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Editorial

No drug is absolutely safe under all circumstances of use or in all patients. Any drug, no matter how common it's clinical uses, has the potential to cause harm. It is true that adverse reactions are a cost of modern medical therapy, but indigenous drugs used in traditional medicines are also not safe, tried and true. Adverse drug reactions are thus inevitable consequence of pharmacotherapy. Although, it is mandatory to ensure those drugs are safe and effective before launching into the market. The anticipated benefit from any clinical use must be balanced by the potential risks.

Patients, and to some extent physicians, are unaware of the limitations of the pre-marketing phase of drug development in defining common risks of new drugs. Frequency of adverse reaction more than 1 in 1000 patients may not be detected prior to release of drug into market. It must be emphasized that drug safety concerns are not confined to new chemical entities. They extend to new indications of existing products, new formulations, novel drug delivery systems and new combinations. ADR monitoring for a pharmaceutical product, thus, essentially lasts throughout its lifetime as a marketed medicine.

However, for rational drug use it is not sufficient to know only the correct dosing. ADRs can arise from many sources, even if a drug is correctly selected and dosed. If we believe in Hippocrate's first principle in treating patients as 'primum non nocere' i.e. above all, do no harm, it follows that we should be aware of the possibility of ADRs and the ways and means to prevent or curtail them. Post-marketing surveillance of drug usage is thus imperative to detect infrequent but significant adverse effects.

ADR monitoring in India

Unfortunately, to date, we do not have a nationwide ADR monitoring set-up, whether spontaneous or otherwise. Although pharmacovigilance is a new and emerging discipline in the world itself, it is relatively far newer to India. Limited number of physicians, pharmacists and faculty members in medical colleges are aware of the methodologies and activities in the field of pharmacovigilance. However, the Central Drugs Standard Control Organization (CDSCO), an establishment of Directorate General of Health Services, Ministry of Health & Family Welfare, has recently initiated a pharmacovigilance project across the country. This project envisages setting-up peripheral, regional and zonal pharmacovigilance centers for spontaneous as well as drug specific adverse drug event monitoring and causality analysis. Let us hope for the better results after its initiation.

The Journal of Pharmacovigilance & Drug Safety

With this introduction, we may now concern ourselves with the aims and objective of this *The Journal of Pharmacovigilance & Drug Safety*. The main objective of this journal is to 'confront' our readers with the information about what is being done in the field of pharmacovigilance, pharmacoepidemiology and drug safety the world over. To that end, we invite scientists, physicians, nurses, pharmacists and consumers of medicine to share their experiences with this journal and send research articles, case reports and other materials on the above fields. We also intend to survey the important Newsletters and Journals and shall publish relevant news items in the journal. Naturally, these objectives coincide with the aim and objective of the establishment of Society of Pharmacovigilance, India (SOPI) itself. We hope that in this endeavour the international and national community of medical scientists will assist us with both critically edited texts material on adverse drug reaction and their analytical studies, i.e., the hardware and software of pharmacoepidemiology. Finally, we keep in mind also the eventuality that this journal may become a full fledged scholarly journal during the following years, depending upon the response of our readers and colleagues. Suggestions to improve the contents of the journal are most welcome.

S. Ziaur Rahman

Alterations in Liver Enzymes and Trace Elements in Anti-tubercular Treatment Induced Hepatitis

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Abstract

Objective: The present study was proposed with the aim of defining the clinical profile and likely mechanism of antitubercular treatment induced hepatitis with alterations in the values of Zn and Cu both at onset of hepatitis and values after recovery from hepatitis.

Methods: This study consisted of 500 patients receiving antitubercular treatment out of which 46 cases who, on the basis of laboratory findings, were diagnosed as cases of hepatitis. The patients developing hepatitis were divided into two groups-cholestatic (A) and hepatocellular (B) for the purposes of comparing the Cu and Zn levels in the serum. Serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), alkaline phosphate and serum bilirubin were estimated at weekly intervals, till recovery, to assess the liver function besides the estimation of serum copper (Cu) and zinc (Zn).

Results: The values for SGOT and SGPT were raised and returned to pretreatment level following withdrawal of antitubercular therapy. Serum alkaline phosphatase did not alter, while serum bilirubin was raised significantly. Serum zinc (Zn) levels were decreased at the onset of hepatitis in both groups when compared with respective values at recovered stage while the levels of serum copper (Cu) were increased.

Conclusions: Serum zinc levels significantly decrease and serum copper levels increase, irrespective of the nature of hepatitis, including ATT induced hepatitis.

