 ADR reports, there were only 37 (9 % CI, 7, 12) on NCE. We defined NCE as new pharmaceutical ingredients registered in Sri Lanka within five years of the date of reporting the ADR.

Table 1 compares the number of ADR reports on selected NCE in our database with that of WHO database (up to March 2006). It also presents some global pharmacovigilance recommendations made for those NCE during the study period. It is clear that our centre has not contributed to any of these global pharmacovigilance recommendations.

Table 1: ADRS REPORTED FOR SELECTED NCE; OUR DATABASE (INFO_VIG) *VS.* WHO DATABASE (AS OF MARCH 2006)

NCE	Number of ADRs in our database	Number of ADRs in the WHO database	Global pharmacovigilant recommendations*
Rofecoxib	Nil	31627	Voluntarily withdrawn by the Industry
Celecoxib	02	23346	New Safety warnings were introduced
Paroxetine	Nil	34081	Use become contra-indicated in children < 18 years
Fluoxetine	Nil	56403	New Safety warnings were introduced for use in children < 18 years
Rosuvastatin	01	4503	Safety warning about high dose causing rhabdomyolysis
Terfenadine	Nil	6094	De-registered by the FDA,USA , India
Cisapride	Nil	7771	Withdrawn from the UK & USA Market in 2000
Rosiglitazone	Nil	7214	Safety warnings about liver toxicity and cardiac failure

**** From Vigimed and Uppsala Monitoring Centre's regular publications***

Post marketing Spontaneous ADR Reporting Scheme mainly aims at detecting (i) any safety issues related to NCE, and (ii) new safety warnings related to established medicines. It is because during pre-marketing clinical trials only carefully selected patients up to a number of 3500 would have been exposed to a medicine. Therefore pre-marketing clinical trials are insensitive in detecting Type B ADRs and less common Type A ADRs. Data from our Post marketing Spontaneous ADR Reporting Scheme shown above reflects that we have not been able to achieve these aims of Post marketing pharmacovigilance.

Health professionals in Sri Lanka are still unaware of the real meaning of "Spontaneous Reporting" of "Suspected ADRs" because they report the ADRs which have been diagnosed as certain by them. They do not report suspected Adverse Drug Events if the causality is not judged certain by them. Therefore our database is ineffective in generating signals. Hence, there is an urgent need to market pharmacovigilance and its requirements among Sri Lankan healthcare professionals.

3. Info_ Vig as a source of expertise to the Ministry of Health:

This takes many forms, and some are beyond the scope of this article. Few which need to be looked at are;

- providing technical advice to Ministry of Health on patient safety issues such as quality or therapeutic failure of medicines, medication errors, serious adverse events, paediatric medicine safety issues and capacity building
- providing evidence based information on quality and safety of medicines to the Drug Regulatory Authority of the Ministry of Health for purposes of registration / recall/ withdrawal.
- providing technical assistance in establishing national medicine policy

If we look at the aims of pharmacovigilance recommended by the World Health organization, the foremost one is;

"To improve patient care and safety in relation to the use of medicines, and all medical and paramedical interventions"

The vast majority of state health care is safe, but in some instances patients face serious consequences due to various reasons some of which are unavoidable and unpredictable; analyzing the root cause of these problems will avert similar incidents in the future. In Sri Lanka, there is no distinct line drawn between these patient safety issues and adverse drug reactions. In most instances, the root cause for these incidents is found to be multifold. However, the reporting institution always points towards an error / quality failure in the medication itself. As Sri Lanka is a country with many generics available in the market this assumption is very difficult to disprove.

Most of these "Adverse Events" are therefore reported to the Director/ Medical Supplies Division (MSD) by the Director of the respective hospital implicating a problem in the medications. These reports are usually considered as complaints to the Director/MSD for further action. In most instances, the MSD authorities face several problems in dealing with them. This led to the formation of a Technical Committee in 2004 to advise the MSD/ Ministry of Health on managing these issues. It comprises Clinical Pharmacologists from the Info_Vig, Director/ MSD, pharmacists and administrative staff / MSD, representatives from the Drug Regulatory Authority (DRA) and National Drug Quality Assurance Lab (NDQAL). Most problems happen because systems do not work as they should. This committee is working towards identifying such failures in the system and recommending remedial actions. It is also aimed at changing the culture of "complaint" and "inquiry" into "adverse event/medication error" and "evaluation" respectively.

During this two year period, this committee has received over 30 reports on "adverse events"; all were not investigated. Decision to investigate was made case by case. Evaluations of these events are carried out in many ways, such as (i) based only on paper documents, (ii) inviting the key people to the committee meeting, and in some instances (iii) on site evaluation by a team (clinical pharmacologists and pharmacists from the MSD) visiting the respective hospital and collecting the required information. Table 2 outlines one of these events, actions taken, and recommendations made.

Table 2: ONE EXAMPLE OF PATIENT SAFETY ISSUES EVALUATED BY THE INFO_VIG AND MEDICAL SUPPLIES DIVISION JOINT COMMITTEE

Reported incident	Actions and recommendations
Consultant anaesthetists from 3 Teaching Hospitals reported over 10 incidents where they observed a clinical picture of excessive cholinergic symptoms when two drugs were given for reversal after general anaesthesia. ? Drug A was over active ? Drug B was ineffective	• Both medicines were tested in the NDQAL - Drug B did not show any problems, Drug A was found to be 10 times higher in strength • Batch was withdrawn • Local agents were informed

Pharmacovigilance programmes and drug regulatory authorities are mutually supportive. Info_Vig functions as a source of evidence based information on quality and safety of medicines to the Drug Regulatory Authority for purposes of registration, recall or withdrawal. Senior members of our Info_ Vig serve in the Drug Evaluation Sub Committee where decisions on registration of medicines are handled. Rofecoxib, gatifloxacin and astemizole are some of the recently deregistered products. Also we have drafted guidelines on registration requirements for multivitamins, cough syrups and cosmetics. We also provide on the job training for the pharmacists working in the Drug Regulatory Authority on issues related to drug registration. The department regularly publishes the Drug Index which gives the information on registered products in Sri Lanka

4. Info_ Vig as a medicine information centre:

Though it cannot be included in the strict confines of pharmacovigilance, a few lines on this activity has to be presented as it is the other arm of Info_Vig. Even before the launch of Info_Vig, all Departments of Pharmacology in Sri Lanka functioned as drug information centres to healthcare professionals. With the birth of Info_Vig, the functions of the medicine information service are now more structured. It assists the health professionals by providing reliable, evidence based and balanced information on various issues such as pharmacotherapy of a disease, selection of an appropriate medicine for an indication, adverse drug reactions, drug interactions, drug doses, availability, choice of medicines in pregnancy and lactation. Table 3 gives the number of documented information queries handled by the centre over the years.

Table 3: THE TOTAL NUMBER OF DOCUMENTED QUERIES RECEIVED BY THE INFO_VIG: 1999 – 2006

Year	Number
1999	92
2000	85
2001	64
2002	53
2003	62
2004	59
2005	44
2006	30
Total	**489**

Presently together with a Clinical Pharmacist from the United Kingdom who has been working in the Medicines Information Service, UK, we are in the process of developing Standard Operation Procedures and a form of algorithm on how to search and provide information for different categories of queries such as prescribing

in children, prescribing in renal disease, prescribing in liver disease, prescribing during breast feeding, choice of antibacterial agents, overdose and so on.

Empowerment of patients is one step ahead in the road towards rational use of medicine and medicine safety. In the last couple of years we have been regularly writing a column on medicine information in a popular weekend paper. The column also requests the readers to communicate their concerns regarding medicine safety issues to our centre; which is showing presently some results.

5. Info_Vig as a source of expertise in disease control and public health programmes:

The World Health Organization identifies pharmacovigilance as a priority for every country with a public health disease control programme [2]. Info_Vig actively participates and provides pharmacovigilance expertise to the activities of immunization programme, tuberculosis control programme and anti - filarial campaign. Info_Vig was involved in the establishment of the global training network on Vaccine Safety in our country. This area needs further strengthening as many public health programmes are yet to incorporate pharmacovigilance into their activities.

6. Info_Vig's contribution to safety of medicines in children:

Pharmacovigilance in paediatrics is another key activity of Info_Vig. It works closely with the Sri Lankan College of Paediatricians, Lady Ridgeway hospital for Children, which is the premier children's hospital in Sri Lanka and many paediatricians working in the periphery. Few of the activities are listed below;

- Info_Vig together with few paediatricians researched into the risk of hepatic toxicity associated with the use of multiple supra-therapeutic dose of paracetamol in children. This association led to many patient education programmes in managing fever in children
- In 2006, Info_ Vig, together with key paediatricians revised the pediatric dose recommendations for paracetamol
- We are frequently invited to conduct educational programmes to pediatric care givers on areas of safe and effective pharmacotherapy, pharmacovigilance and safe use of medicines in children
- Info_Vig is a key member of a committee presently drafting a document on rational use of medicines in children

7. Info_Vig's contribution to capacity building programmes:

We, in collaboration with various departments of Ministry of Health, and other stake holders, such as the pharmaceutical industry, universities, non governmental organizations and professional associations regularly conducts educational programmes in the area of pharmacovigilance, rational use of medicines, and pharmacotherapy monitoring

8. Info_Vig's contribution to revise the Essential Medicine List for Sri Lanka:

After 1999, last year the Ministry of Health decided to revise the Essential Medicine List for Sri Lanka. A committee worked on this; Info_Vig members functioned as the Chairperson and Convener of this Committee, and greater portion of expertise and technical input was provided by Info_Vig.

Promoting rational use of medicines:

It is a favorite exercise by Info_Vig, and our department. We always recognize the close link between rational use of medicines and pharmacovigilance. Hence, we make use of any opportunities to promote rational use of medicines among healthcare providers. It takes many forms ranging from writing guidelines, delivering plenary lectures on rational use of medicines to problem based learning activities and day–to–day ward teaching to medical undergraduates.

Research:

The research activities of Info_Vig are in form of operational researches. When a problem related to pharmacovigilance is repeatedly coming up, then we plan a study to analyze such events. The paracetamol study mentioned above is one such example.

During its 10 year history, pharmacovigilance in Sri Lanka is continuously meeting new challenges. Learning from the challenges, it is becoming a dynamic clinical and scientific discipline. Following can be considered as our broad achievements in relation to pharmacovigilance;

- Some important inroads nationally on decisions regarding patient safety issues
- Ensuring that the risks in medicine use are anticipated and managed
- The ADR (and other medicine safety issues) reporting culture is slowly getting embedded in clinical practice
- The para medical staff, especially the pharmacists and consumers are educated on medicine safety issues and encouraged to ensure safe use of medicines.
- Analysis of individual ADR reports has resulted in some form of preventive measures at the local hospital and national level
- Improved communication and development of good rapport with the partners in pharmacovigilance; clinicians, academics, ministry administrators, industry, pharmacists, consumers, the media and Uppsala Monitoring Centre/WHO
- Providing regulators with the necessary information to amend the recommendations on the use of medicines
- Education of health professionals to understand the effectiveness/ risk of medicines that they prescribe/administer/ dispense
- The centre is now well recognized by all stake holders as a National Advisory body on pharmacovigilance and related disciplines
- Improvement in the quantity and quality of ADR reports over the last decade

However, as we have pointed out the major limitation is still our ineffectiveness in generating signals and not contributing much to the global pharmacovigilance activities. Also Info_Vig is yet to improve recognition for medicine related problems, lapses in drug registration procedures and inadequate communication with remote health institutions. Our activities are constrained by many factors such as lack of financial, electronic, technical and human resources.

In future, we hope to focus on;

- Changing the mindset of the reporters and promoting them to report suspected adverse events which will ensure generating signals on NCE
- Expanding our out reach to the peripheral health institutions to make them as active partners in pharmacovigilance
- Developing a web page for our centre (in progress) and introduce electronic reporting system, storage and transmission of data/ information
- Continuing and strengthening the educational programmes on pharmacovigilance
- Designing a good database for electronic storing of the ADR reports in the centre
- "Marketing" the centre to obtain some regular funding and to employ at least one permanent staff
- Getting Vigibase which would facilitate our communication with UMC/WHO
- Training the pharmacists employed in the MSD and DRA in some of the ground level pharmacovigilance activities.

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REVIEW ARTICLE

METHODS FOR THE DETECTION OF MEDICATION ERRORS

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A medication error is a preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient or consumer. Such events may be related to professional practice, healthcare products, procedures and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring and use [1].

Various studies have been carried out to find out the impact of the medication errors, but the subject received prime attention when in 1999, a report from the Institute of Medicine (IOM) highlighted that the medical errors were the 8th leading cause of death in USA. Nearly 44,000 deaths occur in America every year due to medication error and total of 98,000 people are admitted to the hospital due to medication errors. It was also estimated that the total cost of the medication error ranges between $17bn-29bn annually. The data available on medication errors in India is limited. However, the available data suggests that out of all visits to the medical emergency department, 6% are drug related adverse drug events and they accounts for 45% of all adverse drug events (ADEs). Of all ADE related visits, 52% were preventable and out of ADEs related admissions 55% were considered preventable [2,3].

Drug therapy cannot be successful unless both, the prescribing and medication delivery processes are conducted correctly. The current estimates of the incidence of medication errors are unquestionably low because many errors are neither documented nor reported.

The report [4] of the Institute of Medicine (IOM) has devoted an entire chapter describing the methods to report the medication errors. This recognizes that the methods of self-reporting are indeed aimed to learn from errors. But the chapter is silent on the use of other methods for error detection. A single method cannot study every aspect of the problem; therefore, error detection requires a multidirectional approach. Each method of error detection has a certain advantage to detect certain types of errors. Thus, the precise knowledge of the outcomes is critical for interpreting results measured by a given method [5, 6].

Methods for Reviewing Medication Errors:

According to a study[5], the following methods are considered efficient for detection of medication errors in various in-patient settings.

1. Directly observing medication administrations
2. Reviewing patients charts
3. Reviewing incident reports involving medication errors
4. Attending medical rounds to listen for clues that an error has occurred
5. Interviewing healthcare personnel to stimulate self-report
6. Analyzing doses returned to the pharmacy
7. Testing urine for evidence of omitted drugs and unauthorized drug administration
8. Examining death certificates
9. Attending nursing change-of-shift report
10. Comparing medication administration record (MAR) with physicians' orders

11. Performing computerized analysis to identify patients receiving target drugs that may be used to treat a medication error or to search for serum drug concentration that may indicate an overdose
12. Comparing drugs removed from an automated drug-dispensing device for patients with physicians orders

The study concluded that the first three methods received greater attention of healthcare professionals for being efficient and cost-effective, among the all given above. The efficiency was defined as the time required performing the tasks associated with each error detection method. The starting and ending times for each task were recorded by each data collector, and the total time spent on each patient was indicated for each task [5].

Direct Observation Method

The Direct observation method requires the data collector to accompany the nurse administering medications and observe the preparation and administration of each dose. The observer records exactly what the nurse did with the medication and witnesses the drug's administration to the patient. The recorded data includes related procedures, such as measuring the patient's heart rate and giving medications with food. Each observer attends the change-of-shift report on the nursing unit to meet the nursing staff and answer questions they have about the study. The observer then follows the first nurse to begin preparing medications and observes other nurses periodically to try to witness the administration of at least 50 doses.

The observer makes handwritten copies of the medication orders that are in the patient's chart and compares each dose observed with each prescriber's order. The orders which are not interpretable are usually excluded from the study. Any deviations between the prescriber's order and what was observed is recorded as an error. After examining all of the doses witnessed, the observer then tallies all of the doses omitted. The medication error rate is calculated by dividing the number of errors by the sum of the number of doses given plus the number of omissions and then multiplying the result by 100.

A major concern about the validity of observational data is the potential effect of the research on the individuals observed. People may behave differently when they know they are being studied than at other times, a phenomenon sometimes referred to as the Hawthorne effect [7]. In the case of observational method, the error rate may increase if the researcher causes interruption or the nurses feel nervous. Conversely, the error rate may decrease if nurses become more careful in the presence of researcher. On the other hand, covert observation reflects most unbiased results or reality, because the people being studied are unaware of the observation.

The observation method offers the following advantages in all areas of research:

- It is not necessary for subjects to have the knowledge about errors.
- If subject or any other healthcare professional is not willing to report, the detection of errors is not affected.
- Remembering of the errors by anyone, who is supposed to report later, is not required.
- The ability to communicate is not required.
- Selective perception of subjects is unrelated.
- Observer inference is involved, and
- The effect of the observer on the observed, is not significant.

The ways of protecting the validity of the observation method against observer bias include using experienced observers, such as pharmacists and nurses, and training the observers to be objective, inconspicuous, and lenient [8].

Years of experience with the observation technique have revealed many practical

advantages over other methods:

1. The method is easy to understand,
2. Data are easy to use for identifying trends and benchmarking,
3. Data are available within hours,
4. The method is system oriented and views errors in doses as defects in a system,
5. The method is objective and does not blame anyone,
6. The method is sound, with all doses being examined and errors witnessed,
7. The method enables problem-based continuing education that focuses on "our" errors,
8. The method facilitates evidence based testing that can evaluate proposed system changes,
9. Quality can be measured quantitatively by third parties, and
10. The method establishes track records for national use, such as those used by CMS in long-term-care facilities.

Chart review Method

Chart review method is based on the research method described by Bates and colleagues[9] and modified in accordance with suggestions made by Bates for this study. A list of study patients who are directly observed during the medication administration session is provided to the chart reviewer after the observer completes his/her work. The charts are reviewed, the day after the medication administration session to allow for errors that occurred during that time to exhibit effects on the patients. The following sections of each medical chart are evaluated by the data collectors: physician's orders, laboratory test results, physician's progress notes, nurse's notes, and the Medication Administration Record (MAR). Trigger events that can result from a medication error includes laboratory test results that exceeds normal values to a degree that it is likely, that an error has occurred (e.g., blood glucose concentration of >400 mg/dL can indicate that an insulin dose is omitted). Forms are provided to data collectors to remind them of trigger events. A list of medication orders is extracted from each patient's chart to facilitate the comparison of each order with the MAR.

In most of the chart-review studies, data collectors are staff nurses. These nurses are trained intensively over a two-week period. Initial training includes reviewing definitions and cases. Data collectors then begin data collection in the wards with close supervision by research staff. It is important for the data collectors to develop good relationships with the nurses, pharmacists, and physicians while remaining relatively unobtrusive. In addition to charts, medication order sheets are reviewed daily. Voluntary and solicited reports are obtained from staff. Finally, additional sources of error detection such as pharmacy logs, incident reports, and computerized detection systems are reviewed.

Jha et al.[10] compared chart review with other methods of detecting medication errors. The largest number of ADEs were detected by chart review (398), followed by 275 by computer monitoring and 23 by voluntary reporting. Chart review was also more effective than the other methods in detecting preventable and potential ADEs. Chart review was not particularly effective in detecting drug administration errors, however.

Data collection forms:

Following types of data collection forms are used in Chart Review Method of Medication Errors detection [6].

Voluntary report form: The most important characteristics of the voluntary report form are briefness, simplicity, and high visibility. In addition, it should be easily accessible. Staff is asked to include the patient's name, the date, and a brief description of the incident and whether there were serious consequences for

the patient. The staff member may include his or her name, but this is optional. If the name is indicated, the data collectors can sometimes obtain additional details about the incident.

Incident form: The incident form typically includes a tear sheet with the patient's name and medical record number. The sheet is separated immediately after the form is filled out and stored separately to protect patient confidentiality. Also recorded on this form are the following:

- The date, time, and location of the incident,
- The name, route, and dose of the drug involved,
- The category of the drug,
- The stage of the drug-use process where the error occurred (ordering, transcribing, dispensing, administering, or monitoring),
- The hospital services involved,
- Any extra work resulting from the error, and
- A narrative description of the error.

The data collectors also document the type of error (e.g., dose, route, or frequency error). The data collectors initially classify the incident as an error, a potential ADE, or an ADE.

ADE and potential ADE follow-up form: On this form, the data collectors indicate which body system was affected by an event. They also record whether the event was intercepted and any predisposing factors, such as a known allergy not being documented or the drug order being taken orally. Necessary measures, such as the use of an antagonist, extra laboratory or radiological testing, and prolonged hospitalization, are documented. These data have been useful in estimating morbidity and costs associated with ADEs. Documentation of the morbidity and a narrative description of the event are included.

Physician review form: All incidents, classified by the data collectors as potential ADEs are verbally presented to a panel of two physicians. The two physicians make the final determination if an incident is an error, potential ADE, or actual ADE. Severity of the incident is rated on a 4-point Likert scale, preventability on a 5-pont Likert scale, and attributation via the Naranjo algorithm [11]. Potential prevention strategies are assigned.

Incident Reports Method

Data collectors are allowed two to three weeks to pass after the observation period before returning to analyze reports and classify any errors reported. Incident reports have to be filed at least 7 days before the first day of observation in hospitals, at least 30 days before the first observation day in skilled-nursing facilities, and no more than 7 days after the last observation day (to allow enough time to identify incidents and file reports for events occurring on the observation day). The time required to complete this process are recorded for each incident report. To assess the accuracy of each data collector's work, the research pharmacist reviews photocopied incident reports, if available, or go to the facility to review the original documents.

Comparing medication administration record (MAR) with physicians' orders

With an electronic medical record (EMR) or computerized physician order entry (CPOE) system reviewers can also review all the documents and data on the computer, but automatic extraction using computer programs and text searching or natural language processing can detect any keywords such as ''allergy'' or ''falls'', specific laboratory values such as potassium levels of 6.5 mEq/l, or drug names such as an angiotensin II receptor blocker. These concepts can be linked to form rules—for example, heparin and low hematocrit [12].

A positive yield from a rule is called a trigger. The use of triggers is much more practical and less labour intensive than conventional chart reviewing because the triggers can be automated

by computer and the reviewer's search is much more focused. Gurwitz and colleagues [13], used computer based triggers and other means to find 1523 ADEs from 27,617 patients; the computer based triggers found 66% of ADEs. Triggers can also be used to monitor for ADEs and medication errors in daily practice once their discrimination ability is established.

Interviewing health care personnel to stimulate self-reports

There are two main types of self-reports from health professionals:

1) Those from physicians, nurses, pharmacists, or other health professionals who become aware of any ADE, potential ADE, or medication error (sometimes called an "incident report") and
2) Those generated by research assistants, nurses, or patient safety officers who visit wards or clinics to solicit any possible incident and record it.

The process of using self-reports from health professionals is especially useful for identification of incidents in inpatient settings. Investigation of iatrogenic disorders such as ADEs and medication errors always provokes concerns about liability among health professionals and such concerns may inhibit the self-report. It is thus important to educate health professionals about the purpose of the study, which is to clarify the treatable factors associated with ADEs and medication errors and not to reprimand the responsible individuals. A non-punitive culture is important to maximize data capture at the study sites [12].

Examining death certificates

In this method, reviewers look at the death occurred in a hospital setting during a specified time period. Physicians are trained to review hospital medical records and give their opinion on the occurrence of adverse events and the quality of hospital care and its impact on patient outcomes. Although the wording of the question used to assess hospital deaths has differed somewhat among studies, the studies have produced very similar conclusions. Perhaps the most often quoted study is the Harvard Medical Practice Study [14], which assessed negligence related to adverse events, including deaths, in New York. However, several other studies have asked whether deaths would have been preventable by optimal quality of care[11], and have found similar results.

The method has drawback that it may overestimate the deaths result as it is impossible to tell how much deaths could be prevented if optimal healthcare would be given to the patients. So, the questions remain: when a reviewer classifies a death as definitely or probably preventable or due to medical errors, is there a 90% chance or a 10% chance that a death would have actually been prevented if care had been optimal? How long would patients have lived if care had been optimal? How does the interpreter reliability of reviewer's ratings affect these estimates?

A similar kind of study was done by Rodney A and co-workers [15], which contained medical records from 1995-1996. The study was designed as retrospective implicit review to examine the reliability of reviewer ratings of medical error and the implications of a death described as "preventable by better care" in terms of the probability of immediate and short-term survival if care had been optimal. The results showed Similar to previous studies, almost a quarter (22.7%) of active-care patient deaths were rated as at least possibly preventable by optimal care, with 6.0% rated as probably or definitely preventable [13].

CONCLUSIONS

Other methods like urine analysis and serum drug concentration determination techniques are really effective and accurate to detect whether the error of omission or other types of dosing errors. But these methods require a timed

approach, making the patients uncomfortable and also will add to the cost of detection of medication errors. The only reliable, feasible, accurate, fast and cost-effective methods are the first three methods i.e.

1) Direct Observation Method
2) Chart Review Method
3) Incident Report Method

Out of these the observational method is proved to be most useful and accurate. According to a study done by Elizabeth A et al. the research pharmacist confirmed 457 of the 2556 comparison doses to be in error, producing a true error rate of 17.9%. Direct observation detected 300 of these errors and 73 false positives, which produced an error rate of 14.6%. For the same doses, chart review detected 17 of the 457 errors and 7 false positives, yielding an error rate of 0.9%, while incident report review detected only 1 error for an error rate of 0.04%. However, the data collectors missed 157 errors during direct observation, 440 during chart review, and 456 during incident report review [5].

The accuracy of the three different types of data collectors was compared with the research pharmacist's standard by calculating the kappa statistics for direct observation and chart review. When kappa values were calculated for each type of data collector, the highest kappa values for direct observation were those for pharmacy technicians (0.74) [5].

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REVIEW ARTICLE

SELF MEDICATION: PREVALENCE AND PATTERN IN URBAN COMMUNITY

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ABSTRACT

INTRODUCTION

Medicines are part of human life. Use of medicines is highly prevalent in urban community whether prescribed by treating doctor or over the counter medication. Self-medication practice and pattern has been studied all over the world. Self medication seems to be widely prevalent as reported in various studies.

OBJECTIVES

The study was carried out to find out the prevalence and pattern of self medication in Ahmedabad city.

METHOD

This is a cross-sectional questionnaire based study of adult population of Ahmedabad city.

RESULTS AND CONCLUSION

Out of 881 respondents about 77% reported taking self medication. Pain and fever (84.8%) were the most common symptoms leading to self medication. Analgesics were the most common group of the drugs consumed for self medication. However alternative medicines also form a sizeable part of self medication. Relatives/friends/neighbours and chemist (Pharmacy shop) are the major sources of information for self medication. Students and educated class frequently resort to self medication, while uneducated are less likely to self medicate.

Key words- Self medication, Urban Community Survey.

INTRODUCTION

Medicines and medicine taking are part of our way of life. Medicines are widely consumed whether in from of prescribed drugs or as self medications in form of over the counter (OTC) drugs.[1] self medication is a age old practice. Self medication involves the use of medicinal products by the consumers to treat self-recognized disorders or symptoms, or the intermittent or continued use of medication prescribed by a physician for chronic or recurring diseases or symptoms. In practice, it also includes use of the medication for family members; especially where the treatment of children or elderly is involved is defined as 'medication that is taken on patient's own initiative or on advice of pharmacist or a lay person'. Self-medication has an important role to play in health care and, with the continued improvement in people's education, general knowledge and socioeconomic status, self medication has been successfully integrated into many healthcare systems throughout the world [2]. There are wide differences in prevalence of self medications across the world [3-8]. Differences in the prevalence as well as pattern of self medication exist between urban and rural communities. Self medication with prescription drugs is especially problem in developing countries like India where pharmacies freely supply medicines over-the-counter, as do informal drug shops and small groceries. Sometime people even self medicate with

prescription drugs on the advice of traditional healers. Furthermore, self-medication drugs are known to interact with many prescription only drugs, alcohol and foods. [1, 10] We report a community based study conducted in Ahmedabad city to find out the prevalence and pattern of self medication.

METHODOLOGY

The study was a questionnaire-based survey carried out in Ahmedabad city situated in Gujarat state in the western part of India. The city has a population of about 3.5 million and literacy rate of about 83 %.(7). A 7-item questionnaire was prepared in vernacular language (Gujarati), which included questions related to self-medication in one year recall period. The questionnaire was validated prior to its use for data collection. Data was collected from people aged 18 years and above in one month period using stratified sampling. The questionnaire was filled up by the respondents themselves except in case of those who were illiterate or had difficulty in filling the questionnaire.

The data was analyzed using EPI software, Version 6.04B (jointly developed by Center for Disease Control, USA and WHO).$P<0.05$ was considered as statistically significant.

RESULTS

Out of 913 respondents targeted, 881 answered the questionnaire and where included **Table 1** shows the socio-demographic characteristics of the study participants.

Table-1: SOCIODEMOGRAPHIC CHARACTERISTICS OF RESPONDENTS

(n=881)

	CHARACTRISTICS	NO. (%)
(A)	**GENDER**	
	Males	565(64.1)
	Females	296(33.6)
	Data not available	20(2.3)
(B)	**AGE (YEARS)**	
	18-40	585(66.4)
	41-60	227(25.8)
	>60	39(4.4)
	Data not available	30(3.3)
(C)	**EDUCATION**	
	Graduates & Postgraduates	672(76.3)
	School level	124(14.1)
	Uneducated	67(7.6)
	Data unavailable	18(2.0)
(D)	**OCCUPATION**	
	Student	279(31.7)
	Professional	259(29.4)
	Business	116(13.2)
	Housewife	123(14)
	Skilled worker	32(3.6)
	Labourer	25(2.8)
	Retired	2693.0)
	No data	21(2.4)

PREVALENCE

Out of 881 participants, 676 (76.3%) reported self-medication in previous one year. About 45% (307) resorted to self-medication sometimes or many times. Students formed the largest group for self-medication among all occupational groups. Prevalence of self-medication was significantly higher in educated class (high school and above) than in less educated population as 75% of uneducated group never self-medicated.

CONDITIONS FOR SELF-MEDICATION

Pain and/or fever formed the commonest indications (84.8%) for self-medication followed by common cold (52.8%), gastrointestinal disturbance (24%) and others (5%).

DRUGS/DRUG GROUPS USED FOR SELF-MEDICATION

Analgesics formed the largest drug group (532 out of 676) followed by cough and cold medicines, antacids and other drugs (Table-2). While most of the respondents used allopathic medicines, use of alternative medicines was also reported. Theses include ayurvedic (103), homeopathic (20) and home remedies (67).

Table-2: DRUG GROUPS USED FOR SELF-MEDICATON

Drugs	No.(%)
Analgesics & NSAIDs	532 (78.69)
Cough & cold preparations	229 (33.87)
Gastrointestinal*	178 (23)
Antibiotics	36 (5.32)
Vitamins	13 (1.92)
Ayurvedic & other CAM	103 (15.23)

* Include antacids, antimotility drugs, antiemetics

SOURCE OF INFORMATION

Acquaintances (relatives, friends, neighbours-297) were the commonest source of information for self-medication followed by chemist (223), TV (74) print media (47), own past experience with the medicine (40), doctor (34) and others (45).

Table-3: SOURCES OF INFORMATION-SELF-MEDICATION

Source of information	No. of Respondents (%)
Friend/neighbour/relative	297(43.34)
Chemist	223(32.98)
TV and print media	121(17.89)
Past experience	85(12.57)
Doctor	34(5.02)

REASONS FOR USE OF ALTERNATIVE MEDICINES

Side effects with allopathic medicines (120) was the commonest reason followed by high cost, ineffectiveness of allopathic medicines and others like safety of alternative medicines.

120 out of 676 respondents knew that self-medication can be harmful.

DISCUSSION

Our study shows that self medication is highly prevalent in urban population. In the previous studies the prevalence varied between 31% to 82% [4,5,6]. High prevalence in our study may be attributed to the demographic characteristics of majority of respondents. Students (32%) and professionals (29%) together form about 60% of study population. Most of them are educated and also below 50 years of the age. While most of the students reported self medication many times, majority of educated respondents (high school and above) also reported self medication frequently. Other studies also report high prevalence of self medication in students [8, 9] and young age group [3]. Our study shows higher involvement of educated population while most of illiterate rarely self-medicate. This is in contrast to earlier study [6] showing no difference among these groups.

Pain and/or fever was the most common condition for self-medication followed by

common cold as reported in previous studies., while analgesics-NSAIDs formed the largest drug group for self-medication[5,6,7]. Use of antibiotics is lower compared to other groups.[4,5].

This study reveals wide spread use of ayurvedic and other complementary and alternative medicines (CAM) for self- medication. The reasons cited for using CAM were side effects, high cost and lack of effectiveness of allopathic medicines and lack of side effects of alternative medicines. The high prevalence of use of ayurvedic medicines and home remedies is the result of cultural influence as the respondents are born in culture where these medicines are part of therapy for generations. However use of these drugs as self-medication may lead to increased possibilities of drug interaction with the prescribed medicines. This concern has been raised by other studies also. [2, 10]

Acquaintances (friends, relatives and neighbours) formed the commonest source of information for self medication followed by chemist shop and media. Previous studies reported chemist as the major source [7, 9].

Most of the respondents (556/676) showed lack of knowledge regarding possibility of harmful effects by self medication. Thus overall knowledge regarding self medication is inadequate. This has been reported in a study on medical students [8].

CONCLUSION

This study reveals a high prevalence of self medication in urban community, use of both allopathic and alternative medicine for self medication and inadequate knowledge regarding consequences of self medication. Some educative measures like articles in newspapers, awareness programs- lectures, posters or talks in audiovisual media would improve the awareness in community regarding this essential component of drug therapy.

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REVIEW ARTICLE

PREVALENCE OF NON-COMPLIANCE IN THE USAGE OF ANTIBIOTICS IN THE STATE OF GUJARAT

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ABSTRACT

The present survey was done with the objective to determine the prevalence of non-compliance in the usage of antibiotics in the state of Gujarat. Information regarding non-compliance was collected from Ahmedabad, Anand, Gandhinagar and other minor parts of Gujarat. Information about the prescribed antibiotic including dose, frequency, duration and route of administration prescribed was recorded. Then the actual regimen followed by the patient was noted after the prescribed duration. In the present study, non-compliance with the prescribed medication was observed in 39.83% of the patients. The major reasons for non-compliance were found to be ignorance among the patients regarding consequences of non-compliance (77.39%), improvement in symptoms (36.17%) and polypharmacy (34.04%). Other reasons found were no improvement in symptoms (6.38%), cost (2.12%), adverse effects (2.12%) and diseased states (1.06). The types of non-compliance found were discontinuation of prescribed antibiotics (61.70%) and decreased frequency of the doses (39.36%). Thus, from the present study it was found that ignorance, improvement in symptoms and polypharmacy were significantly responsible for patient non-compliance in the usage of antibiotics.

Key Words: Non-compliance, antibiotic, polypharmacy

INTRODUCTION

Patient non-compliance is a major factor in therapeutic failure both in routine practice and in scientific therapeutic trials. It is the extent to which the actual behaviour of the patient fails to coincide with medical advice and instructions. It may be partial, complete or erratic. In addition to therapeutic failure, undetected non-compliance may lead to the best drug being deemed ineffective, when it is not [1]. Approximately one-third of the patients take their treatment as prescribed, one-third partly comply and one-third never comply. Poor compliance is found in all socio-economic and racial groups and there is no satisfactory method of predicting who will fail to comply with the treatment [2].

Non-compliance on the part of the patient has been found to cause deterioration of patient's health, the need for additional consultations, the use of extra drugs, additional hospital admissions and increase in direct and indirect costs of management (3, 4, 5). Use of suboptimal doses of drugs in serious diseases and sacrificing efficacy for avoidance of serious adverse effects has been documented. It particularly affects drugs of low therapeutic index like heparin, anticancer drugs, amino glycoside antimicrobials etc. [1].

Patient non-compliance may contribute to antibiotic resistance and has become a significant patient safety concern. The phenomenon of resistance can impose serious constraints on the options available for medical treatment of many bacterial infections [6]. The infections caused by them are stronger and resistant bacteria are harder to cure, patients stay sicker for a longer time and infections become more costly to treat [7].

It was also proved in a global survey that there was a poor understanding in 10 of 11 countries

of how non-compliance can increase the potential for resistance development [8]. Another global survey (COMPLy, Nice, France) showed that only slightly more than a third of individuals polled, know that non-compliance with a prescription of antibiotics can lead to antibiotic resistance [9]. The same survey also showed that non-compliance rate exceeded 30% in some countries. Similarly, 51% believed that leftover antibiotics could be saved and used later on and 73% of those who had leftover antibiotics actually saved them for later use.

Thus, the present survey was done with the objective to determine the prevalence of non-compliance in the usage of antibiotics in the state of Gujarat.

METHODOLOGY

Prevalence of patient non-compliance in the usage of antibiotics was determined by collecting information from various regions of Gujarat which included major cities like Ahmedabad, Anand, Gandhinagar and other parts like Sadra, Patan, Dashela and Wanakbori. A case record form was prepared to record the demographic data of patients, their clinical details, the causative organism responsible for infection and laboratory reports. Information about the prescribed antibiotic including dose, frequency, duration and route of administration prescribed was recorded. Then the actual regimen followed by the patient regarding the dose, frequency, duration and route of administration was noted. To obtain this information, the patients were followed up after the prescribed duration. This was accomplished by meeting the patients at their residence, at the chemist's shop or at the clinic or dispensary. Symptoms experienced by the patient (before and after treatment), concurrent medications taken and diseased states of the patients were also recorded in the case record form. Finally, in patients showing non-compliance, the reasons and types of non-compliance were recorded and evaluated. In the patients giving more than one reasons of non-compliance, all of them were recorded separately and accordingly the percentage of patients was calculated.