KEY WORDS: Hepatitis, ATT, Zinc, Copper, Liver Function Tests

Introduction

Zinc and copper are essential trace elements. They have extensively been studied in health and with regard to many diseases both in human and experimental animals. Despite this progress many major lacunae in knowledge still persist. Changes in serum copper (Cu) and Zinc (Zn) levels have been observed in hepatic diseases (1-2). In a study, determination of fasting serum levels, in a total of ninety eight patients of hepatocellular carcinoma, exhibited significantly decreased zinc levels and elevated copper levels (3). Further, it was observed that the changes in the content of these microelements depended on the severity of the hepatic disease; even in patients who were hepatitis B surface antigen (HBsAg) positive, these trace elements exhibited similar changes (4-5). On the basis of experimental observations, use of Zinc-acetate as an effective and non-toxic treatment for copper toxicity has been advocated (6) and life long treatment with chelating agents (d-penicillamine) or with zinc has been found to be sufficient to stabilize and achieve clinical remission in most patients (7-8). The foregoing studies support the generalization that during liver disease, be it cholestatic or hepatocellular, serum Cu levels increase and serum Zn

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levels decrease. No studies are, however, available to show any correlation of serum levels of these microelements with antitubercular treatment (ATT) induced hepatitis. The present study was therefore, undertaken to estimate zinc and copper levels in patients of pulmonary tuberculosis developing hepatitis due to ATT and to explore their relationship with restoration of liver functions.

Material and Methods

The study was conducted in collaboration with Department of Tuberculosis and chest diseases, J.N. Medical College Hospital, A.M.U., Aligarh and included patients of pulmonary tuberculosis from both out-patients and in-patients departments. A total of 500 patients were recruited in the study. Exclusion criteria were children below 12 years, pregnant women, patients with compromised renal or hepatic functions, history of jaundice, patients with extra pulmonary tuberculosis, history of alcoholism, patients receiving injections during past ten weeks and patients positive for hepatitis-B surface antigen (HBsAg). Patients were given standard four drug treatment with antitubercular drugs and invariably included isoniazid and rifampicin with or without pyrazinamide. The patients were subjected to investigation for their liver function tests (LFT) including serum glutamic oxaloacetate transaminase (SGOT), serum glutamic pyruvate transaminase (SGPT), serum alkaline phosphatase, serum bilirubin and concurrently, from the same serum sample, zinc (Zn) and copper (Cu) levels were also estimated. Those patients having levels with in normal range were followed up. LFT were repeated at weekly intervals. Forty-six of these patients developed hepatitis during the course of therapy. In these patients, the antitubercular treatment was withdrawn and patients were regularly investigated for liver function tests and serum Cu and Zn levels till recovery from hepatitis.

Method of estimation of Serum Copper (Cu) and Zinc (Zn) Levels

Estimation of serum zinc (Zn) and copper (Cu) levels were done by GBC, 902- double beam atomic absorption spectrophotometer. The method followed is a standard method developed in 1955 by Walsh and as quoted by Kryska et al (5).

Analysis of Samples

The samples were diluted with distilled water in a dilution of 1:10. The atomizer was rinsed by aspirating deionized distilled water containing 1.5 ml con. HNO3/litre. The diluted samples were atomized and their absorbance was determined. The zinc and copper have their own characteristic wavelengths (Zn- 213.9nm; Cu 324.7nm). The amount of energy of characteristic wavelength absorbed in the flame is proportional to the concentration of the element in the sample. The results of estimation were confirmed by comparing with standard solutions. Student's 't' test was applied to compare the data obtained during hepatitis and at recovery.

Results

Forty-six out of the 500 patients of pulmonary tuberculosis treated with antitubercular drugs, developed hepatitis detected by clinical examination and confirmed by liver function tests. Hepatitis was observed in both male and female patients nearly to equal extent. In this study, hepatocellular (Group B) as well as cholestatic (Group A) hepatitis as suggested by LFT, were seen during ATT; former being apparently more common. In both the groups transaminases (SGOT, SGPT) were markedly increased at the onset of hepatitis.

The value SGOT, SGPT at onset were 99.04+2.07 and 101.38+3.38 respectively, which were significantly higher than the values obtained on recovery, which were 16.76+0.66 and 12.46+0.60 respectively. Serum alkaline phosphate values did not change much where as changes observed in serum bilirubin levels were statistically significant. The results of LFT estimations are summarized in Table 1.

Table 1: Liver Function Tests in Antitubercular Treatment Induced Hepatitis

Liver Function Tests	At the Onset of Hepatitis	After Recovery from Hepatitis
SGOT (IU/L)	99.04 ± 2.07*	16.76 ± 0.66
SGPT (IU/L)	101.38 ± 3.38**	12.46 ± 0.60
Alkaline Phosphatase (KAU/100 ml)	17.76 ± 0.46	12.62 ± 1.81
Serum Bilirubin	2.00 ± 0.22**	0.64 ± 0.03

n=46. The values are mean ± SEM
*P<0.05, **P<0.001 as compared with respective values at recovered state

The levels of microelements were also found to be altered during ATT-induced hepatitis. Serum Zn levels were significantly (P<0.5) decreased at the onset of hepatitis in both groups when compared with respective values at recovered state. The serum Cu levels were, however, significantly increased in both the groups of hepatitis (see table 2).