RESULTS

In the present study, data of 236 patients prescribed with antibiotics was collected. The demographic data of the patients enrolled is represented in tables 1 and 2. Out of the total patients enrolled, 142 patients (60.17%) were found to be fully compliant with the prescribed treatment and the remaining 94 patients (39.83%) were found to be non-compliant (Fig1). The major reasons for non-compliance were found to be ignorance among the patients regarding ill-effects of non-compliance (77.39%), improvement in symptoms (36.17%) and polypharmacy (34.04%). Other reasons found were no improvement in symptoms (6.38%), cost (2.12%), adverse effects (2.12%) and diseased states (1.06%) (Fig 2). The types of non-compliance found were discontinuation of prescribed antibiotics (61.70%) and decreased frequency of the doses (39.36%) (Fig 3).

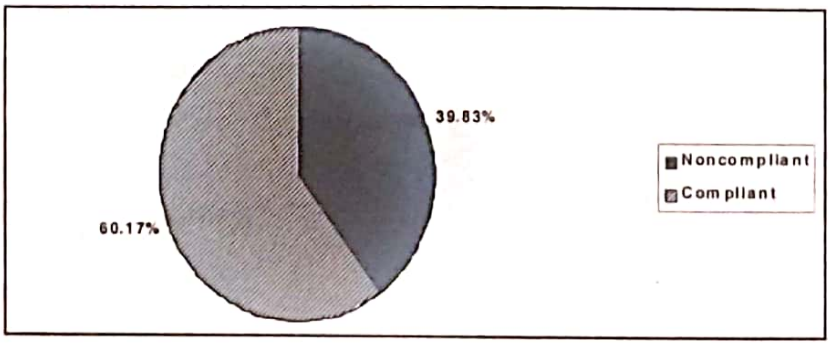


Figure 1: Distribution of patients according to compliance with antibiotic treatment

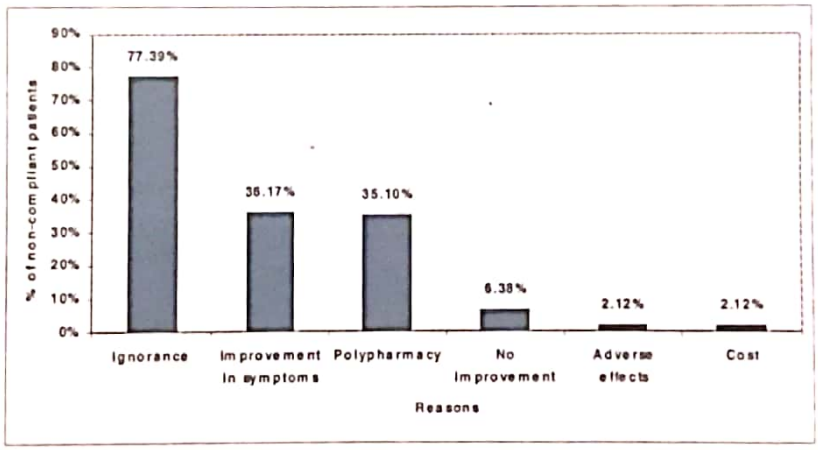
Table 1: DEMOGRAPHIC DATA OF THE PATIENTS ENROLLED IN THE STUDY

Total No. of patients	236
Age range	2-85 years
Sex	Female 45%
Male	51%
Diseased	19

Figure 2: Reasons for Non-compliance

Table 2: DISTRIBUTION OF PATIENTS ACCORDING TO PLACE

Place	No. of patients
Ahmedabad	94
Gandhinagar	6
Vanakbori	91
Anand	14
Dashela	10
Patan	14
Sadra	7



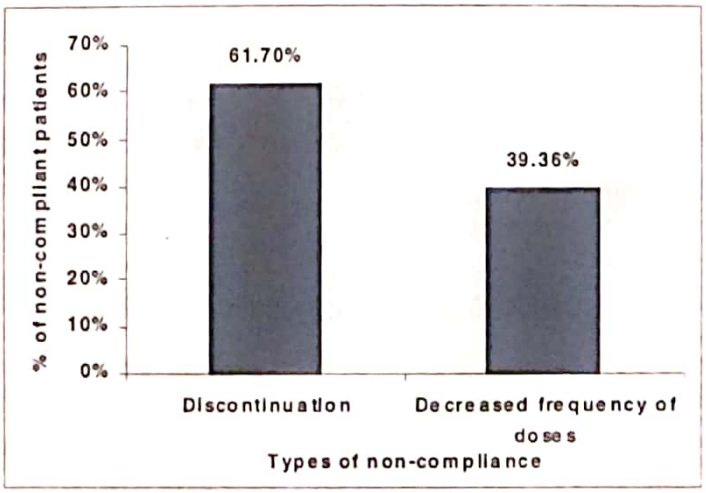


Figure 3: Types of Non-compliance

DISCUSSION

In the present study, 39.83% of the patients were found to be non-compliant to the prescribed medication. Most of the adherence studies done on the adult patients have revealed that about 50-70% patients fail to complete a course of therapy [10]. Thus from the present study it is seen that the prevalence of non-compliance in Gujarat is less as compared to the normally observed percentage of non-compliance.

The major reason found for non-compliance in the present study was ignorance among the patients regarding the consequences of the noncompliance. Because of this, most of the patients were found to forget to take the medication. This type of non-compliance comes in the category of unintentional omission of doses, which is one of the most common mistakes made by the patient (1, 7). In some patients, ignorance resulted into indifference in taking the medication regularly. Some studies suggest that one-third of the patients never have their prescriptions filled, or leave the hospital without obtaining their discharge medications [11]. Ignorance and indifference relating to the ill effects of non-compliance also results in forgetfulness and finding excuses for not taking regular medications, a common excuse being difficulties faced in taking medications during work hours. It may be related to the fact that patients still working, while unwell, may face difficulties in taking medication during work hours [12].

Another major reason found for non-compliance in the present study was improvement in the symptoms of infections. 36.17 % of non-compliant patients were found to decrease the dose and frequency of prescribed antibiotic or totally stop the treatment as they experienced improvement or relief from the symptoms. This type of non-compliance is especially seen in milder infections where symptomatic relief is observed before the recommended treatment time [13-15]. The patients may thus be feeling better and therefore, do not appreciate the need to continue their medication [16]. A pan-European survey has showed that patient expect clinical improvement after 3 days of antibiotic treatment. This may be a belief responsible to cause non-compliance with the therapy [17].

Polypharmacy is another reason contributing to non-compliance, which was seen in 34.04% of non-complying patients in the present study. Polypharmacy is very common in geriatric patients who under several diseased states are supposed to take several medications during the day. The frequency and complexity of drug regimen may affect compliance. Many studies attest to compliance being inhibited by polypharmacy. i.e. more than three drugs-taking occasions per day (1). It has been reported that increasing the number of doses to be taken daily by one increased the probability of a patient being non-compliant by 72 % (18) and drugs taken only once/twice a day increase adherence (10). Polypharmacy is also prevalent in patients suffering from other diseased condition as well and may contribute to non-compliance. In present study, this was the reason seen in 1.06 % of patients. Patient compliance with complicated prescriptions is poor. This is because the patient is supposed to take different medications at different times. Such non-compliance is frequently perceived as occurring exclusively with chronic conditions [18].

Other minor reasons for non-compliance are no improvement in the symptoms, cost and adverse effects of the prescribed antibiotic. No improvement in the symptoms results in dissatisfaction in the patients regarding the treatment. It was found to be the reason for non-compliance in the present study in 6.38% of non-compliant patients. It is reported that expectations from the medications and lack of faith in the prescriber causes dissatisfaction among the patients and results in non-compliance [19].

Adverse effects to the prescribed medication

can also be the major deterrents for compliance. Though not much significant in the present survey, even minor side effects like nausea, vomiting etc. can be suggestively responsible for non-compliance. In the present study, non-compliance observed because of the adverse effects experienced was seen in only 2.12% of non-complying patients. They mainly complained of adverse effects like nausea, vomiting and constipation. Adverse effects may be immediate and because of them the benefits perceived may be remote (1). The patient may not be aware of the adverse effects but it has been found that there are a number of patients who fear interactions of medicines with alcohol or other medications (7). If patients experience symptoms, which they attribute to adverse effects of drugs, then they will stop taking medicine (20).

Non-compliance due to cost was seen in 2.12% of non- complying patients. This is particularly a problem with newer antibiotics, which may be beyond the financial reach of some patients (e.g. Azithromycin) (7). Moreover, in a country like India, where the major population belongs to the middle class or the lower middle class, this factor is of paramount importance. But, it was not found to be a significant factor in the present study because of the availability of free medicines at Government hospitals. However a more detailed study is required to observe the relationship between the socioeconomic status of the patients and the degree of non-compliance.

Another aspect of this study included the types of non-compliance observed in patients. Mainly two types of non-compliance were noted among the patients. Total stoppage of treatment or discontinuation of the prescribed antibiotics was observed in 61.70% of non-complying patients and 39.36% of non-complying patients were found to take fewer doses of medications as compared to that of prescribed dosage and frequency. The first type of non-compliance is generally observed if the patient incorrectly assumes that medication is no longer needed or symptomatic relief has been achieved. Alternatively, the patient may not get a prescription refilled because of laziness (11). Thus the patient prematurely discontinues the medication. The second type of non-compliance is also found to be common and can be intentional or non intentional. Intentional decrease in dosage and frequency of medication can be because of the same reasons mentioned earlier. However, occasionally, unintentional decrease in dosage may also occur when patients make errors in taking the medication or take the doses at the incorrect time (10).

CONCLUSIONS

Thus, from the present study it was found that in the state of Gujarat, ignorance regarding the consequences of non-compliance is the most significant factor responsible for non-compliance. This factor can be minimized if various members of the healthcare team create sufficient awareness among patients regarding the consequences thereof. The community pharmacists and hospital pharmacists can play a major role in this area by counseling the patient.

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RESEARCH ARTICLE

A SURVEY ABOUT THE KNOWLEDGE, ATTITUDE AND PRACTICE OF ADVERSE DRUG REACTION REPORTING AMONG DOCTORS IN BANGALORE CITY

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ABSTRACT

The national pharmacovigilance programme will complete two years of its existence on November 23, 2006.The short term objective of the programme was to foster a culture of notification in it's first year of operation. This study was aimed to evaluate the knowledge, attitude and practice of doctors in Bangalore towards ADR reporting, find reasons for under-reporting and to suggest methods to improve the reporting culture. The survey was conducted among 100 doctors including dentists practicing in different hospitals, nursing homes and clinics in Bangalore using a Questionnaire. The most common clinical manifestations of ADRs were dermatological and gastrointestinal and nausea/vomiting were the commonest ADR seen. The common causative drugs were Antibiotics followed by NSAIDs. 84 respondents had seen ADRs and 69 had seen SADRs in the past year. Only 11 respondents were aware of the National pharmacovigilance programme and only 1 of the respondent knew location of the nearest pharmacovigilance center. The most important cause for not reporting was not being aware of the pharmacovigilance programme (89%). All respondents thought that maintaining a database of ADRs were important and 99 % of them are willing to report if ADR forms are made available to them. Submitting a printed form was preferred by 62%, online submission was preferred by 22 % while 16% felt both were convenient. Though all doctors felt maintaining a database of ADRs is important and are willing to report, there is lack of general awareness about the national pharmacovigilance programme and where to report. This can be solved by awareness programmes for practicing doctors and undergraduate students as well as by providing easy access to ADR reporting forms.

INTRODUCTION

Pharmacovigilance is a branch of pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term side effect of medicines [1]. The success of a pharmacovigilance programme depends on the reporting of suspected adverse drug reactions. The main tool of pharmacovigilance is spontaneous reporting by health professionals. Spontaneous reporting is defined as a "System whereby case reports of adverse drug events are voluntarily submitted from health professionals and pharmaceutical manufacturers to the national regulatory authority" [2].

In India the Central Drugs Standard Control Organization (CDSCO) initiated a country-wide Pharmacovigilance programme under the guidance of DGHS, Ministry of Health & Family Welfare, Government of India and the National Pharmacovigilance Programme (NPP) was launched on November 23, 2004 [3].

The NPP has setup 2 zonal centers, 5 regional centers, and 24 peripheral centers to monitor adverse drug reactions and also collect the ADR data, review and evaluate it. This key information will be sent to ADR database (vigibase) at Uppsala monitoring committee, maintained by WHO.

The Uppsala Monitoring Centre (UMC, WHO), Sweden is maintaining the international database of adverse drug reaction (ADR) reports received from several National Centres. By september

2005, 78 countries were participating in this programme and the database had 3.5 million adverse drug reaction reports. Vigibase online (web based) system is used for submission of ADR reports.

The National Pharmacovigilance Programme completed two years of its existence on November 23, 2006.The short term objective of the programme was to foster a culture of notification in the first year of operation [3]. But under-reporting of adverse drug reactions is still a problem and even though India is participating in this programme its contribution to UMC database is less [4].

Bangalore is the capital city of Karnataka state with a population of 6.1 million. The health infrastructure includes 12 medical colleges (5 offering only postgraduate degrees), 16 dental colleges and more than 250 hospitals and nursing homes. There are approximately 13,000 hospital beds and Bangalore is soon emerging as the health capital of India [5].

Bangalore is equipped with one peripheral center for adverse drug reaction reporting. The annual reports of the REGIONAL PHARMACO-VIGILANCE CENTRE (SOUTH) showed that the number of ADR reports received from the peripheral pharmacovigilance centre in Bangalore was 170 [6]. This clearly is a very less number for a city which has a large pool of healthcare professionals. Our survey aims to test the knowledge, attitude and practices of doctors in Bangalore towards ADR reporting and find causes for under reporting.

Objectives of this survey were

1. To estimate the incidence of adverse drug reactions in medical practice and the most common clinical manifestations of ADRs.
2. To test the knowledge, attitude and practice of doctors about the National Pharmacovigilance programme and ADR reporting.
3. To make recommendations for future activities in fostering ADR reporting culture in doctors.
4. To spread awareness about NATIONAL PHARMACOVIGILANCE PROGRAMME

MATERIALS AND METHODS

This knowledge attitude practice (KAP) survey was conducted among 100 doctors in Bangalore city in major hospitals, nursing homes and clinics, for a period of one month between August 2006 to September 2006. Specialized consultants as well as general doctors were considered for the survey.

For the study purpose, the following documents were used. A self-prepared questionnaire and an information leaflet. The questionnaire included two sections. The first section collected personal information about the doctor, the common clinical manifestations of adverse drug reactions (ADRs) classified system wise, approximate number of cases of ADRs seen in the past one year, common causative drugs, methods of diagnosis of suspected ADRs, important data considered while managing suspected ADRs and reporting practices in past one year. The second section collected information about the attitude of doctors towards adverse drug reaction reporting and their awareness about the National pharmacovigilance programme. On receipt of the completed questionnaire a leaflet providing information about the nearest pharmacovigilance peripheral centre and the person in charge of that particular centre, as well as webpage links for online adverse drug reaction reporting (JIPMER link) was provided to the respondent doctor.

RESULTS

Out the 100 respondents 48 were undergraduates, 52 were postgraduates and respondents included 5 dentists. Among them 35 doctors were practicing in medical colleges, 49 in speciality hospitals and 16 in nursing homes and clinics.

Adverse drug reactions are commonly seen in medical practice with 84 doctors having seen an ADR and 69 among them having seen an Serious adverse drug reaction (SADR) in the past 1 year [Table-1] & [Table-2].

Table-1: NUMBER OF ADR CASES SEEN BY DOCTORS IN LAST ONE YEAR

Doctors (%)	CASES
16%	NIL
41%	<5
25%	5 -10
11%	10 – 25
7%	>25

Table-2: CONSEQUENCES ADR SEEN BY DOCTORS

CONSEQUENCE of ADR	(%)
Resulted in Death	5%
Was life threatening	22%
Needed inpatient treatment	62%
Prolonged hospitalization	22%
Congenital anomaly / birth defect	2%

Dermatological and gastrointestinal manifestations were most common. Nausea and vomiting being the most common presentation. Most common causative agents were antibiotics, predominantly the penicillin class followed by cephalosporins. NSAIDs were the next common group of causative drugs.[Table-3], [Table-4].

Table-3: MOST COMMON MANIFESTATION OF ADRS

MANIFESTATION	%
Nausea / vomiting	68%
Urticaria	56%
Hypotension	51%
Bronchospasm/Asthma	48%
Anaphylaxis	48%

Table-4: MOST COMMON CAUSATIVE DRUG CLASS FOR ADRS

DRUG CLASS	Number of drugs mentioned
Antibiotics	95
NSAIDS	68
Cardiac drugs	9
Anticancer drugs	8
Steroids	4

The most important diagnostic criteria used by the respondents in diagnosing a suspected ADR were the temporal relationship of the reaction starting after drug intake. The other criteria's considered important were the clinical manifestations, cessation of reaction on de-challenge, adverse reaction profile of the drug and lab investigations. Re-challenge was considered least important. [Table-5].

Table-5: METHOD OF DIAGNOSIS FOR SUSPECTED ADR

RESPONSE	(%)
If reaction started after drug intake	83%
Clinical manifestations	63%
If reaction stopped after drug is stopped	61%
Based on adverse reaction profile of drug used	50%
Laboratory investigations	16%
Re-introduce drug to see if reaction reappears	11%

On a question regarding the importance given by them to the data elements of ADR reporting form while managing a suspected ADR, the responses revealed that they give more importance to the date of start of reaction, generic name of the drug, dose taken and its expiry date, while less importance was given to the brand name, manufacturers name and batch /lot number. [Table-6].

Table-6: IMPORTANT DATA WHILE MANAGING SUSPECTED ADR

DATA ELEMENT	(%)
Date of start of reaction	70%
Date of start of suspected medication	58%
Generic name of the drug	65%
Brand name of the drug	35%
Manufacturers name	30%
Batch no/lot no	30%
Expiry date of drug	62%
Dose	68%
Route	43%
Frequency	41%
Indication for use	58%
Pre-existing illness in patient	57%
Other concomitant medication	38%
Concomitant Herbal medication	44%

In the past one year 27 respondents claimed to have reported ADRs and majority of them reported it to the pharmacist (18 respondents) or to the manufacturer of the drug (10). Few of them (7) reported them as presentations in conferences and meetings and as articles (3) in journals. Only 1 respondent reported to the pharmacovigilance centre.

The most important sources of information about ADRs in order of importance were text books of medicine/pharmacology (82%), journals (69%), drug information leaflet (40%), online databases(26%) and materials given by medical representatives(15%).

All respondents (100%) felt that maintaining a database of ADRs was important. But only 11 respondents (11%) were aware of the National Pharmacovigilance programme (NPP) and only 1 among them knew the location of the nearest pharmacovigilance center.