Table 2: Serum Levels of Copper and Zinc in Antitubercular Treatment Induced Hepatitis

	Group A (n=20) Cholestatic Hepatitis		Group B (n=26) Hepatocellular Hepatitis	
Trace Elements	At Onset	After Recovery	At Onset	After Recovery
Zinc (µg/dl)	94.20 ± 3.06*	144.59 ± 2.52	114.42 ± 2.53*	166.89 ± 2.74
Copper (µg/dl)	167.57 ± 2.05*	140.58 ± 1.90	200.97 ± 3.03*	164.24 ± 2.12

n=46. The values are mean ± SEM
*P<0.05 as compared with respective values at recovered state

Discussion

Any agent that induces hepatitis causes inflammation and/or necrosis of hepatocytes. Injury caused by drugs may start with a picture quite unlike that of hepatitis. List of drugs implicated in drug induced disease is extensive. Around fifteen drugs account for greater than 80% of acute hepatic reactions. Acetaminophen heads the list. Other well known and commonly used drugs include halothane, methyldopa, isoniazid, oral contraceptives, rifampicin and valorous acid which are potentially more hepatotoxic. Patients when given antitubercular treatment consisting of isoniazid, rifampicin and pyrazinamide singly or in combination are at higher risk for hepatic damage (9). In a controlled consecutive study, though non significant correlation of age with antitubercular treatment induced hepatitis was found (10),

but we excluded children form our study for the sake of maintaining homogeneity in he study group. Similarly, patients positive for HBsAg were excluded as, hepatitis B and Tuberculosis are endemic in India and inclusion of these patients could vitiate results. Low nutritional state is considered to be one of the factors contributing to relatively high incidence of ATT induced hepatitis in studies from developing contries (11-12). Drug induced hepatitis is a potentially serious adverse effect of the currently used chemotherapeutic regimens in tuberculosis, containing isoniazid. rifampicin and/or pyrazinamide 13, 14. The present study was planned to monitor patients on antitubercular chemotherapy for alterations in their hepatic status as characterized clinically and by LFT. Nearly 10 percent of patients (46 out of 500 patients) exhibited hepatitis as evidenced by increase in SGPT, SGOT and serum bilirubin. There was no relationship between sex of the patients and hepatic adverse drug reaction. The levels of serum copper increased, while, that of serum zinc decreased in all patients showing hepatoxicity to antitubercular drugs. The changes in levels of these trace elements are similar to as reported for other types of hepatitis. Although the level of serum Zn and Cu are not diagnostic markers for either tuberculosis of antitubercular treatment induced hepatitis, but could serve as additional evidence suggesting liver damage in conjunction with changes in serum enzymes. Zinc administration has been attempted in hepatic copper toxicosis with promising reluslts (15-16). It is yet difficult to assign it any role in hepatic in general or specifically in ATT induced hepatitis. It is yet not known why these changes in serum levels of microelements occur. It shall be premature to speculate that in hepatitis, zinc is required by hepatic reparative enzymes and copper using enzymes are decreased in the liver, reflecting opposite changes in serum without further substantiation. Accumulation of copper has been associated with damage to liver. In the context of previous observations (3-8), the generalization that in hepatitis, serum copper levels, increase and serum zinc levels decrease is justified by the results obtained in the present study. However, the difference that hepatitis as confirmed by serum enzymes and bilirubin levels in the present study was drug induced, made no difference in the serum level changes of microelements.

Acknowledgement

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Increasing Aminoglycoside resistance in clinical Gram-negative bacterial isolates: a reflection of increased aminoglycoside usage – our worst nightmare?

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Abstract

Objectives: To determine the aminoglycoside resistance rates in various Gram-negative bacterial isolates, aminoglycoside prescribing habits at our hospital and to find out the correlation between aminoglycoside usage and aminoglycoside resistance (if any).
Methods: Ninety-eight, non-repeat, clinical isolates of various Gram-negative bacteria, obtained from the hospitalised patients were included to determine the aminoglycoside antibiotics resistance rates. Aminoglycoside prescribing habits in the wards were noted and correlation between aminoglycoside prescribing habits and aminoglycoside resistance was evaluated. Preliminary screening of the isolates for the presence of R-plasmids was also performed.
Results: All the isolates included in the present study were multidrug-resistant. Resistance to amikacin was noted in 54(55.1%) isolates whereas; resistance to tobramycin and gentamicin was noticed in 82(83.6%) and 32(32.6%) isolates respectively. Noting the aminoglycoside prescribing habits, we found that these are prescribed in a frequency amikacin~75%, tobramycin~20% and gentamicin~5% in our hospitalised patients. More than 90% isolates were found to harbour R-Plasmids.
Conclusions: Markedly high resistance to tobramycin and amikacin was noted. Noting the aminoglycoside prescribing habits and aminoglycoside resistance, direct correlation was observed. It is thus suggested that unwanted and irrational use of antibiotics should be restricted. Hence, not only there is a need to vigil adverse drug reactions, adverse drug effects in the form of emergence of antibiotics resistance due to increased and unwanted use should be limited by strict vigilance.

KEYWORDS: aminoglycoside resistance, aminoglycoside prescribing habits, correlation, Gram-negative bacteria, susceptibility rates,

Introduction

The wide emergence of antimicrobial resistance is a problem of increasing importance worldwide (1). The increased use of a variety of antimicrobial, including aminoglycoside, and the clinical introduction of numerous closely related compounds are clearly related to the emergence and dissemination of resistant strains.