The important causes for not reporting ADRs were; not being aware of the programme (89%),not knowing where to report(34%), not having ADR reporting forms(32%), view that the drug reactions are already well known(28%),time constraints(17%)and not knowing what to report(13%).Table-7

Table-7: IMPORTANT REASONS FOR NOT REPORTING

RESPONSE	%
NOT AWARE OF THE PROGRAMME	89%
DO NOT KNOW WHERE TO REPORT	34%
DO NOT HAVE REPORTING FORM	32%
DRUG REACTIONS ARE ALREADY WELL KNOWN	28%
TIME CONSTRAINTS	17%
DO NOT KNOW WHAT TO REPORT	13%

If ADR reporting forms are made available most doctors (99%) are willing to report. The preferred mode of reporting being submitting a paper form to the pharmacovigilance center (62%), while 22 % prefer online submission and 16% said both were convenient.

DISCUSSION

Adverse drug reactions are commonly encountered in clinical pratice and majority of the respondent doctors have witnessed ADRs and SADRs in the past year. All the respondent doctors felt that maintaining a database of ADRs is essential but the most important reason for not reporting was not being aware of the National Pharmacovigilance programme and the procedure for reporting. Most of doctors are willing to report if ADR reporting forms are made available to them.

The National Pharmacovigilance programme has to step up its efforts to foster a "reporting culture" and this can be done by spreading awareness about the programme and the ADR reporting mechanism in medical practitioners. Some suggestions by us are :

1. Include the National Pharmacovigilance programme in the Pharmacology curriculum of undergraduate medical students.
2. Make ADR reporting forms available to major hospitals and nursing homes through the peripheral pharmacovigilance centre.
3. Create awareness about NPP among practicing doctors by providing information leaflets about the reporting procedure and where to report ADRs.
4. Online downloadable forms and online submission can be popularized by providing cross links in major healthcare and hospital websites.

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RESEARCH ARTICLE

EVALUATION OF THE PATTERN OF HIV INFECTION IN PATIENTS OF AHMEDABAD

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ABSTRACT

NACO estimated that the number of Indian HIV patients had increased from 3.97 million in 2001 to 5.13 million in 2004, which is globally second to South Africa. Upsurge in the spread of HIV infection necessitates guiding the general population regarding the preventive pattern of infection and vigorous implementation of preventive measures. In the present study, 191 HIV patients were studied to evaluate the prevailing pattern of the disease, age, sex, signs and symptoms, drugs used, opportunistic infections and cost of therapy. Unsafe sex (78-79%) was the leading mode of transmission of infection with majority of the patients (85%) being adult (15-44 yrs age group). Male to Female ratio for the occurrence of HIV infection was 2.131:1 and majority of the patients (94%) showed weight loss as the major symptom for HIV infection. 33% of patients suffered from opportunistic infection, principle among it was T.B. (24-25%). In the govt. sector, majority of the patients (89.73%) were in stage I of Anti Retro Viral (ARV) Therapy while on contrary in private sector, majority of the patients were in stage III. In both the sector, majority of the patients (71.2 % and 56.76%), were devoid of any complaint associated with drug use. Total cost of treatment was approximately 800-7000 Rs. /month. Thus general population should be guided to use preventive measures such as safe sex, use of disposable syringe, checking of HIV status of expected mothers, education on alarming symptoms of HIV infection, and use of appropriate prophylaxis to prevent the development of opportunistic infection.

Key words: HIV, prophylaxis, and education.

INTRODUCTION:

At the beginning of the 21st century, Human Immunodeficiency Virus (HIV), which causes the Acquired Immune Deficiency Syndrome (AIDS), continues to have its greatest impact in the developing world. AIDS is ranked as the number four cause of death globally but the number one cause of death in Africa [1]. Although infection and death rates for HIV/ AIDS have slowed considerably in developed countries, the pandemic continues to spread in much of the developing world. Sub-Saharan Africa currently has the biggest regional burden, but the disease is spreading quickly in India, Russia, China, and much of the rest of Asia [2]. In addition to that, globally India is second only to South Africa in terms of the overall number of people living with HIV [3]. As well as, National AIDS Control Organization (NACO) estimated that the number of Indians living with HIV increased from 3.97 million in 2001 to 5.31 million in 2004 [4]. Even more alarming is a 2002 report by the CIA's National Intelligence Council which predicated 20 to 25 million AIDS cases in India by 2010, which is more than any other country in the world [5]. Contrary to all this, Indian government sources

have announced figures disputed by international organizations, and vice versa, all of which has only added more confusion [6]. Moreover the country has no national information system to collect HIV prevalence information from the private sector, which provides 80% of health care in the country [7].

All these number controversy reveals Governments' apathy towards infection or lack of adequate efforts to combat with HIV infection, especially in the states like Bihar, Gujarat, and West Bengal. The situation is worsened by incomplete knowledge about HIV.

Therefore the present study was aimed to focus on the need for increasing the awareness towards prevailing HIV infection, and making an effort of providing education to general population regarding the prevention and treatment of infection by assessing the prevailing pattern of HIV infection in Ahmedabad.

OBJECTIVE

To assess the prevailing pattern of HIV infection in patient of both the government sector and private sector in Ahmedabad.

METHODOLOGY

The study was done at OPD (outdoor-patient-department) on patients in civil hospital (as a government sector) and in a Private hospital at Ahmedabad in Gujarat. A total of 117 patients in civil hospital (as a government sector) and 74 patients in Private sector were included in the study. The patients were included in the study on the basis of following inclusion and exclusion criteria:

Inclusion Criteria

Patients of either sex or any age suffering from AIDS

Patient diagnosed with HIV Positive.

Ability to understand and the willingness to sign and date a written informed consent document at the screening visit before any protocol-specific procedures are performed.

Exclusion Criteria

Patients who had an exposure to HIV but whose HIV status is unknown

Patients included in the study were interviewed for the details in accordance with the questionnaire. The questionnaire format consists of information given below:

1. Epidemiology of the disease
2. Reasons for the occurrence of Disease/ Mode of Transmission
3. Major symptoms before infection
4. Drugs used and cost of treatment
5. Existence of the opportunistic infection.

RESULTS

Epidemiology of the disease

In our study 191 responses were recorded among them 117 were from the government sector and 74 patients were from private sector. Majority of the patients (85%) were found to be in the younger (15-44yrs) age group and 12.5% belonged to the older age group (>44 years) (Figure 1). Among the total number (191) of patient's evaluated majority were male (130 patients) and the ratio of male: female was being 2.131:1(Table-1). There was no significant difference in the socio-economic status of the person infected as evident by almost equal percentage of patients in low and high socio-economic group in both the Government sector and private sector (Table-1).

Table-1: DEMOGRAPHIC PARAMETERS EVALUATED IN HIV PATIENTS OF AHMEDABAD

SR. NO.	PARAMETERS EVALUATED (%)	GOVERNMENT SECTOR	PRIVATE SECTOR	TOTAL
1.	No. of male patients (%)	83 (70.93%)	47 (63.51%)	130 (68.06%)
2.	No. of female patients (%)	34 (29.07%)	27 (36.49%)	61 (31.94%)
3.	High socioeconomic group	53 (45.30%)	32 (43.24%)	85 (44.50%)
4.	Low socio economic group	64 (54.70%)	42 (56.76%)	106 (55.50%)
5.	Awareness regarding mode of transmission	93 (79.48%)	56 (75.67%)	149 (78.01%)
6.	HIV Patient on T.B. Prophylaxis	36 (30.77%)	48 (64.85 %)	84 (43.98 %)
7.	Occurrence of T.B. in HIV patient on T.B. Prophylaxis	4 (11.11%)	3 (6.25%)	7 (8.34%)

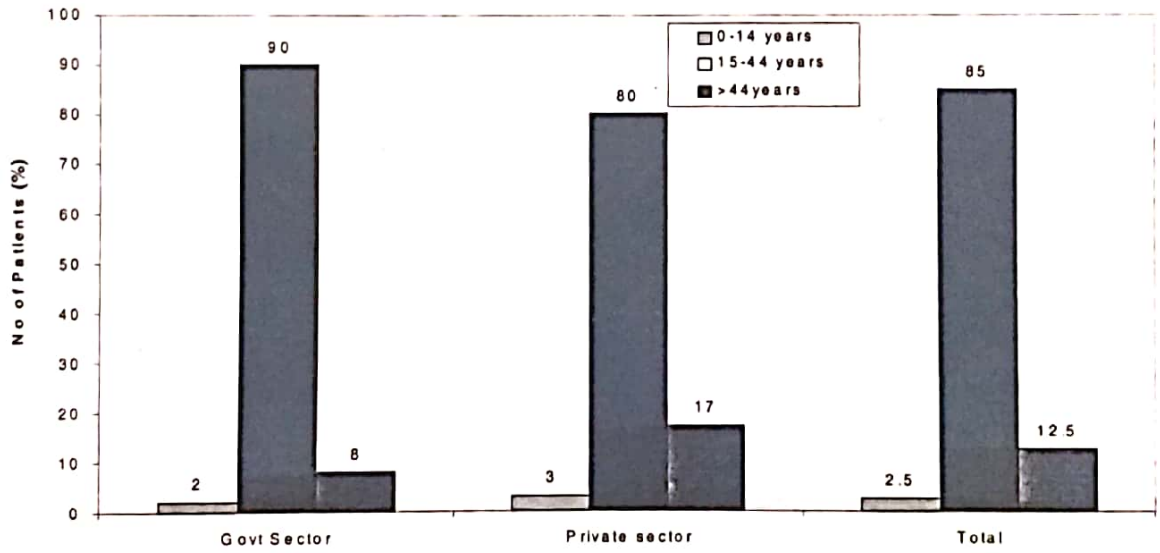

Figure 1-A : Age group of patients infected with HIV in Ahmedabad

Mode of transmission

Sexual contact was found to be the leading mode of transmission of infection in both the sector (Govt.: 79.49% & Private sector: 78.38%), which is in accordance to NACO (Figure 2). The incidence of perinatal transmission in both the sectors was almost equal. Awareness regarding mode of transmission of HIV infection even before acquiring infection, was observed among majority (78.01%) of the patients (Table 1). The majority (70.49%) of females who were infected through sexual contact had acquired the infection from their life partners.

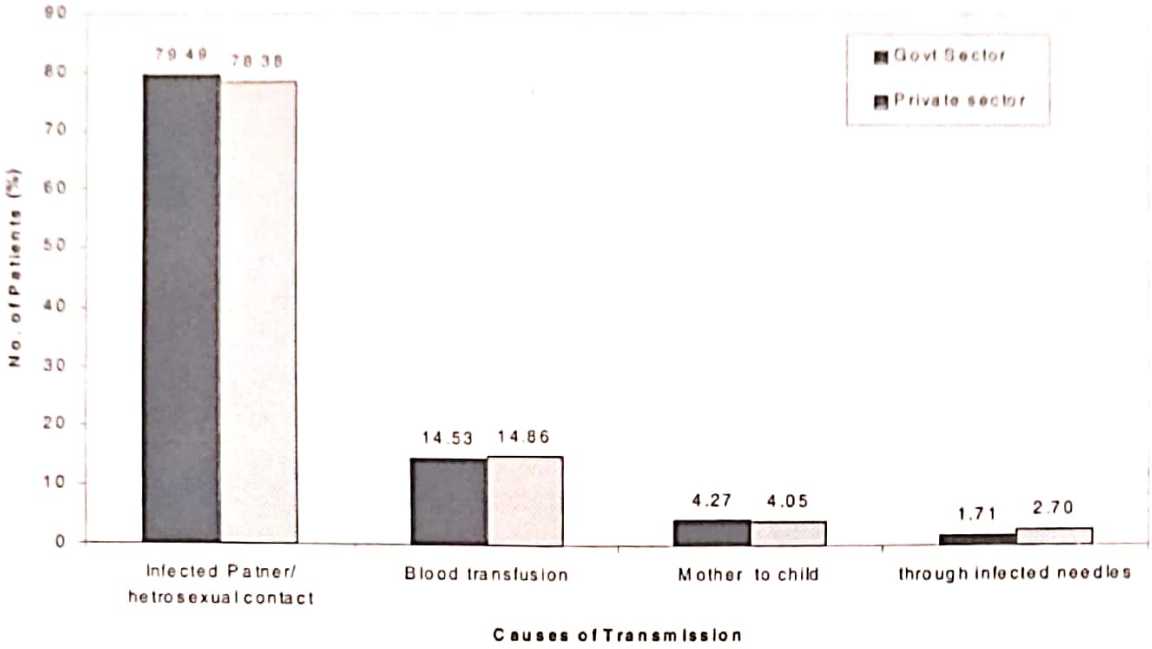

Figure 2: Mode of transmission of HIV infection in Patients of Ahmedabad

Major symptoms before infection

Majority the symptoms observed in patients with HIV infection before treatment were fever, fatigue, headache, weight loss, pharygitis, oral lesions and maculopapular rash. (Figure-3). Weight loss was most prominent among all of them. On a comparison with average healthy weight of an individual, 32.48% and 35.68% patients experienced 10-20% weight loss while 22.22% and 6.76% patents experienced 20-30% weight loss from Government and private sector respectively. (Figure-4)

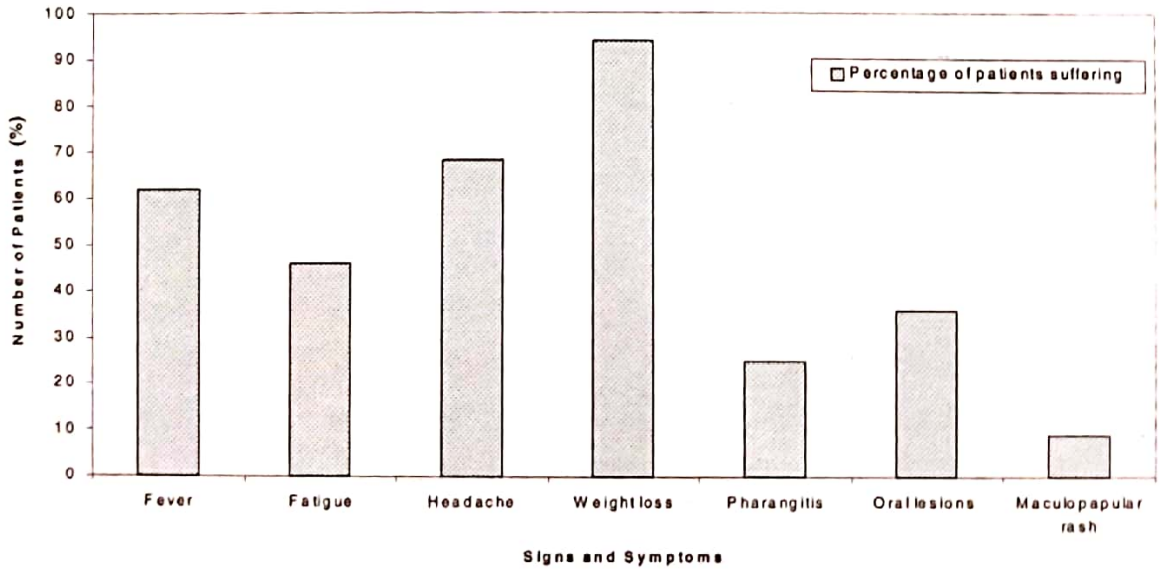

Figure 3: Major Signs and symptoms observed in HIV infected patients before treatment in ahmedabad

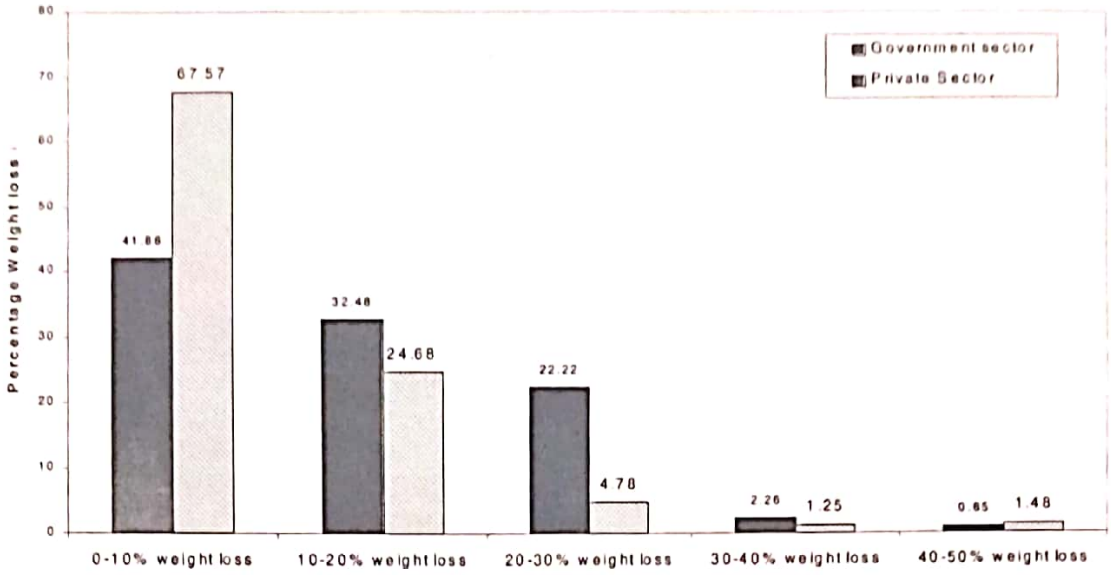

Figure 4: Percentage weight los in HIV infected patients in Ahmedabad

Drugs used and cost of treatment

In the govt. sector, majority of the patients (89.73%) were in stage I of Anti Retro Viral (ARV) Therapy while 8.54 % were in stage II. Moreover, fewer patients were in stage III; while on contrary in private sector, majority (45.95%) of the patients were in stage II and 21.62% were in stage III (Figure 5).The number of patients with decreased severity of acute illness as judged by quality of life parameters like weight gain, decrease in fever and oral lesions was higher in private sector than as seen in government sector which preferred a milder form of therapy.