In the past few decades, various Gram-negative bacterial isolates, including *Escherichia coli*, *Klebsiella pneumoniae*, *P. aeruginosa* etc., has become increasingly recognised as the aetiological agent in variety of serious infections (2). Furthermore, the emergence of resistant strains has further complicated the situation and reduced the potential of aminoglycoside in empiric therapies (3).

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The excessive morbidity and mortality associated with ineffective empirical therapy in infections underscores the need of reliable data on which to base the choice of empirical therapy (4). Considering these points, the present preliminary study was designed to determine the aminoglycoside resistance rates in various Gram-negative bacterial isolates and to find out any correlation between the aminoglycoside prescribing habits and aminoglycoside resistance.

Materials and Methods

The present study was conducted in the department of Microbiology, J. N. Medical College and Hospital, Aligarh, India. Ninety-eight, non-repeat, clinical isolates of various Gram-negative bacteria (as shown in Fig. 1), including *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Proteus mirabilis*, obtained from the clinical samples of the hospitalised patients were included in the study.

Aminoglycoside susceptibility rates of the isolates were determined by the method of Bauer *et al.* (5) on Mueller Hinton agar (Hi-Media Lab. Ltd., India) using commercially available paper discs (Hi-Media Lab. Ltd., India). The aminoglycoside antibiotics used and their concentrations are shown in Table 1. Experiments were performed in triplicate and means of zone of inhibitions were derived. Results were interpreted according to the standard table provided by the supplier.

Aminoglycoside prescribing habits in various wards of our hospital were noted and the mean prescribing habit was determined. Antibiogram of the bacterial isolates was compared with the mean aminoglycoside prescribing habit and correlation between aminoglycoside usage and aminoglycoside resistance was noted.

Results

The results of the antibiotic susceptibility of the bacterial isolates are shown in Table 1. All the isolates were multi-drug resistant. Among the commonly prescrided aminoglycoside antibiotics, the maximal resistance was noted to tobramycin in 82 (83.6%) isolates followed by amikacin and gentamicin in 54 (55.1%) and 32 (32.6%) isolates respectively. More than 90% of the isolates were found to harbour R-plasmids as revealed by preliminary plasmid screening (Fig. 2). Noting the aminoglycoside prescribing habits and aminoglycoside resistance, direct correlation was observed between the two (Table 1).

Figure 1. Numbers of Gram-negative bacterial isolates included in the present study

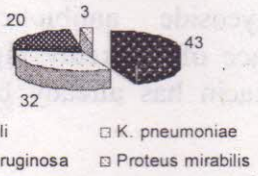

Fig. 2: 0.8% Electrophoretic gel showing plasmid bands in P. aeruginosa strains included in the present study. Arrow indicates the position of the plasmid. The Flourescence at the origin indicates retained genomic DNA.

Table 1: Aminoglycoside antibiotics resistance and frequency of aminoglycoside prescribing habits in Gram-negative bacterial isolates

Aminoglycoside antibiotic tested	% Resistant (n)	% Frequency of prescribing habits
Amikacin (30 µg)	55.1 (54)	~ 75
Tobramycin (30 µg)	83.6 (82)	~ 20
Gentamicin (10 µg)	32.6 (32)	~ 5
Netilmicin (30 µg)	58.1 (57)	NP
Kanamycin (30 µg)	91.8 (90)	NP
Neomycin (30 µg)	81.6 (80)	NP

Figures in parentheses indicate number of bacterial isolates. NP = Not prescribed commonly

Discussion

The aminoglycosides have been shown to be synergistic with β-lactam antibiotics and are commonly used in combination with these agents in empiric therapies. Although the resistance to aminoglycosides is increasing, they continue to play an important role in the treatment of serious infections (6). Therefore, periodic monitoring of resistance rates and patterns is mandatory, with special reference to aminoglycoside antibiotics, as the emergence of markedly high resistance to amikacin has already being noticed (7).

Among the commonly prescribed aminoglycosides at our hospital, markedly high resistance to tobramycin and amikacin was noted. Though, resistance to other aminoglycosides like netilmicin, kanamycin and neomycin was noticed to be markedly high, these aminoglycosides are not prescribed routinely at our hospital in the infections caused by Gram-negative bacterial isolates. The resistance to these aminoglycosides could be due to cross resistance of routinely prescribed aminoglycosides. Amikacin is still reported to be most potent aminoglycoside against Gram-negative bacterial isolates in various other countries (4) which may be due to their strict National antibiotic policy however, emergence of amikacin resistance in some of the recent studies, including the present study, emphasizes the need of re-evaluation of the national antibiotic policy and restrict the unwanted use of amikacin in therapeutics. Though we performed a base line study to determine the aminoglycoside resistance in various Gram-negative bacterial isolates and to find out the effect of aminoglycoside prescribing habits on emergence of drug resistance, a need is there to conduct large scale studies on the current aspect and to cover wide geographical areas to exactly evaluate the effect of aminoglycoside prescribing habits on aminoglycoside resistance