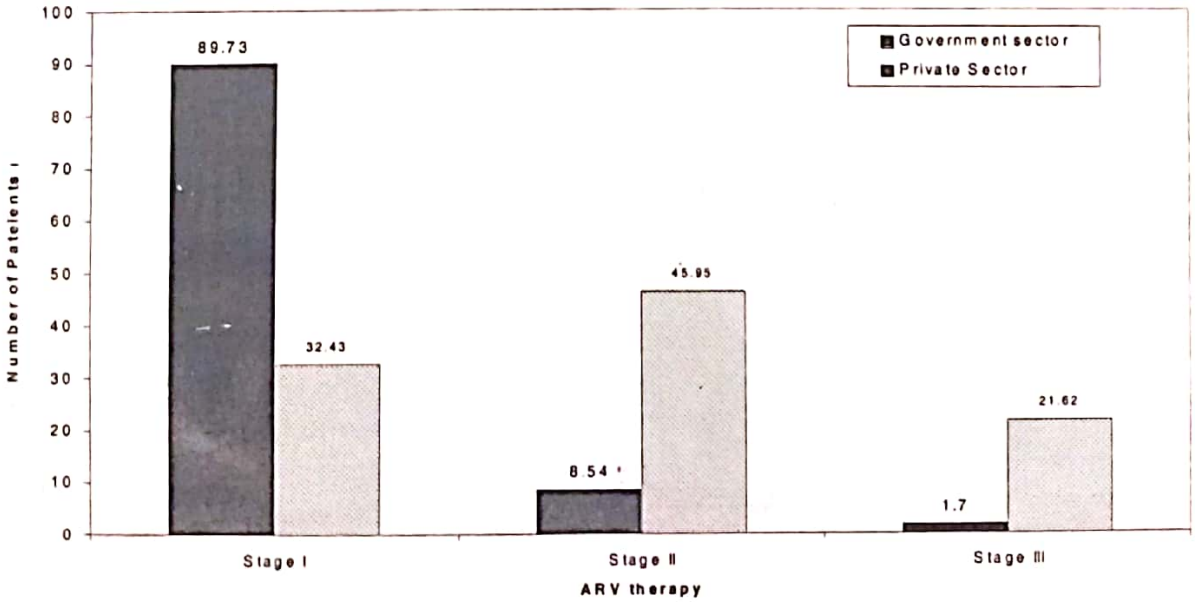

Figure 5: ARV therapy in HIV infected Pateints in Ahmedabad

In both the sector, majority of the patients (71.2 % and 56.76%), were devoid of any complaint associated with drug use. Among the various complaints reported in small no. of patients Kidney, Liver, spleen and lymph associated problem ranked highest and were observed more in patients from Private(22.97%) sector rather than Govt. sector (9.09%)

Stage I costs approximately 600-800 Rupees / per month and stage II costs 1100-1200 Rupees / per month. Stage 3 costs 5000-7000 Rupees/ month.

Existence of the opportunistic infection

Before HIV infection, 83.76 % & 81.08% patients in government and private sector respectively reported lack of any infection or chronic disease condition (Figure 6). A small number of patients (14-15 %) reported of having blood transfusion and/ or surgical procedures at some point of life before acquiring infection in both the sectors evaluated. Small populations of patient have also reported to suffer from GIT, upper respiratory tract infection before infection. But none of them reported of having suffered from major disease like tuberculosis (T.B.) or other opportunistic infections (OI) like Pneunocystis jirovecii Pneumonia (PCP), toxoplasmosis, encephalitis, cytomegalovirus retinitis etc (Figure 6).

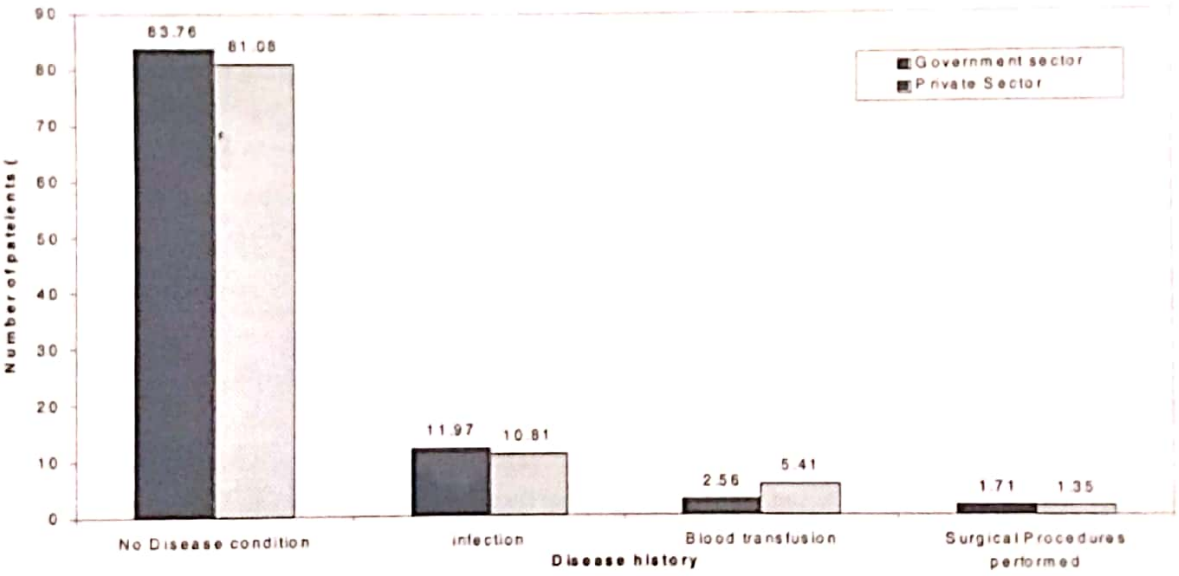

Figure 6: History of other disease in HIV infected patients before infection

Occurrence of opportunistic infection in HIV infected patients was found increased (Figure - 7). Among the various opportunistic infections acquired, occurrence of T.B. was ranked the highest in both the Govt. sector (25.24%) and private sector (24.72%) (Figure 7). Moreover it was also noted that, 30.77 % patients in the government sector and 64.85 % patient in private sector were on prophylaxis therapy for T.B (Table-1). Among the patients evaluated 8.33 % of patients suffered from T. B despite continuous prophylaxis for T.B. (Table-1).

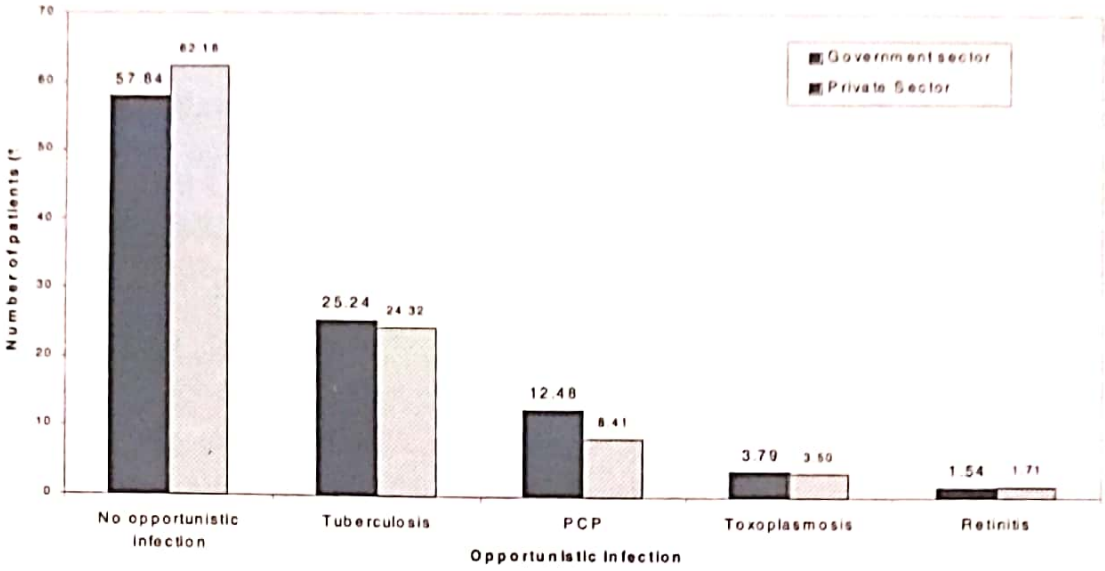

Figure 7: Occurence of Opportunistic Infection in HIV patients in Ahmedabad

DISCUSSION

According to NACO, "AIDS is affecting mainly young people in the sexually active age group". Majority of the HIV infected patients (87.7%) were in the younger age group (15-44 years)" [4]. This is particularly alarming since today's generation of young people is the largest in history. Nearly half of the world's population (almost 3 billion people) is under the age of 25. About 85 per cent of the world's youth live in developing countries. Asia alone is home to 70 per cent of the developing world's young people.

The poorest, least developed countries tend to have the largest shares of young people as a proportion of their populations [8]. It is this young generation on who lays the responsibility of bearing the next generation.

Similar results were obtained in our study which showed that 85.00% patients i.e. majorities were in adult age group (15-44) years. This data suggest that measure need to be taken to prevent the younger generation against HIV infection.

In addition our study also revealed that, 12.5% were above 44 years, which is not in accordance with NACO's estimation for India. Reasons for the increase in the number of patient in the above adult age group (above 44 years) might be attributed to longer survival period post infection with the advent of anti-retroviral therapy.

In the HIV sentinel surveillance, 2003 conducted by NACO, males account for 73.5% of AIDS cases and females 26.5%. The ratio being 3:1 for male: female. [9]. A near similar results were obtained in our study also with males: female's ratio being 2.131:1.

NACO says that the predominant mode transmission of infection in the AIDS patients is through heterosexual contact (85.7%), followed by Injecting drug use (2.2%), blood transfusion and blood product infusion (2.6%), perinatal transmission as 2.7% and others as 6.8% [8]. Though heterosexual transmission is primary mode, unsafe drug injecting is also a problem in India [9].Similar results were observed in our study with 80.00% patients affected through heterosexual mode of transfusion.

It is necessary to highlight that the majority (70.49%) females who were infected through sexual contact had acquired the infection from their life partners. This necessitates that only awareness regarding the HIV infection is not sufficient for preventing the spread of infection but efficient counseling and if required strict norms be implemented to prevent at least the

female sexual partner from acquiring the infection from their male infected partners.

The clinical presentation of an acute primary HIV infection can be confused with a typical viral illness; however, it should be suspected in persons with high risk behaviors or presence of sexually transmitted diseases. Common signs and symptoms of HIV infection are non-specific, generally occur within days-to–weeks of the initial exposure and include fever, fatigue, myalgias, athralgias, headache, lymphadenopathy, pharyngitis and oral lesions [10]. Similarly in the present study majority of the symptoms observed in patients before treatment were non specific and could be confused with viral infection. Most prominent among all the symptoms was weight loss thus requiring general population to be guided to be conscious about the unexplained weight loss as one of the alarming symptom of HIV infection.

There is a general consensus that all persons with AIDS or symptomatic HIV disease should promptly receive Highly Active Antiretroviral Therapy (HAART) [11]. The optimal combinations of Antiretroviral Therapy (ARV) are unknown; however, most guidelines recommend starting with a minimum of two Nucleoside Reverse Transcriptase Inhibitor (NRTIs) plus a "boosted" Protease inhibitor (PI) or a Non Nucleoside Reverse Transcriptase Inhibitor (NNRTI) [12]. Even in the present study it was found that combination or regimens of drugs including Zidovudine , Lamivudine, Stavudine, Indinavir, Nelfinavir, Retonavir, Abakavir and Nevirapine were preferred for treatment of HIV infected patients over single drugs given alone in both the sectors. However in the initial 15 days of treatment half dose of Nevirapine was prescribed to prevent the possibility of skin reactions.

Most experts in the field of AIDS treatment agree that early intervention with aggressive therapy appears valid. The theoretical benefits of early aggressive ARV therapy include systemic viral dissemination by suppressing the initial burst of viremia and decreasing the severity of the acute illness [13]. A similar result was observed in the present study. The number of patients with decreased severity of acute illness was higher in private sector than as seen in government sector which preferred a milder form of therapy. Government sector preferred using Stage I (Lamivudine or stavudine plus Nevirapine) and Stage II (zidovudine and Lamivudine plus separately Nevirapine.) for treatment as compared to Private sector which relied on more aggressive Stage II & III (zidovudine and Lamivudine plus separately Nevirapine and Indinavir, Nelfinavir, Retonavir, or Abakavir) of therapy. However, side effect profile after drug treatment was less with stage I & II therapy as evident from more no of patients devoid of side effects from Government sector as compared to private sector. More over Kidney lymph liver and spleen problems were highest in patients from private sector who were on aggressive stage III of ARV therapy.

Cost of treatment was not a major concern since government provided drugs free of cost to HIV infected patients, in the government sector.

The most predominant opportunistic infection among AIDS patients is tuberculosis, indicating a potential future high spread of the HIV-TB co-infection [14]. Without HIV, the lifetime risk of developing TB is 10%, compared to at least 50% in HIV-infected. Incidence of T.B. infection can be decrease by adequate prophylaxis. In addition more than 90% of surviving HIV-infected TB patients can be cured of TB, and can live longer, healthier lives using appropriate anti- TB drugs [15]. Similar pattern was observed in our study where people on prophylaxis against TB had lesser incidences of TB than HIV infected patient without TB prophylaxis. Moreover HIV is also the most powerful risk factor for progression from TB

infection to TB disease. TB in turn accelerates the progression of HIV to AIDS and shortens the survival of patients with HIV infection [14], which necessitates that the risk of T.B. Prevails and prophylaxis should be promoted vigorously.

CONCLUSION

The outcome of the study point towards the necessity of initiating a nationwide drive against HIV infection where by the general population should be guided to use preventive measures such as safe sex, use of disposable syringe, checking of HIV status of expected mothers, alarming symptoms of HIV infection, and appropriate prophylaxis to prevent the development of opportunistic infection.

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RESEARCH ARTICLE

COMPARATIVE SAFETY AND EFFICACY OF MISOPROSTOL AND DINOPROSTONE AS CERVICAL RIPENING AGENTS

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ABSTRACT

To compare the safety and efficacy accompanying two commercially available prostaglandin analogues, misoprostol and dinoprostone as cervical ripens agents. Patients with a term, vertex, singleton pregnancy and a Bishop score of 4 or less were randomly assigned to receive misoprostol pessary (n = 35, 50 μg intravaginally) or dinoprostone gel (n = 31, 0.5 mg intracervically) at 6 hourly intervals. Patients were monitored throughout the period. If there is no progress in cervical dilatation or effective uterine contraction even after maximum dose of dinoprostone or misoprostol, patients were taken to cesarean section operations. Patients who achieve Bishop's score more than 7 but the delivery was not progressing, were augmented with oxytocin drip. The measures of safety noted included the presence of contraction abnormalities, fetal heart rate abnormality, meconium passage, 1 and 5 minutes Apgar score, admission to neonatal intensive care unit and maternal side effects. No uterine hyperstimulation was observed in both groups. However, abnormal fetal heart rate was observed in 3(8.6%) cases in misoprostol group and 2(6.5%) in dinoprostone group. There was no statistically significant difference in meconium passage in two groups. Apgar score less than 7 at 1 minute was seen in 6(19.4%) and 11(31.4%) neonates in dinoprostone and misoprostol group respectively. However Apgar score less than 7 at 5 minutes was found in only one neonate of dinoprostone treated patient. Both drugs were found to be equally effective in improving Bishops score. No significant difference was seen in the mean induction to delivery time in dinoprostone and misoprostol group. Cesarean section operations occurred in dinoprostone and misoprostol groups were 32.3% and 28.6% respectively. There was significant reduction in the need for oxytocin augmentation in misoprostol (37.1%) group than in dinoprostone (67.7%) group. Vaginal misoprostol is an effective, safer and cheaper alternative to dinoprostone as a cervical ripening agent especially in underdeveloped countries with poor socioeconomic condition.

Key words: Dinoprostone, Misoprostol, cervical ripening, induction, Bishops Score, Apgar score.

INTRODUCTION

Induction of labor refers to the process whereby uterine contractions are initiated by medical or surgical means before the onset of spontaneous labor. Induction of labor is common in obstetric practice [1, 2]. Labor induction in the presence of an unfavorable cervix may be prolonged, tedious and eventuate in a cesarean delivery. Induction of cervical ripening is critical to successful induction of labor in a pregnant patient whose cervix has not gone through the ripening process. Cervical ripening before induction with prostaglandin agents has been demonstrated to decrease induction time and need for oxytocin. Assessment of cervical ripening is accomplished by calculating a Bishop score (BS). When the BS is less than 6, it is recommended that a cervical ripening agent be used before labor induction [2, 3, 4].

When compared with placebo, use of vaginal prostaglandins increased the likelihood that a vaginal delivery would occur within 24 hours. The only drawback appears to be an increased rate of uterine hyperstimulation and accompanying FHR changes [5, 6].

Dinoprostone has been the agent of choice for preinduction and cervical ripening for several decades and currently is the only pharmacological agent approved by the US

Food and Drug Administration for this purpose. Several trial have found another synthetic prostaglandin (PG) E_1 analog, misoprostol administered by either vaginal or oral route more effective than placebo and dinoprostone in cervical ripening and shortening the insertion to delivery interval [7,8,9]. It is inexpensive and is stable at room temperature than dinoprostone. However, the apparent increase in uterine hyperstimulation with or without fetal heart rate (FHR) changes and the rare but serious complication like rupture uterus are of concern [10-14]. Studies to establish safety, addressing the risks of uterine hyperstimulation, uterine rupture and serious neonatal and maternal morbidity are needed.

The aim of this study was to compare safety and effectiveness of intravaginal misoprostol with our traditional protocol for cervical ripening and labor induction with repeated intracervical dinoprostone in women with unfavorable cervices and intact membranes.

MATERIAL AND METHODS

The study was conducted at labor ward of Dhulikhel Hospital Kathmandu University Teaching Hospital, Dhulikhel, Nepal from March 2006 to July 2006. The study comprises 66 patients. Among these women, 31 received Dinoprostone 0.5 mg intracervically at 6-hourly interval and 35 received Misoprostol 50mcg vaginally at 6 hourly interval.

Approval was obtained from ethical and research committee of the hospital to conduct the study. Exclusion criteria were previous cesarean delivery, grand multiparity (>5), breech, contraindications to induction, BS of = 4, contractions more than 3 per 10 minutes before drug administration and premature rupture of membranes (PROM). Inclusion criteria were = 37 wks of gestation, indication for labor induction, BS = 4, intact membrane and cephalic presentation.

Subjects gave informed consent and were randomly assigned to receive either misoprostol pessary 50 mcg per vagina or our hospital's standard induction protocol 0.5 mg of dinoprostone intracervically in an unblinded fashion. BS was assessed just before insertion of the drug. FHR and uterine contractility was taken prior to drug administration. All patients underwent continuous FHR and uterine contraction monitoring every 15 minutes for first two hours then every 4 hours of each dosing.

Tachysystole was defined as a contraction frequency of more than five within 10 minutes for two consecutive 10 minutes period. Uterine hyperstimulation was defined as exaggerated uterine response with late FHR decelerations or fetal tachycardia greater than 160 beats per minutes or other worrisome FHR changes. An abnormal FHR pattern was defined as the presence of either fetal tachycardia, bradycardia, late decelerations, or a moderate to severe deceleration of FHR. Labor was defined as regular painful uterine contractions with cervical change or spontaneous rupture of membranes. Failed induction occurred when painful, regular contractions with cervical change were not achieved and the patient was delivered by cesarean with failed induction as sole indication. Active phase was defined as complete cervical effacement and dilatation of at least 3 cm. [15,16].

Misoprostol pessary was administered every 6 hourly by the attending doctor in the posterior for nix with maximum dose of up to six. BS was reviewed continuously. In another group, dinoprostone gel was administered twice intracervically, 6=hrs apart. A vaginal examination was performed before the administration of the second dose. If there were more than 3 contractions for more than 30 seconds in 10 minutes or labor had started or cervical score was 6 or more, the second dose of cervical ripening agent was not given.