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Nimesulide Induced Coronary Artery Insufficiency – A Case Report

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Abstract
Adverse Drug Reactions (ADRs) are one of the leading causes of morbidity and mortality in health care. However, hospitalized patient populations have placed much higher estimates on the overall incidence of serious ADRs. Nimesulide, which recently came under attack in India because of hepatotoxicity it produced in children, is one of the Cyclooxygenase 2 (COX2) inhibitors used commonly for fever and pain. Although, lots of the ADRs are listed with nimesulide, but none of the literature suggests its safety profile in patients with coronary artery insufficiency. Efficient postmarketing drug surveillance is needed, but unfortunately such surveillance does not exist or is inadequate in India. This issue is particularly relevant with new drugs, which as is the case of non-steroidal anti-inflammatory drugs, can be sold in inadequately regulated countries, where the influence of pharmaceutical firms on drug prescribing is greater. To put this in perspective, this study is done to analyse and assess the ADR of nimesulide in patients with coronary artery disease as reported spontaneously to our department. Although, it is true that because of under-reporting many adverse reactions remained undetected, but we could found one definite case report on aggravation of coronary artery disease with nimesulide. There is a need to highlight the impact of over the counter, irrational use and overprescribing of drugs in the society in general and in medical fraternity in particular.

KEY WORDS: Adverse Drug Reactions, Nimesulide, Coronary Artery Disease.

Introduction

None of the reports in medical literature indicate the superior efficacy of nimesulide as antipyretic as compared to paracetamol and anti-inflammatory compared with other drugs of this class such as diclofenac and piroxicam. Numerous studies have established the life threatening adverse events with nimesulide such as hepatotoxicity (1), renal toxicity, severe skin reactions including fixed eruptions, gastrointestinal toxicity, potentiation of seizures, potentiation of colitis in passive cigarette smoking (2). Though, it is reported that like other non-steroidal anti-inflammatory drugs (NSAIDs), nimesulide should be used with great caution in patients with compromised renal function, cirrhosis of liver, congestive heart failure, renovascular disease or those who are volume or salt depleted. But, none of the reaction associated with cardiovascular system with nimesulide has yet been reported. Moreover, a plethora of scientific data shows that nimesulide should not be used as the primary mode of treatment as an antipyretic or analgesic, when much better and safer choices are available (3). No rationale exists for selecting nimesulide as the first drug of choice for fever or pain. The aim of the present report is to inform clinicians that coronary artery insufficiency may be aggravated in already coronary compromised patients and thus should be cautioned while prescribing the drug. The notification of any reactions should not be "under-reported".

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Case History

A 62-year-old male who was known case of coronary artery insufficiency and was maintained on Tab Myo 24 (Amlodipine 5 mg + Atenolol 50 mg; half) once a day, Tab Monotrate (Isosorbide-5-mononitrate) 20 mg twice daily, Tab. Ecosprin (Aspirin 75 mg) once a day, Tab Dytide (Triamterene 50 mg + Benzthiazide 25 mg) half tab once a day, Tab Ativan (Lorazepam) 2 mg at bed time and Tab multivitamin once a day for the last 2 years. He had no other problem as told by the patient, life was going well when he was advised Tab Nimesulide 100 mg twice daily for the complaint of knee joint pain. After two days of treatment i.e. on third day, he felt chest pain and breathlessness. He afterward consulted a cardiologist; there was no history suggestive of smoking, alcohol intake, diabetes mellitus, viral infection, TB, trauma, foreign body inhalation, headache or vomiting. On examination, he was found not having cyanosis, icterus, pallor or pedal edema. Jugular venous pressure was not raised, no lymphadenopathy was found, however, BP was 160/106 mmHg; respiratory rate was 20/min; pulse rate 90-92/min, regular and good volume, normal vesicular breathing without crepitations or other added sounds; heart sounds were normal and no murmur; other examination revealed no hepatosplenomgaly or ascites. On ECG, no abnormality was detected (no sign of ischemia, infarction, fibrillation and heart block). Patient was diagnosed as a case of Unstable Angina with Hypertension and was advised complete rest with prescription of Tab Sorbitrate *if needed* along with Tab Myo 24 (Amlodipine 5 mg + Atenolol 50 mg; half) once a day, Tab Monotrate (Isosorbide-5-mononitrate) 20 mg twice daily, Tab. Ecosprin (Aspirin 75 mg) once a day, Tab Lasix half tab once a day, Tab Ativan (Lorazepam) 2 mg at bed time and Tab multivitamin once a day. The response was not satisfactory, though, BP and pulse came to normal. The patient was then asked to stop suspected drug nimesulide and no other NSAIDs to be taken. Symptomatic improvement was seen after 6 hours and the patient was completely well free from any symptoms after 24 hours of stoppage of nimesulide. He was also advised not to use nimesulide in future.