Once in labor, women were cared for according

to current obstetric practice. If there was no progress in cervical dilatation, effacement or effective contractions even after maximum dose of cervical ripening agents, patients were taken for cesarean section operation. Patients who achieved BS more than 7 but the delivery was not progressing for longer than 1 hour were augmented with oxytocin drip for maximum of 12 hours. After that, if women did not reach active phase, cesarean for failed induction was done.

The prespecified outcomes were interval from start of induction to vaginal delivery, vaginal delivery achieved within 24 hrs after randomization, change in BS, abnormalities of uterine contractility with and without FHR changes, mode of delivery, need of oxytocin augmentation, maternal morbidity and side effects (e.g., fever, chills, gastrointestinal symptoms) and short-term neonatal outcome (e.g. Apgar score, meconium passage, neonatal intensive care unit admission etc.).

Statistical analysis was done using Statistical Package for Social Sciences (SPSS) program version 11.5 using ÷2 square test and Z test. For variables distributed normally, the results were presented as mean and standard deviation (SD). Quantitative variables are expressed as number and percentage.

RESULTS

A total of 66 women were randomized. Baseline characters were similar between two groups in terms of patient's age, gestational time, parity and the preinduction BS.

31 patients received dinoprostone gel 0.5mg intracervically up to 2 doses and remaining 35 patients received misoprostol pessary 50 mcg, intravaginally with maximum dose up to six, every six hourly.

The number of doses of dinoprostone required for preinduction was 1.65±0.48 (mean±S.D), and that of misoprostol was 2.14±1.2.

Although there was increase in the BS after treatment in both groups, there was statistically insignificant difference between two groups in terms of either the change in BS after drug administration or the BS measured pre treatment (Table 1).

There were no significant differences in the mode of delivery (P = 0.618). 10(32.3%) patients out of 31 from dinoprostone group and 10(28.6%) patients out of 35 from misoprostol group had cesarean delivery (Table 2).

Indications for cesarean section were similar: in misoprostol group, 4(40%) cesarean sections were performed for failed induction and 5(50%) were due to fetal distress. Remaining one was due to oligohydramnios. In dinoprostone group, 5(50%) cesarean was due to failed induction and another 5(50%) was due to fetal distress.

The difference in mean induction to delivery time was not statistically significant in two groups (17.19 hrs in dinoprostone versus 17.99 hrs in misoprostol group, P = 0.83).

Even though 19 (90.5%) out of 21 patients from dinoprostone group and 18 (72.0%) out of 25 patients from misoprostol group delivered within 24 hrs of initiation of induction, this difference was not found to be statistically significant (P = 0.42).

Augmentation of oxytocin was required in significantly greater number of patients in dinoprostone group than in misoprostol group (21[67.7%] versus 13[37.1%], P = 0.013). Women in the misoprostol group were much less likely to require oxytocin compared with dinoprostone group.

No cases of uterine hyperstimulation were observed in both groups. However abnormal FHR was observed in 2(6.5%) cases in dinoprostone group and 3(8.6%) cases in misoprostone group. Again there was no statistically significant difference between the two groups with regards to meconium passage (7[22.6%] in dinoprostone group versus

8[22.9%] in misoprostol group, P = 0.97). Our study indicates misoprostol 50 mcg 6 hourly to be an effective preinducing agent with no major maternal side effects, such as uterine hyperstimulation or uterine rupture (table 3).

Minor maternal side effects reported were nausea, vomiting and diarrhea. 2(6.5%) patient from dinoprostone group and 3(8.6%) from misoprostol group experienced vomiting, whereas 3(8.6%) patients from misoprostol group and another 1(2.9%) patient from the same group experienced nausea and diarrhea respectively.

Birth weights of neonates were similar between groups. There was no statistically significant difference in Apgar score at 1 minute and 5 minute between two groups. One-minute Apgar score less than 7(6[19.4%] and 11[31.4%] in dinoprostone and misoprostol group respectively) and Apgar score at 5 minutes less than 7 (1[3.2%] in dinoprostone group) were not significantly different between misoprostol and dinoprostone groups. Supplemental oxygen requirement was 10(32.3%) in dinoprostone group and 11(32.4%) in misoprostol group. None of the newborns required intubations, or admission to neonatal intensive care unit (Table 4).

DISCUSSION

Labor induction is one of the most commonly performed obstetric procedures, with upto 40% of all patients undergoing inpatients cervical ripening [17]. Prostaglandins are highly efficacious cervical ripening agents used to shorten induction to delivery intervals, improve induction success, and reduce morbidities associated with prolonged labor induction. The use of these agents, however, is associated with the potential for uterine hyperstimulation with FHR changes [12-16]. Many previous studies have proven effectiveness of misoprostol and dinoprostol for preinduction. Our study was designed to assess the safety and effectiveness of vaginal misoprostol and intracervical dinoprostone when used as cervical ripening agent.

The major finding in this study was that misoprostol is as effective as dinoprostol in cervical ripening. Improvements in BS by both of these agents were comparable. One comparative study done in India showed that there was significant improvement in the BS of both group but no significant difference between two groups in mean change in BS [18].

Our study finding shows that there is no difference in the efficacy of the two drugs in terms of preinduction to delivery time. Number of deliveries within 12 hours of treatment initiation was also not significantly different between dinoprostol (29%) and misoprostol (28.6%) groups. More number of patients from dinoprostone (61.3%) group delivered within 24 hours of treatment initiation than misoprostol (51.4%) although this difference was found to be statistically insignificant. The preinduction to delivery time was found to be significantly shorter in misoprostol (11 vs. 18 hours) treated group in a study carried by Ramsey et al [21]. However his study showed no significant difference in delivery within 24 hours between the two groups. Various studies have shown considerable variation as far as induction to delivery time is concerned ranging from 9 hours to 17.9 hours [19, 20]. Meta-analysis of misoprostol for cervical ripening and labor induction in 8 trials including nearly 1000 women revealed that misoprostol-treated subjects had a higher incidence of vaginal delivery within 24 hours of initially receiving misoprostol and a shorter time interval from start of medication to delivery when compared with control subjects by approximately 4.5 hour [22].

The present study indicates that misoprostol was associated with less need of oxytocin augmentation. Cesarean section occurred in both

groups were found to be comparable. Study done by (Jose et al.) found better result with oral misoprostol with less need for oxytocin augmentation and lesser cesarean section operations for failed induction [23].

We didn't find any cases of hyperstimulation, uterine rupture or PROM. A Meta analysis conducted by Sanchez-Ramos et al. confirms the safety of intravaginal misoprostol with similar incidences of uterine hyperstimulation in misoprostol and control group [22].

The Cochrane Pregnancy and Childbirth Group reviewed trials comparing misoprostol with placebo, oxytocin, or prostaglandin E_2 for cervical ripening [24]. The study showed that vaginal misoprostol (25 to 100 mcg) was more effective than dinoprostone for inducing vaginal delivery within 24 hours. However, uterine hyperstimulation with associated changes in the FHR was more common in women who received misoprostol than in women who received dinoprostone. No difference in the rates of cesarean delivery, serious neonatal or maternal morbidity or mortality was seen between women who received misoprostol and those who received dinoprostone.

Several studies have reported hyperstimulation and tachysystol with misoprostol. But we do not found any such cases. It may be due to the reason that others have used higher doses of misoprostol like 100 mcg and 200 mcg whereas we have used a lower dose of 50 mcg, which might explain absence of excessive uterine activity. There is less risk of hyperstimulation with lower dose of misoprostol but also decreases the effectiveness for labor induction [25, 26]. It may be seen from several studies done in the past that also the route of administration has some effect on incidence of hyperstimulation [27]. In a randomized, double masked trial of 178 women found similar efficacy between 200 mcg oral and 50 mcg vaginal administration, but the oral route was associated with more frequent uterine contractility, including an unexpected high rate of hyperstimulation syndrome (44.1%). To decrease that high rate, lower oral doses of misoprostol was used in several other studies, but the effectiveness was also lowered [27].

Regarding neonatal outcomes, perinatal results evaluated by means of Apgar score, birth weight, meconium stain and admission to intensive care unit were comparable between two groups. Similar perinatal outcome in the two groups has also been found by other workers [22, 28].

Although intravaginal dinoprostone is currently the drug of choice for labor induction, it is quite expensive and must be refrigerated to maintain its potency. When we did the comparison of cost we found that there is a significant price difference between misoprostol and dinoprostone for induction of labor. In our hospital dinoprostone is 7 times more expensive than misoprostol. The cost will be increased further if oxytocin augmentation is needed has also advocated the use of misoprostol being cost effective [21].

Findings of this study suggests that the less expensive drug misoprostol is safer for mother and fetus with comparable BS and interval to vaginal delivery as dinoprostone Although this study has not found an increase in serious morbidity or mortality with vaginal misoprostol use, the sample size was not sufficiently large enough to exclude the possibility of uncommon serious adverse effects. Potential areas of interest for misoprostol use for labor induction include oral administration and a crushed or gel form, in addition to lowering the dose and increasing the interval between administrations. Researchers can design further trials to develop the safest dose, form and route of misoprostol administration.

CONCLUSIONS

Misoprostol appears to be safe and beneficial for inducing labor in a woman with an

unfavorable cervix. It is equally efficacious for cervical ripening and labor induction as dinoprostone in terms of improvement in BS.

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Table 1: COMPARISON OF CHANGE IN BISHOP SCORE

Bishop score	Dinoprostone (n = 31)	Misoprostol (n = 35)	P value
Initial bishop score	3.35 ± 0.91	3.00 ± 0.90	.11
After 6 hours	5.48 ± 2.0	4.90 ±1.5	.22
After 12 hours	6.23 ± 2.2	6.38 ±1.9	.81
Change in 6 hours	2.17 ± 2.0	2.00±1.6	.72
Change in 12 hours	2.90 ± 2.1	.65±1.9	.23

(Mean ± S.D)

Table 2: COMPARISON OF MODE OF DELIVERY

Mode of delivery	Dinoprostone (n =31)	Misoprostol (n=35)
Vaginal	21(67.7%)	25(71.5%)
Spontaneous Vaginal delivery	21(67.7%)	24 (68.6%)
Assisted vaginal delivery	0(0%)	1(2.9%)
Cesarean section	10(32.3%)	10(28.6%)

Table 3: ADVERSE EFFECTS

Adverse effects	Dinoprostone (n=31)	Misoprostol (n=35)	P value
Hyperstimulation		0(0%)	0(0%)
Abnormal fetal heart rate	2(6.5%)	3(8.6%)	.74
Meconium passage	7(22.6%)	8(22.9%)	.97

Table 4: COMPARISON OF NEONATAL OUTCOMES

Outcome	Dinoprostone (n=31)	Misoprostol (n=35)	P value
Birth weight (kg)	2.76± 0.41	2.90± 0.47	.23
Apgar Score <7 at 1 min	6(19.4%)	11(31.4%)	.26
Apgar Score <7 at 5 min	1(3.2%)	0(0%)	.28
Supplemental oxygen	10(32.3%)	11(32.4%)	.99
Neonatal Intensive Care Unit		0(0%)	0(0%)
Neonatal mortality		0(0%)	0(0%)

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RESEARCH ARTICLE

ADVERSE DRUG REACTION MONITORING AND EVALUATION AT A PRIVATE CORPORATE HOSPITAL

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ABSTRACT

Adverse Drug Reactions represent an important public health problem. The occurrence of adverse drug events in hospitalized patients can lead to an increase in the length of hospital stay and to excess cost. In order to prevent the adverse outcome of drug therapy insight into the occurrence of adverse drug events during hospitalizations is important. The aim of the study was to detect, document, assess and report the suspected adverse drug reactions and to issue the alert card and guideline preparation to minimize the incidence of ADRs. A prospective study was made on the patients admitted in the department of general medicine of the study hospital, over a period of 6 months. An ADR reporting form was designed and was taken for regular ward rounds in the department of general medicine along with the physicians for detecting and reporting ADRs. Causality assessment was done by using the Naranjo algorithm and WHO scale. Of the 21 adverse drug reactions reported, 8(38%) were hospitalized due to an adverse reaction compared to13 (62%) who were affected by adverse reaction after hospital admission. System most commonly affected by adverse reaction was the skin in 8(38%) and gastro intestinal system in 6(29%) patients. The drug class mostly associated with adverse reaction was NSAIDs in 10(48%) patients followed by Antibiotics in 3 (14%). Causality assessment was done using the Naranjo and WHO scales. The results interpreted using Naranjo's revealed that in 1(5%) patient the reactions was definite, probable in 18(85%), possible in 2(10%) while that using WHO scale were 1(5%) certain , 16(76%) probable, and 4(19%) possible. Results of reporter status by various health professionals revealed that 13(62%) were physicians, pharmacists 7(34%) and nurses 1(5%). As part of the management in 19 (90%) of the cases the drug was withdrawn, dose altered in 1(5%) of the case and no change was made in 1(5%).Adverse reactions encountered were treated and the final outcome was measured. About 16(76%) of the patients recovered, while in 5(24%) of the cases the adverse reactions decreased. No fatal cases were reported. Active reporting of ADRs from individual hospital settings by the clinical pharmacist should be made mandatory to ensure rational drug therapy and complete patient care. In near future the Clinical Pharmacists will play a vital role in assimilating the data regarding adverse reactions to drugs. This can be successfully achieved if a continuous monitoring of adverse events is practiced.

Key words: *Adverse drug reaction, Causality scale.*

INTRODUCTION

Adverse drug reactions are persistent and important problem of India in terms of morbidity, and cost. ADR s may lead to hospitalization, or occur during hospitalization, prolonging the length of a hospital stay. The Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) defines an adverse drug reaction (ADR) as an undesired effect of a medication that either increases toxicity, decreases desired therapeutic effect, or both. This term covers drug reactions of all degrees of severity and is used with a fair degree of uniformity throughout the world. However, for convenience, other commonly used terms are also described. In European countries, adverse drug reaction monitoring is commonly referred to as pharmacovigilance. The Americans use this term in a broader sense and call it, pharmaco-epidemiology [1]. Following the thalidomide disaster of 1961, when Dr. McBride of Australia

reported increased frequency of birth defects (seal limbs) that left 10,000 babies disabled for life, monitoring centers were started the world over. According to WHO adverse drug reaction is defined as "Any response to a drug which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease or for modification of physiological function" [2].

Consistent with this definition, an allergic reaction and an idiosyncratic reaction are also considered ADRs. Symptoms of drug withdrawal, drug abuse syndromes, and accidental poisoning and drug over-dosage complications are not considered as adverse effects (AJHP Technical Assistance Bulletin 1980). It is important to distinguish an adverse drug reaction (ADR) from an adverse drug event (ADE). While the two terms have been used interchangeably, the differences are important. An adverse drug reaction is the result of the intrinsic properties of the drug and cannot be prevented. An adverse drug event is a injury resulting from medical intervention related to a drug and includes ADRs, but also includes preventable reactions, including those caused by human error [3]. The WHO definition of an ADR does not necessarily include drugs administered or taken in error or given by an erroneous method. As progress is made toward better assessment and management of drug risk, the line between adverse drug reaction and adverse drug events blurs. While much of the research in recent years has been on identifying risk factors for adverse drug events and ADE prevention, much of what is learned can apply to ADRs as well. Indeed, comprehensive management of drug risk requires that adverse drug reactions and adverse drug events be considered equally. Objectives of the study was

1. Detection and documentation of suspected Adverse Drug Reactions.
2. Assessment of Severity, Predictability, Preventability and Causality of the suspected Adverse Drug Reactions.
3. Active reporting of Suspected Adverse Drug Reactions to the study department and to the regional pharmacovigilance centre.
4. Issue of alert card and guideline preparation to minimize the incidence of ADRs [4].

METHOD

The study was conducted at a private corporate hospital in Coimbatore. It is a 450-bedded multi-specialty medical institution and one of the largest hospitals in Coimbatore. The hospital is unique and well known for its service to the people who come from various parts of the country. The department selected for the study was the general ward of General Medicine Department. The reason for selection of the Department of General Medicine since many studies from literature showed that a great number of Adverse Drug Reactions were seen in this department. In the department of General medicine one could observe combination of various disorders which compels the physician to prescribe more category of drugs as a result of which greater chances of observing ADRs and drug interactions were possible.

All cases of adverse drug reaction observed in the department of general medicine with inpatient population were included in the study. The out patient cases, ADR related to poisoning, fresh blood or blood products, vaccines and over dosage, were excluded from the study. The protocol of the study that includes the objectives, methodology etc. was submitted to the Dean of the study Hospital. The authorization from the Dean was procured. All the health care professionals of the hospital were informed about the study program through Dean's official circular.

A specially designed Data entry format was used to enter all patient's details, which include

patient information, reason for admission, past medical and medication history, laboratory investigations, medications prescribed, suspected adverse drug reactions, system affected, description of the reaction, management of ADR, dechallenging and rechallenging information, causality assessment scales, severity of the reactions, predisposing factors, suspected drug interactions. An ADR reporting form was designed to aid reporting and collection of ADR and was taken for regular ward rounds in General, Special and Deluxe wards of the department of general medicine by the author. The study was carried out for a period of six months from March 2006 to August 2006.A pilot study was carried out for a period of 10 days in the Department of General Medicine to find the scope of the study in that department. All the prescriptions were monitored for the adverse drug reactions. Literatures, which support the study, were collected and they were properly reviewed, for study on adverse drug reactions and drug Interactions. A data entry format for collecting patient details was prepared and, during the ward rounds the entire patient's data were recorded in the format. Alert cards were prepared and given to patients of high risk. It was made mandatory to take photographs of the suspected serious Adverse Drug Reactions whenever possible with the consent of the patient. A patient consent form was filled before noting down the case.

Assessment of adverse drug reactions: Each patient's demographic data, date of admission, date of discharge, causative medication, past medication details, reactions, intervention made, severity, and outcome were documented. The causality relationship between the ADR and the suspected drug therapy was assessed using the Naranjo algorithm and WHO scale. The assessment of outcome of each ADR was done by monitoring the length of stay and by categorizing them as continuing, recovered, and fatal. Severity, Preventability, and Predictability were also assessed using standardized scales. The suspected adverse drug reactions are reported to the pharmacovigilance center (Regional pharmacovigilance center -south).