On second occasion, the patient unknowingly consumed nimesulide (of some other brand name) as 'over the counter' for common colds and again felt heaviness in chest, difficulty in breathing and increased intensity of headache. On examination, patient was having raised BP as 170/110 mm Hg; pulse rate 100/min, regular and good volume, body temperature 100 degree F, no cyanosis, icterus, pallor, pedal edema or lymphadenopathy. Jugular venous pressure was also not raised, vesicular breathing with fine crepitations, low pitched rhonchi were present bilaterally; heart sounds were normal with no murmur; other examination revealed congested throat, no hepatosplenomgaly or ascites. ECG was within normal limit. Patient was advised steam inhalation, warm saline gargles, Cap Ampiclox (Ampicillin 250 mg + Cloxacillin 250 mg) 6 hourly for 5 days & Syp Brozedex (Cough Syrup). After use of these drugs, the symptoms of common colds were relieved, but chest heaviness persisted. The patient was further interviewed by the physician, which revealed that he was taking Tab nimesulide as and when needed as 'over the counter'. He was warned to stop nimesulide immediately and take tab paracetamol *if needed*. This caused sudden relief from continued chest pain for the last 7 days and he became completely well.

Discussion

Naranjo ADR Probability Scale Evaluation (4), when assessed the likelihood of reaction

Coronary Artery Insufficiency with nimesulide gave an idea about a score of 5. Hence "Use of the Naranjo ADR Probability Scale indicated a 'probable' relationship between the adverse effect (CAI) and (nimesulide) therapy in this patient." Similarly, WHO Causality Categories (5) when evaluated also confirms its 'probable' link. In this case, chest heaviness (pain) appears to be due to coronary artery spasm by nimesulide and not due to common colds (respiratory infection) because the treatment for common colds as mentioned in the text cured the symptoms of colds without any relief from the chest heaviness. On withdrawing nimesulide, there was relief from this complaint, showing a close association between nimesulide and chest heaviness. The coronary spasm was not observed with paracetamol (an NSAID different from nimesulide in its structure and activity spectrum). It appears that nimesulide might precipitate the coronary spasm in a compromised patient because of its pharmacological activities. Moreover, some case reports have suggested a causal relation between the use of NSAIDs and the onset of CHF (6,7). Authors believe when more safer drugs as aspirin, paracetamol are already available it is irrational to prescribe me-too drugs of doubtful efficacy. Nimesulide should be avoided in old patients having coronary artery diseases with poor cardiovascular reserve.

Nevertheless, ADRs on cardiovascular system with nimesulide have not yet been reported but literature review suggests the risk of cardiovascular events associated with selective COX-2 inhibitors like celecoxib and rofecoxib. The most commonly reported events were heart rate and rhythm disorders, increased BP, congestive heart failure, myocardial infarction, cerebrovascular events and thrombo-embolic events (8). A study evaluated the relative expression and immunoreactive levels of COX-1 and COX-2, in the renal cortex and medulla of rats with congestive heart failure. The same study also revealed upregulation of medullary COX-2, but not of COX-1, in rats with advanced heart failure (9). Authors believe that COX 2 may be up regulated as compensatory mechanism in advanced heart disease and the inhibition of compensatory mechanism may further deteriorate the condition.

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Adverse Drug Reaction – Reports of Three Cases

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Adverse reactions in some form or other are of varying severity and occurred with almost every drug. Three cases of adverse reactions with drugs available freely as over the counter are being reported here owing to its clinical significance. All these cases are singled out from Loknaik Jai Prakash Narayan Hospital, New Delhi.

Case I: A 20 year old male patient attended the medical OPD with a typical history of malaria viz. high grade intermittent fever associated with rigors for three days. Peripheral smear for malaria parasite was positive. The patient was admitted since his general condition was not satisfactory. Apart from moderate pallor, there were no other positive finding on clinical examination. He was given 4 tablets of chloroquine phosphate stat at the time of admission, another two tablets in the evening and two more the next morning. However, the condition of the patient started deteriorating after the last dose of chloroquine. He started passing high colored urine and developed mild icteric tinge in the sclera. The jaundice deepened and within next two days, patient went into acute renal shut down and expired on fifth day of admission.

Comments: At the time of development of jaundice, haemoglobin was 7gm% and serum bilirubin was 4mg%. Urine examination revealed presence of urobilinogen and absence of bilirubin. These findings point out to the haemolytic origin of the jaundice. The cause of excessive haemolysis in this patient could have been the deficiency of the enzymes glucose-6-phosphate-dehydrogenase. However, no specific test was done to diagnose this deficiency as it was suspected only when the patient went into acute renal shut down. A possible causal relationship can be established case as (i): there was no history of chloroquine intake in the past. (ii): no drug, other than chloroquine, is given in hospital set-up.

Case II: A 40-year-old Hindu female came to the medical OPD with history of fever and cough associated with mild mucoid expectoration. Clinical examination revealed occasional scattered crepitations in the chest. In the OPD, few investigations were done viz. hemoglobin 8 gm%, total leucocyte count 11,000/cu mm, differential leucocyte count P_{78}, L_{22}. She was advised to take capsule ampicillin 250 mg orally 6 hourly. On the fourth day of therapy, she returned to the hospital with fever, malaise, headache, redness of the eyes and a generalized erythematous rash. She also had few maculopapular lesions and scattered thickened hyperpigmented plaques. As a case of ampicillin induced Steven Johnson's Syndrome, she was admitted to the ward. Soon the suspected drug ampicillin was withdrawn following which there was a marked improvement in her condition. Drugs used for the treatment of reaction were erythromycin 500 mg 6 hourly, prednisolone 60 mg/day in divided doses, condy's wash and GV paint for local application.