RESULTS

A total of the 21 admission adverse drug reactions a out of them 8 (38%) were hospitalized due to an adverse drug reaction compared to13 (62%) who were affected by Adverse Drug Reaction after hospital admission. Systems most commonly affected by Adverse Drug Reaction was the skin in 8(38%) and gastro intestinal system in 6(29%) patientsThe drug class mostly associated with adverse reaction was NSAIDs in 10(48%) patients followed by Antibiotics in 3 (14%). Other drugs constituted 38%.The results interpreted using Naranjo's revealed that in 1(5%) patient the reactions was definite, probable in 18(85%), possible in 2(10%).The results interpreted using WHO scale revealed that in 1(5%) patient the reaction was certain, 16 (76%) probable, and 4 (19%) possible.Results of reporter status by various health professionals revealed that 13(62%) were physicians, pharmacists 7(34%) and nurses 1(5%).As part of the management in 19 (90%) of the cases the drug was withdrawn, dose altered in 1(5%) of the case and no change was made in 1(5%). Adverse reactions encountered were treated and the final outcome was measured. About 16 (76%) of the patients recovered, while in 5(24%) of the cases the adverse reactions decreased. No fatal cases were reported.

DISCUSSION

Pharmacist participation with the medical rounding team on a general medicine unit contributes to a significant finding of preventable adverse reactions. The increase in the number of ADRs will continue unless health care professionals as well as the general public, report ADRs in a timely manner. The

introduction of many powerful drugs in the last decade also makes it important to balance the anticipated benefits and potential risks. Adverse drug reaction monitoring in India still have to take off even though national Pharmacovigilance centre has made two Zonal centers, one for North and East regions at All India Institute of Medical Sciences, New Delhi and second zonal centre for west and south regions at KEM Medical college, Mumbai and Madras Medical College, Chennai.

Active reporting of ADRs from individual hospital settings by the clinical pharmacist should be made mandatory to ensure rational drug therapy and complete patient care. In near future the Clinical Pharmacists will play a vital role in assimilating the data regarding adverse reactions to drugs. This can be successfully achieved if a continuous monitoring of adverse events is practiced.

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RESEARCH ARTICLE

A CLINICAL STUDY ON FOLLOW UP OF HEPATITTS B PATEINTS FOR THEIR CARRIER STATE

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ABSTRACT

The present study was undertaken to evaluate the incidence of chronic active hepatitis or chronic carriers from patients of acute hepatitis treated with the combination of antiviral drugs.

In our study we follow up the medication records of old patients who suffered from viral hepatitis, 2 to 12 years back. Out of 2040 patients, 415 patients had taken treatment for hepatitis B positive. They were contacted and their blood samples were collected for laboratory investigations like HBsAg (Hepatitis B surface antigen], Anti- HBs [Antibodies of HBsAg], Anti- HCV [Antibodies of hepatitis C virus], total serum protein, albumin and globulin. Blood samples of the Patients who were positive for HBsAg were analyzed for HIV by DNA polymerase chain reaction (PCR).

From our study it was observed that 2 patients showed surface antigen positive in their sera and found to be negative in HBV DNA by PCR assay. It was concluded that these patients may be called as FALSE CARRIERS and they will not transmit the disease to their family members and others as well. Unnecessary treatment may be avoided in these patients.

INTRODUCTION

Of all the hepatic disorders none is more universal in nature than chronic hepatitis B, Infact 2 billion population is at risk of chronic hepatitis B. An estimated 350-400 million subjects worldwide are inflicted with chronic hepatitis B (1). The state has incidence of 0.1 to 20% in different parts of the world. Thus WHO declared that chronic hepatitis B is the 9th leading cause of death in this world.

Hepatitis B virus (HBV) is a small, enveloped virus classified as a member of the hepadnavirus family (1, 2). The marked differences observed in the global prevalence of HBV infection are associated with variations in the predominant routes of HBV transmission. In endemic regions such as Asia and Africa, HBV infection is often acquired early life, either vertically from perinatal transmission (or) horizontally from contact with other infected individuals. In areas of intermediate prevalence (eg. Eastern Europe, the Middle East), transmission of HBV occurs primarily through horizontal transmission with in the family (eg. Child to child), through sexual transmission, contact with contaminated blood products, (or) through acupuncture (or) ritual practices involving skin incision (1,3). In India, traditions of tattooing, ear/nose piercing has been known to be associated with HBV transmission.

A hepatitis B carrier is someone who has hepatitis B virus in the blood for more than six months (chronic infection) but usually has no signs (or) symptoms of hepatitis B. The carrier usually feels well, has normal liver enzymes and need not have HBeAg (A marker of the core of the virus, usually means that there is a great deal of viral replication allowing the core to be present in blood) present in the blood, but remains infected with virus and is capable of passing the disease on to others. Although most carriers of hepatitis B lead normal healthy lives, in some carriers the hepatitis becomes active again, placing them at significantly higher risk than the general population for liver cirrhosis and then liver failure and liver cancer(4).

The present study is highly essential, because from the opinion of physicians specialized in hepatitis, it was observed that some of the old patients who were treated for hepatitis few years before have become now hepatitis B (or) C positive and they may be in a state of chronic hepatitis. So this study is aimed at following old reference of medication case sheets for their carrier state of hepatitis B (or) chronic hepatitis B (or) C and to find out whether they are suffering from cirrhosis liver.

MATERIAL AND METHODS:

COLLECTION OF PATIENTS MEDICATION CASE SHEETS

The patients were selected on the basis of hepatitis B positive patients who had suffered two to twelve year back (5). The patients medication case sheets were collected and screened out for the inclusion of our study from BHARAT RATNA KAMARAJ JAUNDICE AND LIVER HOSPITAL AND RESEARCH CENTRE, MADURAI 625001.

SELECTION OF PATIENTS

Case sheets of old patients who suffered from viral hepatitis, two to twelve years back had been perused and out of these 2040 patients, 415 patients had taken treatment for hepatitis B positive. All 415 patients were communicated through letter and personal visit to their home and offices, asking them to come to the hospital for clinical evaluation.

CLINICAL LABORATORY INVESTIGATIONS

The patients who were all came for follow-up study on the basis of our correspondence, their blood samples was collected from antecubital vein and serum was separated by centrifugation and subjected to the following laboratory investigations such as HBsAg, Anti- HBs, Anti-HCV, total serum protein, albumin and globulin(6).

HBV DNA (HEPATITIS B VIRAL DNA) TEST

Patients who got normal report are asked to take regular checkup for every one year and patients whose were positive for HBsAg are asked to undergo the sophisticated test named HBV DNA by polymerase chain reaction (PCR). The HBV DNA test by PCR used to determine the presence of HBV DNA circulating in the blood, which is measure of virus replication in the liver, Primary use is in monitoring treatment and clarifying some complex situations.

If HBV DNA showed positive, patients must undergo Anti-viral drug treatment, if negative, patients advised for regular check up on every one year to assess how long they are going to harbour the HBsAg (7, 8).

SIGNIFICANCE OF ANTI-HBs TITER (ANTIBODIES OF HBsAG)

This is the only test, which can be used to assess presence of protective immunity after immunization with hepatitis B vaccine. If the anti- HBs titer is less than 10 IU/L [Normal value = 10 IU/L], then the patients were advised to take hepatitis B vaccine 3 doses and boost their immunity against repeat infection with viral hepatitis B.

Moreover we studied the difference in total serum bilirubin levels [Normal value = 0.2 -1 mg/dl] and total serum protein [Normal range = 6-8 gm/dl] levels of Hepatitis B positive and Hepatitis B negative patients at the on set of the disease.

DRUG TREATMENT

Treatment for hepatitis B patients includes combination of Antiviral drugs such as chloroquine [150 mg tid], Ribavarin [100mg tid], Lamivudine [100 mg od], Methylene blue [10ml injection od], Alkasim i.e.disodium hydrogen citrate [6 teaspoonful tid]. All these drugs are to be taken for a period of 4-6 weeks (10).

BIOSTATISTICAL ANALYSIS

Statistical analyses were carried out between hepatitis B positive and hepatitis B negative patients based on total serum bilirubin level and total serum protein level by using student's 't' test(12,13). Values of significance were set at $P<0.001$ for both tests.

RESULTS & DISCUSSION

From our follow up study, it was observed that out of 415 patients were communicated, a total number of 61 (14.09%) patients reported to the hospital. All the 61 patients who had come for follow-up study were subjected to done following laboratory investigations such as HBsAg , Anti-HBs , Anti-HCV, total serum protein, albumin and globulin. Out of these 61 patients, 2 patients (3.28%) were found to be HBsAg positive, indicating the probability of being carrier of the virus and remnant all of them were found to be HBsAg negative. Hepatitis B surface antigen test result indicates that two patients having positive result (6, 14, 15). HBsAg positive means patients carry outer surface of the virus, which showing the presence of surface antigen. Only the patients have core antigen with nucleus of the virus they will be named as carriers, otherwise they are called FALSE CARRIERS (16). In order to know the actual status of the two HBsAg positive patients, they were advised to go for HBV DNA test. For both of them result indicates, the absence of core antigen HBV DNA (8, 9, 17). So now it is confirmed that these patients are only FALSE CARRIERS.

Antibody test for Hepatitis B virus indicate that Patients carry antibodies more than a minimum level of 10 IU/L. Even false carriers also had higher level of antibodies (11, 20). No patients were found Anti-HCV positive. So, it can be said that Patients are quite resistant to further hepatitis B infection.

Total serum protein analysis indicates that all the patients had normal total serum protein contents [Normal value = 6-8 gm/dl] and individual proteins such as albumin [Normal value = 3.7 -5.3 gm/dl] and globulin [Normal value =2.3 -3.6 gm/dl] levels are also normal.

TOTAL SERUM PROTEIN AND BILIRUBIN ANALYSIS

More over we studied the difference in Total serum protein and bilirubin levels of both Hepatitis B positive and negative patients at the on set of the disease. The data were collected from previous patients mediation case reports and interpreted for statistical analysis such as student's't' test.

Table 1: TOTAL SERUM PROTEIN LEVELS (GM/DL) AND NO. OF PATIENTS ALONG WITH ITS PERCENTAGE FOR HEPATITIS B POSITIVE AND NEGATIVE PATIENTS

Total serum protein level (gm/dl	No. of patients & percentage	
	Hepatitis B +ve	Hepatitis B -ve
4.1 – 4.5	4 (3.7%)	16 (13.3%)
4.6 – 5.0	8 (7.3%)	18 (15%)
5.1 – 5.5	10(9.2%)	13 (10.8%)
5.6 – 6.0	6 (5.5%)	17 (14.2%)
6.1 – 6.5	23(21.1%)	16 (13.3%)
6.6 – 7.0	21(19.2%)	17 (14.2%)
7.1 – 7.5	27(24.2%)	14 (11.7%)
7.6 – 8.0	10(9.1%)	9 (7.5%)

Test for serum protein level had been carried out for 109 Hepatitis B positive and for 120 Hepatitis B negative patients. Out of them, 28 (26.4%) of hepatitis B +ve patients showed reduction in serum protein level and remaining 81 (73.6%) patients had normal protein levels, whereas only 56 (46.7%) of hepatitis B negative patients had normal protein levels. Results also indicate that viral infections apart from hepatitis B virus (or) other viral replication bring about a reduction in protein synthesis is almost 64 [53.3%] of hepatitis B negative patients. More hepatitis B negative patients show altered protein levels than hepatitis B positive patient.

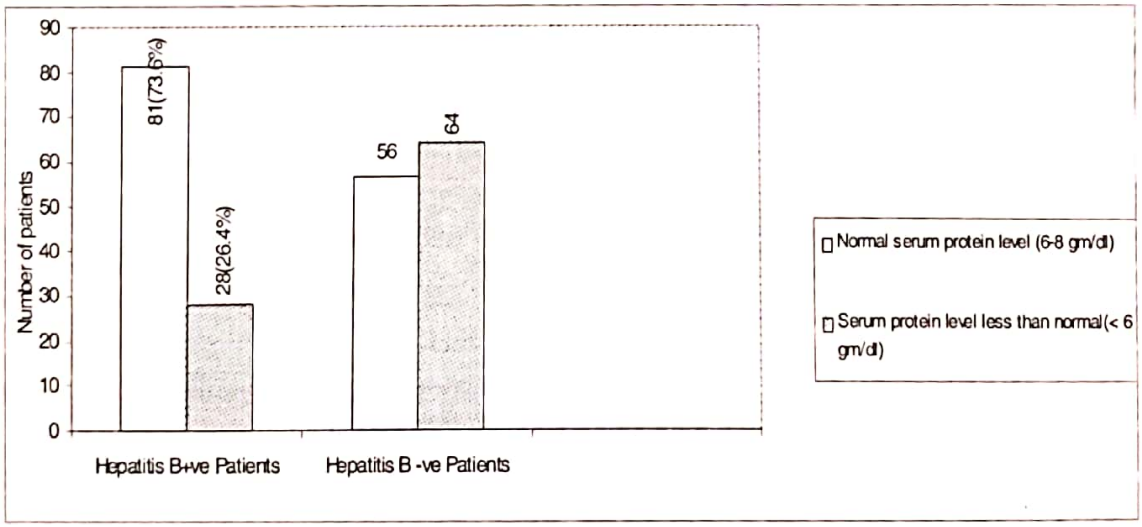

Fig 1: Showing comparison of hepatitis B positive and hepatitis B negative patients based on their normal serum protein level and less than normal.

The difference in total serum protein levels between hepatitis B positive and hepatitis B negative patients was highly significant at 99.99% confidence level ($P<0.001$) in statistical analysis of student's 't' test.

Table 2: TOTAL SERUM BILIRUBIN LEVELS AND NO. OF PATIENTS ALONG WITH ITS PERCENTAGE FOR HEPATITIS B POSITIVE AND NEGATIVE PATIENTS

Total serum protein level (gm/dl	No. of patients & percentage	
	Hepatitis B +ve	Hepatitis B -ve
0.5 – 1.0	26 (9.3%)	46 (15.7%)
1.1 – 1.5	101(36.1%)	56 (19.1%)
1.6 – 2.0	46(16.4%)	49 (16.7%)
2.1 – 2.5	23 (8.2%)	27 (9.2%)
2.6 – 3.0	20 (7.1%)	25 (8.5%)
3.1 – 3.5	11 (3.9%)	20 (6.8%)
3.6 – 4.0	17 (6.1%)	17 (5.5%)
4.1 – 5.0	7 (2.5%)	16 (5.5%)
5.1 – 10.0	22 (7.9%)	27 (9.2%)
10.1 – 15.0	7 (2.5%)	10 (3.4%)

Test for serum billurubin level had been carried out for 280 hepatitis B positive patients and 293 hepatitis B negative patients, out of them, 26 (9.3%) Hepatitis B positive had normal billirubin level (Normal range=0.2 - 1 mg/dl), 101 (36.1%) patients had 1-1.15 mg/dl billirubin level, 46 (16.4%) had 1.6 - 2 mg/dl level and remaining patients had billirubin above this level. Serum billirubin analysis in hepatitis B negative patient indicates that 46 (15.7%) had normal serum billirubin level, 56 (19.1%) had 1.1-1.5 mg/dl serum billirubin level, 49 (16.7%) had 1.6 -2 mg/dl billirubin levels. Results indicate that there is no marked difference in serum billirubin levels among hepatitis B positive and hepatitis B negative patients.

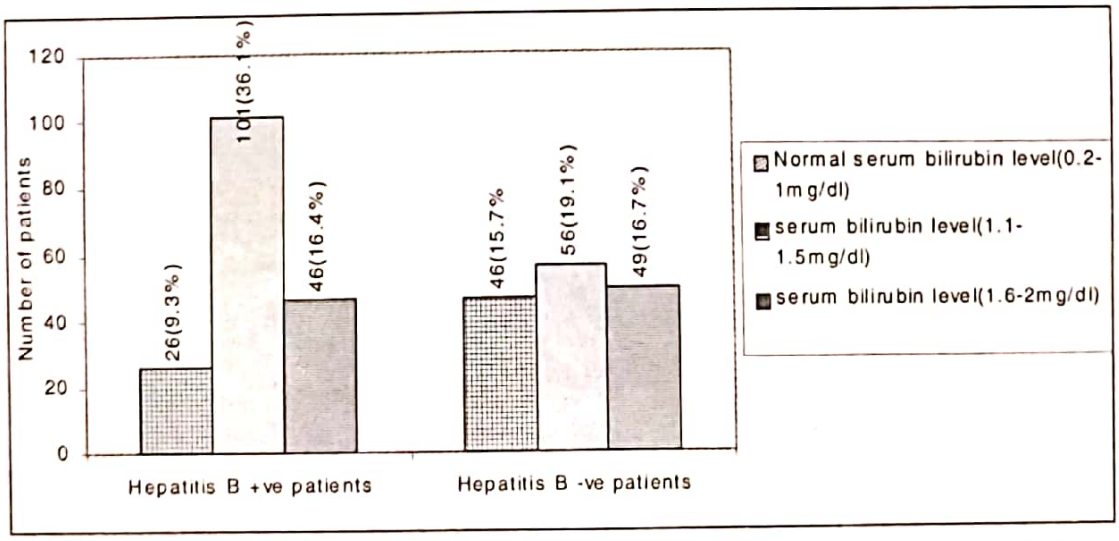

Fig 2: Showing comparison of hepatitis B positive and B negative patients based on normal and abnormal serum billirubin level.

Fig 2 showing, out of 280 hepatitis B positive patients 26 (9.3%) had normal serum billirubin level and out of 293 hepatitis B negative patients 46(15.7) had normal serum billirubin level.

The difference in total serum billirubin levels between hepatitis B positive and hepatitis B negative patients was highly significant at 99.99% confidence level ($p<0.001$).

These two laboratory investigations are much helpful in indicating the extent of hepatocyte destruction. This study indicates that all the hepatitis B patients were effectively treated and radical cure was 100%. The drug treatment included chloroquine, ribavarin, alkasim and methylene blue. Currently hepatitis B patients are treated with lamivudine in place of Ribavarin along with other drugs.

CONCLUSION

It had been proved that the antiviral drugs combination is helpful in rooting out the virus resulting in radical cure of viral hepatitis B to the extent of 100%. Two patient who showed surface antigen positive in their sera, found to be negative for HBV DNA on PCR assay; proving that they are having nert and empty surface antigen only in their blood circulation. So these patients may be called as FALSE CARRIERS and they will not transmit the disease to their family members and others as well.

All the patients showed anti-HBs level more than 10 IU/L, which is denoting good antibody level resisting further attack of hepatitis B infection. Regarding HIV infection no one suffered.

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RESEARCH ARTICLE

COMPARATIVE PRESCRIBING FREQUENCIES OF UNOPPOSED AND COMBINATION HORMONE REPLACEMENT THERAPIES IN THREE DISTRICTS OF KASHMIR PROVINCE

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ABSTRACT

Several prospective clinical studies conducted in the recent past have revealed a beneficial effect of combination hormone replacement therapy over unopposed therapy in terms of reduced cancer risk. This prescription analysis study was conducted at gynecological OPDs of various hospitals in three districts of Kashmir province of the Jammu and Kashmir state namely; district Srinagar, Anantnag and Pulwama. A total of 100 prescriptions were collected out of which 25 prescriptions were collected from district Srinagar, 40 from Anantnag and 35 from Pulwama. The prescriptions collected thereby were analyzed to assess the relative prescribing frequency of unopposed hormone replacement therapy in comparison to combination therapy in Kashmiri women. In the present study, unopposed hormone replacement therapy was found to have been prescribed in as many as 85 % prescriptions whereas combination therapy was prescribed in rest of the 15 % prescriptions only. This indicates that physicians of the valley are either not convinced or they are not well informed of the benefits of combination therapy over unopposed hormone replacement therapy.

INTRODUCTION

Hormone replacement therapy (HRT) is a system of medical treatment for surgically menopausal, perimenopausal and postmenopausal women, based on the assumption that it may prevent discomfort and health problems caused by diminished circulating estrogen and progesterone hormones. The treatment involves a series of drugs designed to artificially boost hormone levels. The main types of hormones involved are estrogens, progesterone or progestins, and sometimes testosterone. HRT is available in various forms. In women who have had a hysterectomy, an estrogen compound is usually given without any progesterone, a therapy referred to as "unopposed estrogen therapy". HRT may be delivered to the body via patches, tablets, creams, troches, IUDs, vaginal rings, gels or, more rarely, by injection. HRT is seen as either a short-term relief (often one or two years, usually less than five) from menopausal symptoms (hot flashes, irregular menstruation, fat redistribution etc.) or as a long term treatment to reduce the risk of osteopenia leading to osteoporosis. Although hormone replacement therapy (HRT) is mainly used to relieve menopausal symptoms, it has shown benefits in several chronic diseases such as osteoporosis, colorectal cancer, and depression; it may also have a protective role in dementia and cognitive decline in postmenopausal women [1].

Hormone replacement therapy (HRT) is a hotly debated topic that has been fueled by many studies reporting contradictory results regarding the risks and benefits of estrogen replacement therapy (ERT). The fallout from this debate has divided physicians over basic treatment options.

The risk of breast cancer has significantly increased among women who were using estrogen alone or estrogen plus progestin as compared with postmenopausal women who had never used hormones [2]. There are several studies that reveal increased cancer risk after the use of both unopposed and combined hormone replacement therapy [3-6]. However it has been observed that the relative risk associated with combined hormone replacement therapy is much lesser as compared to the unopposed therapy and several studies even suggest protective effects of the combined therapy in ovarian, colon, liver and other cancers. A prospective study conducted with 82,905 postmenopausal women, including 389 ovarian cancers from 1976 to 2002 revealed that the use of unopposed estrogen was associated with a significant increase in the risk of epithelial ovarian cancer. Use of estrogen plus progestin was not significantly associated with ovarian cancer risk [7]. Another study that analyzed cancer incidence and mortality in a cohort of 22,597 Swedish women suggested that estrogen-progestin combined therapy exerts a protective effect against colon and liver cancer risks [8]. Results of another prospective study revealed that the use of estrogens without progestogens is associated with a two-fold to three-fold increase in risk of endometrial neoplasia. Use of progestogens either removes this increased risk or delays its onset [9].

A population-based case-control study of endometrial cancer undertaken to evaluate the benefits of progestagen use provided some additional evidence that the use of progestagen for 10 or more days per cycle can reduce the excess risk of endometrial cancer associated with long-term postmenopausal oestrogen use [10]. Pike and Ross concluded that estrogen replacement therapy (ERT) increases a woman's risk of developing endometrial cancer approximately 120% and breast cancer approximately 10% for each 5 years of use. To reduce the greatly increased endometrial cancer risk, progestins were added to ERT for between 5 and 15 days (usually 7 or 10 days) per month in a sequential fashion and it was observed that ERT combined with progestin was not associated with any increased risk of endometrial cancer, therefore progestins need to be given to protect the endometrium [11]. Further menopausal women choosing estradiol therapy alone, especially if obese, should anticipate uterine bleeding and the possibility of an endometrial biopsy [12].

Present study was undertaken with a view to evaluate the relative usage of unopposed hormone replacement therapy in comparison to combined therapy in mostly menopausal women in the state of Jammu and Kashmir. A total of 100 prescriptions prescribing either unopposed or combined hormone replacement therapy were collected from various hospitals of three major districts of the Kashmir province namely, district Srinagar, Anantnag and Pulwama. Collected prescriptions were subsequently analyzed for relative usage of unopposed and combination hormone replacement therapies.

MATERIALS AND METHODS

Present study was conducted at gynecological OPDs of various hospitals in three districts of Kashmir province of the Jammu and Kashmir state namely, district Srinagar, Anantnag and Pulwama. A total of 100 prescriptions were collected from Shere Kashmir Institute of Medical Sciences,Srinagar, Lal Ded Gynae Hospital Srinagar, Govt.Medical College Srinagar, District Hospital Anantnag, Sub-district Hospital Bijbehara and Puwlama. A total of 25 prescriptions were collected from district Srinagar, 40 from Anantnag and 35 from Pulwama. The prescriptions collected thereby were analyzed to assess the relative prescribing frequency of unopposed hormone replacement therapy in comparison to combination therapy in menopausal women of Kashmir.

RESULTS

Unopposed hormone replacement therapy was found to have been prescribed in as many as 85 out of 100 prescriptions whereas combination therapy was prescribed in rest of the 15 prescriptions. Norethisterone was prescribed in 16 prescriptions; allyloestranol in 5; estrogen in 5; ethinyloesteranol in 10; danazol in 6; stilbosterol in 3; testosterone in 3 and estriol succinate in one prescription out of 100 prescriptions. Results are depicted in Table-1&2. Status - (whether hysterectomy done or not) of women is not clean - makes difficult to judge decisions of prescribe

Table-1: UNOPPOSED HORMONE REPLACEMENT THERAPY PRESCRIBING FREQUENCY

Unopposed HRT Prescribed	No. of Prescriptions out of 100
Norethisterone	16
Allyloestrenol	5
Estrogen	5
Ethinyloesterenol	10
Danozol	6
Stilbosterol	3
Testosterone	3
Estriol succinate	1
Total percentage of un-opposed HRT prescriptions	**85**

Table-2: COMBINED HORMONE REPLACEMENT THERAPY PRESCRIBING FREQUENCY

Combination HRT Prescribed	No. of Prescriptions out of 100
Norgestral/levonorgestral+ Ethinyl estradiol	6
Estradiol + Allyl oestrenol	3
Ethinylestradiol+Progesterone	1
Testosterone Combinations	3
Stilbosterol + Drotaverine	1
Ethinyloestradiol + Congugated estrogen	1
Total percentage of combination HRT prescriptions	**15**

DISCUSSION

Sex steroids are not known to damage DNA directly. They can stimulate or inhibit cell proliferation, and thus can modulate tumor developmental progression. Sex steroid-related tumors in women are represented by breast cancer and endometrial cancer, and a possible

relationship exists between sex steroids and both ovarian and colon cancer. Unopposed estrogen therapy is known to increase endometrial cancer risk, and is appropriate only for hysterectomized women. To negate the excess risk of endometrial hyperstimulation, an adequate progestin dose must be given in a continuous combined regimen or for an appropriate number of days in sequential regimens (10 days or more for some progestogens or 12 days or more for other progestogens). An appropriate combination of estrogen and progestin does not appear to increase, and may even decrease, the risk of endometrial cancer [13].

With a view to evaluate recent inconsistent findings that adding progestins to postmenopausal estrogen replacement therapy protects against endometrial cancer, a study was conducted using a population-based case-control study. The authors compared 511 endometrial cancer cases aged 50-79 years in the Philadelphia, Pennsylvania, region during 1999-2002 with 1,412 random-digit-dialing controls regarding postmenopausal hormone replacement therapy (HRT) use. It was concluded that long-term use of unopposed estrogen is associated with increased risk for endometrial cancer, whereas combined estrogen plus progestin hormone therapy is not. Thus, if HRT is to be used in women with an intact uterus, this study confirms the benefit of adding progestins to the regimen [14]. Another study reveals that women who switched to a combined regimen with a progestin added for at least ten days/month (37 cases, 47 controls) had half the risk of endometrial cancer of women who stopped hormone use altogether (86 cases, 78 controls) (adjusted odds ratio = 0.5, 95% confidence interval: 0.3-1.1). Results suggest that unopposed estrogen users may reduce their risk of endometrial cancer more by switching to a combined regimen with progestin added for at least ten days/month than by stopping hormone use altogether [15].

In the present study, unopposed hormone replacement therapy was found to have been prescribed in as many as 85 out of 100 prescriptions whereas combination therapy was prescribed in rest of the 15 prescriptions. This indicates that physicians of the valley are either not convinced or they are not well informed of the benefits of combination hormone replacement therapy.

CONCLUSIONS

The prescription analysis of hormone replacement therapy conducted in three districts of Kashmir province of Jammu and Kashmir state (India) revealed a high prescribing percentage of unopposed hormone replacement therapy over combination therapy. Further before prescribing HRT, no diagnostic evaluation for lipid density profile or cardiovascular diseases was done particularly in rural areas. Further an exhaustive literature survey on the subject suggests that progestin in sequential estrogen-progestin replacement therapy needs to be given for at least 10 days to block effectively any increased risk of endometrial cancer and the continuous combined estrogen-progestin therapy is similarly effective.

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SURVEY ON PROPER DISPOSAL OF SINGLE USE HYPODERMIC SYRINGES AND NEEDLES IN ANAND DISTINCT

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Various routes of drug administration are oral, injection, topical, implant, inhaler etc. Injections are very important and some times indispensable routes of administration for many medications and for immunization; however, studies have shown that there is widespread overuse and misuse of injections [1]. Recent surveys have shown that a very high percentage of injections are unsafe. Unsafe injections can result in the transmission of diseases like AIDS, Hepatitis B, Hepatitis C *etc,* from patient to patient as well as patient to also health worker unsafe injections: estimated annual consequences. Some data related to injections [2, 3, 4], show greater than 16 billion injections/year in developing countries, 95% for curative purposes, Greater than 50% unsafe because of reuse of non-sterile needle-syringes, needle-stick injuries and unsafe recycling. Unsafe injection is largest iatrogenic (man-made) medical disaster of 20th century as they are responsible for 21.7 million Hepatitis B virus (HBV) infections, 2 million Hepatitis C virus (HCV) infections and 100,000 human immunodeficiency virus (HIV) infections Injection popularity is one reason behind over use of injections [1]. Adequate supply is important for safe injection Demand =60 millions; supply=30 millions/month [2]. The objective of the study was to evaluate the public awareness of the risks associated with reuse of syringes and needles, and increase the awareness regarding proper disposal of syringes and needles.

Study was carried out in 3 different groups of doctors, students and person running on pharmacy store. We asked certain questions to different groups of people, the format of questions is given here. Following were the questions for doctors.

1. Whether you are using glass syringe? 2. Are you using hypodermic syringes and needles? 3. After using by which way you desposing hypodermic syringes and needles?

4. Which method you preferring for disposing of single use syringes and needles after use?

Following were the questions for pharmacists:

1. Whether you are selling Hypodermic syringes and needles? 2. Do you know the method of disposal? 3. Do you know risks associated with reuse?

Following were the questions for students: 1. Do you know about single use hypodermic syringe and needles? 2. Do you know the method of disposal? 3. Do you know risks associated with reuse?

It was found that 66% doctors discard the single use hypodermic syringes and needles by incineration. 16% of doctors were throwing the used syringes and needles into dustbin while 8% of doctors were using crushing machine for syringes and tip bending method for needles and 10% doctors supply to biomedical waste agencies. 90% persons running pharmacy store knew about proper method of disposal, 40% students were only aware about the same. It was concluded that most of doctors knew about proper method of disposal but still there are chances of reuse of single use hypodermic syringes and needles when they were discarded

by throwing in to dustbin and supplying to biomedical wastes. In case of persons running on pharmacy stores (10%) and students (60%) did not know about proper method of disposal so there are chances of reuse of single use hypodermic syringes and needles and risks associated with the same. Limitation of study is that it does not include the chance of spreading diseases in case of , if syringes and needles not destroyed by proper methods further the study is limited to certain groups of people. It should be advisable to inform patients about the risks of injections with non-sterile needles. Convince patients that oral treatments are safer and can be equally effective. Both syringes and needles can be infected. Never reuse an unsterilized needle or an unsterilized syringe.

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CELEBRATION OF PHARMACOVIGILANCE WEEK

(Under National Pharmacovigilance programme of India)

Department of pharmacology, Pramukhswami medical college, Karamsad

Pramukhswami Medical College, Karamsad is a peripheral centre of National Pharmacovigilance Programme of India (NPPI). The Department of Pharmacology is running this programme in the institute.Under the programme, the Department celebrated 'Pharmacovigilance Week' during 25th March 2007 to 31st March 2007. The objectives of the celebration were-

1. To generate awareness regarding of adverse drug events among Health Care Professionals (Doctors, Pharmacists, Nurses, Students including medical physiotherapy and nursing faculty).
2. To promote rational and safe use of medicines.

With the above said objectives, the various activities were planned. The CEO, HMPCMCE, formally inaugurated the week. Poster Competition: Poster competition was planned for medical, physiotherapy and nursing staff and students. The subject for poster making was Pharmacovigilance/ Adverse drug reactions reporting/ Drug safety. Out of total 14 entries prizes were awarded to first four winners. Participation certificates were given to all participants. Essay Competition Essay competition was also planned for medical, physiotherapy, and nursing staff and students. The subject for essay writing was 'Pharmacovigilance and Health Care professionals'. Total 8 entries were received from 10 participants. Prize and certificates were awarded to first, second and third winners. Participation certificates were given to all participants. Quiz Competition: Quiz competition was meant for medical teachers/ doctors. Four sets of questions (each set having five questions relating to adverse drug reactions, drug safety and NPPI) were prepared for four different days (26th, 28th, 29th, and 30th March 2007). During quiz round (10.00 am to 11.00 am daily), doctors were visited by staff members of the department and asked to fill up (answer) quiz paper given to them on the spot.Daily one doctor having scored maximum points was declared as a winner. Winners were awarded with prize and certificate.

Different talks were planned to address to various groups of persons for making them familiar with the programme. Village Health Workers' Training: A half day workshop on 'Drug Information and Pharmacovigilance' was arranged for VHWs on 26th March 2007. Twenty VHWs were trained on safe use of drugs. Twenty-five drugs were discussed stressing on their therapeutic uses, adverse effects, safety precautions and proper administration to patients. Academic Meeting was held on Wednesday, 28th March 2007 (8.30 am to 9.30 a.m.), there was a presentation on 'Pharmacovigilance: Clinician's Perspective'. Around 100 participants (staff and students) attended the event. They all were made aware regarding NPPI. CME on 'latrogenic diseases' and 'NPPI' was arranged for General practitioners of near by Anand town on Thursday, 29th March 2007 (8.00 a.m. to 9.30 a.m.). Lecture for nursing students: Lecture on NPPI was arranged for nursing students on Monday, 2nd April 2007 (3.30 pm to 4.30 pm) to make them aware regarding the programme.

Instructions for Authors

Aims and Scope:
The Journal of Pharmacovigilance & Drug Safety (JPDS) is an official, and peer reviewed journal of Society of Pharmacovigilance, India (SOPI), that aims to encourage the practice and research in rational drug usage drug safety and Pharmacovigilance. Hence the journal invites submission of original research articles, reviews, commentaries and case reports on rational drug usage, therapeutic drug monitoring, drug safety, Pharmacovigilance, pharmacoepidemiology, drug surveillance, community medicine, community pharmacy National or International Drug Policies and related issues. Journal will not consider basic drug research in animals unless they have direct relevance to the above-mentioned topics.

Submission of Manuscript:
Manuscripts are reviewed for possible publication with the understanding that they have not been published, submitted, or accepted for publication elsewhere. They will be reviewed for scientific content, technical importance and significance by two independent reviewers of repute. The authors may suggest reviewers, but it is not mandatory and editor has a regent not to accept it. The Journal will entertain research papers for publication under the following categories: Original research articles, Short Communication, Reviews, Commentary, Case reports on drug safety Three copies of manuscripts are required to be submitted along with 3.5 floppy or CD containing the electronic version using Microsoft word or any other word-processing soft ware. The manuscript should be sent to Prof. Ramesh K. Goyal, Editor-in-chief, JPDS, L. M. College of Pharmacy, Navrangpura, Ahmedabad-380 009

General guidelines For the preparation Manuscript
The original text must be printed in double-spaced on 8.5-x 11 -inch/ A4 size paper on one side only. Original inked drawings of structural formulas, figures and original black and white print of photographs must be attached for direct reproduction. Additional sets may be photoduplicated copies. Only standard abbreviations should be used throughout the text. Any nonstandard abbreviation must be defined in the text following first use. Full-length original Research papers should have following sections,

Title Page: It should give the title of the paper, author's name and institutional affiliations, running title and Address of corresponding author with email. The title should be specific, descriptive and concise. Author should include surname followed by first and middle name initials. Title page footnotes, if needed, may indicate present address of the authors or acknowledgement of grant support, including grant numbers.

Abstract:
Abstract: It should be self explanatory (limited to 200 words in one paragraph) suitable for reproduction without change. Abstract should have three sections (a) Objective (not more then 3 lines (b) Methods and Results, (C) Conclusions (not more then 34 lines).
Introduction: It should provide background information providing rationale of the study giving pertinent reference. Introduction should always end with objective of the study/ article.

Methods: One should describe selection of the observational or experimental subjects (Patients including controls) clearly. The age, sex and other important characteristics of the subjects should be identified. The definition and relevance of race and ethnicity should be ambiguous. Give references to established methods including statistical methods.

Results: Present your results concisely and in logical sequence in the text, tables and illustrations. Tables and figures should be devised in such a manner that the findings are accurately conveyed. The same data should not be used for more than one figure or table. Interpretation of the data should be given in the discussion only.

Discussion: The discussion must interpret the results and relate them to existing knowledge on the topic in as lucid a manner as possible, avoiding repetition or duplication of information. Include the implications of the findings and their limitations, including implications for future research. Relate the observations to other relevant studies. It should always end with concluding remarks. Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not completely supported by the data. Recommendations, when appropriate, may be included.

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Standard journal article: List the first six authors followed by et al. For example :e g. Parkin DM, Clayton D, Black RJ, Masuyer E, Friedl HP Ivanow E, et al. Childhood leukaemia in Europe after Chernobyl : 5 year follow-up. Br J Cancer 1996; 73:1006-12.

Organization as author: The Cardiac Society of Australia and New Zealand. Clinical exercise stress testing. Safety and performance guidelines. Med J Aust 1996; 164:284-4.

Books and other Monographs: Personal autor(s): Ringsven MK, Bond D. Gerontology and leadership skills for nurses. 2nd ed. Albany (NY): Delmar Publishers; 1996

Chapter in a book: e.g. Philips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: Pathophysiology, diagnosis and management. 2nd ed. New York: Raven Press; 1995.p.

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Acknowledgments: The author should acknowledgment advice from colleagues, financial/ technical assistance, gifts etc. after obtaining consent from the people whose assistance is acknowledged. Any other footnotes may be given here.

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