Comments: Steven Johnsons Syndrome is a well-established clinical entity with an allergic basis. It is known to occur with Betalactam antibiotics of which ampicillin is one of its member. The incidence is, though, not very high with oral administration.

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Case III: A 28 years old male came to the medical OPD with fever and sore throat. Since the patient was a known case of Rheumatic Heart Disease with Mitral Stenosis, he was admitted to the ward with suspicion of Subacute-bacterial Endocarditis. Clinical examination revealed mild pallor but no palpable spleen. Similarly, there was no microscopic haematuria. Blood culture was sent (which 2 days later was reported to be sterile). Injection streptopenicillin (1 gm + 10 lacs) was started intramuscularly daily. The patient showed peaks of temperature in the evening following administration of the drug. Injections were immediately stopped for 4 days following which, the evening spikes of fever, disappeared. When started again patient developed similar peaks of temperature.

Comments: In this case 'dechallenge' and 'rechallenge' were positive. Since the injection had 2 components viz. streptomycin and penicillin, 'rechallenge' was not tried with each drug individually. It is difficult to incriminate only one component, as either of them could have been responsible for the reaction.

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Adverse Drug Reactions of an Herbal Drug due to Mis-identification: A Case Report

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Introduction

Many indigenous drugs have been described to possess medicinal properties. The use of medicinal plant extracts /concoction for the treatment of various disorders has been based largely on historical and anecdotal evidence, or continues to rely on medicinal plants for PHC (65–80 % of the world population). Traditional herbal medicines constitute a major part of the consumption of therapeutic remedies, often in combination with orthodox medicines. Experience passed on from generation to generation has demonstrated the safety and efficacy of TM. Thus, public has blind faith on TM.

It is a common belief that such drugs are mostly safe and do not cause any harm or S/Es. Many ADR to herbal remedies remain unnoticed since personal experience is not a reliable basis for the exclusion of uncommon reactions to herbal remedies. Since there has been relatively little data available in the scientific literature, particularly with regard to the efficacy of plant extracts in controlled clinical trials. Innovative ways of collecting safety information from this kind of practice will have to be initiated.

Ingestion of alternative medicine, even in overdose, generally produces minimal toxicity, life-threatening events from severe intoxication may occur. As with other poisonings, an understanding of these agents' mechanism of toxicity is key in planning specific management strategies.

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Suddab

Suddab is a well known drug of Indian System of Medicine and is used in different ailments. It's used is mentioned particularly in classical literature of Unani System of Medicine (1-4). At least 38 therapeutic uses are mentioned (5-6). Apart from 38 uses, the application of Suddab (Ruta graveolens Linn) paste combined with vinegar is an effective treatment for epistaxis. The decoction of leaves combined with honey is beneficial for indigestion and increases the appetite. Suddab thus cannot apparently induce epistaxis, nausea/vomiting in general. Over dosage of Suddab can cause nausea & vomiting.

Material & Methods

Roots of *Ruta graveolens Linn.*, which is commonly known as *Suddab* in Unani System of Medicine and is widely used for the treatment of vitiligo. As part of phase IV clinical trial of the drug for vitiligo, adverse drug reactions were monitored. The plant roots were procured from local suppliers, washed for any extraneous material, dried and pulverized. Patients of vitiligo were administered 2-3 gm root powder orally (dose related to extent of disease) twice a day with water. The powder mixed with vinegar was also applied locally over the affected parts of body and patients were asked to take sunbath for 4-5 minutes after application. No other drug was administered concurrently or applied locally.

Observations

Twenty-one patients developed adverse reactions. These include epistaxis 12 patients (all males, 15-25 yrs), nausea / vomiting 8 patients (both sexes, 30-40 yrs) and haematuria 1 patient (female 10 yrs). Dechallenge was positive in all patients. Rechallenge was not attempted. No concomitant drug was given. The plant is in use since long for the treatment of vitiligo and no adverse reactions were ever noticed or reported. The market sample of Suddab was compared with the Unani Literature and also cultivated for its botanical identity. It has been established depending on various Pharmacognostic evaluation of the plant cultivated is the plant of *Euphorbia dracunculoides* Lam. (8) and is closely resembles *R. graveolens* Linn. as replacement of the later. Thus the adverse reactions observed were due to *Euphorbia dracunculoides* and not of *Ruta graveolens Linn.* and caused because of mis-identification.

Table: Comparative study of Ruta graveolens Linn and Euphorbia dracunculoides Lam (7)

Ruta graveolens Linn	**Euphorbia dracunculoides Lam**
Belongs to Rutaceae family	Belongs to Euphorbiaceae family
A small branching perennial under shrub, 45 cm-90 cm, having strong disagreeable odour and bitter-acrid pungent taste, the odour being persistent in dry specimens	A dichotomously much branched annual herb 20-40 cm high, no odour, exudes milky juice from the broken surface of the branches of fresh plants
Cultivated especially in garden (all over India) for ornamental & medicinal purpose	Grows wild as a weed usually in wheat and gram fields
Leaves 2-3 pinnatisect, dark green in colour in fresh plants covered with ashy bloom	Leaves simple, alternate, sessile, linear, lanceolate or linear oblong, 17mm to 7cm long & 2-8mm width
Flowers 4 merous, yellow in terminal corymbs	Inflorescence, a cyathium each consisting of a cup-shaped involucres
Fruits a 5 lobed many seeded capsule dehiscing at the apex	Fruits a trilocular, 3 seeded pubescent, indehiscent capsule 3-4mm in diameter
Seed many in each lobe concave at one margin and at the other, testa blackish in colour	Seeds 3 mm, long ellipsoid rounded at the base, grooved down one side with an arillode at the oblique depressed apex, testa whitish, rugose
Market sample consist mainly of the broken (a few intact) pinnules and young twigs bearing peduncles, capsule scattered here and there comparatively fewer	Market samples consist of the broken parts of the whole plant (roots fewer), greater in number are the stem, leaves and fruits

Discussion

The herbal drugs of ISM can be put in better use as therapeutic agents, if it is genuine, and of good quality. Not all but many are adulterated &/or of low standard. The adulteration may extend its limit & replace the original plant. Traders (dispensers/attar) collect the medicinal plants from forests by employing the unskilled and untrained plant collectors, who has one object, i.e., to collect more & more plants to earn more & more money, due to that the spurious & adulterated drugs are obtained. Sub-standard drug is another problem since traders also not considering prescribed pharmacopoeias methods of preparation, drying & storage. Other problems are of botanical identity of different drugs. Two or more plants are known by the same indigenous names, or two or more indigenous drugs are mentioned under the same botanical name.

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A Case Report on Nimesulide and Its Relation with Angina

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Introduction

When a new drug is licensed, its adverse effects are incompletely known, because only a limited number of healthy volunteers and highly selected patients have taken it. Thus, efficient postmarketing drug surveillance is needed, but unfortunately such surveillance does not exist or is inadequate in India. Nimesulide recently came under attack in India, when a paediatrician at the prestigious hospital in New Delhi, reported two deaths in children associated with the use of the drug (1)

Nimesulide (4-nitro—2 phenoxymethane sulphonamide), which is a nonsteroidal anti-inflammatory drug, has been available in the Indian Market since 1997 for its antipyretic and anti-inflammatory activity. None of the reports in medical literature indicate its superior efficacy as antipyretic as compared to paracetamol and anti-inflammatory compared with other drugs of this class such as diclofenac and piroxicam. Numerous studies have established the life threatening adverse events with nimesulide such as hepatotoxicity (2), renal toxicity, severe skin reactions including fixed eruptions, gastrointestinal toxicity, potentiation of seizures, potentiation of colitis in passive cigarette smoking (3). A plethora of scientific data shows that nimesulide should not be used as the primary mode of treatment as an antipyretic or analgesic, when much better and safer choices are available (4). No rationale exists for selecting nimesulide as the first drug of choice for fever or pain. Nimesulide is not used in the United States, Finland, Spain, Portugal and Israel. These countries have withdrawn the pediatric nimesulide formulation. The drug was never licensed for use in Canada, Britain and Australia.

The continuing use of nimesulide in Indian patients is appalling. Published studies from India indicate rampant abuse of nimesulide. Barring few, no dependable post-marketing surveillance for adverse drug reactions is undertaken in India. Moreover, unlike in the West, Indian doctors are not under any real supervision and therefore do not necessarily keep up with the rapidly changing information about adverse effects. Patients receiving nimesulide should be closely monitored for evolving any serious reactions. Indian patients may not follow necessary guidelines, for simple economic reasons.

Case Report

'Spontaneous Reporting' in Pharmacovigilance is a process of data acquisition, assessment, presentation and interpretation. The provision of information i.e. of interpreted data concerning previously unknown, or otherwise important adverse drug reactions is a major goal (5). Although, uncertainty in case reports regarding the involvement of the suspected drugs together with under-reporting are an inherent drawbacks of spontaneous reporting, but, confirmation of the connection between a drug and an adverse reaction requires case reporting along with analytical or experimental study. Even though there might be several cases of NSAIDs induced coronary artery insufficiency (CAI) that are not being reported, on the contrary we could

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find a definite case of Nimesulide induced Coronary Artery Insufficiency.

A 65-year-old female patient of average built, 152 cm height, 45 Kg weight was a known case of diabetes mellitus for the last 17 years and angina pectoris for the last 10 years. For the above problem, she was maintained on Tab Daonil (Glibenclamide) 5 mg once a day, Tab Glyciphage (Metformin) 500 mg twice daily, Tab Metoprolol 50 ,mg twice daily, Tab Monotrate (Isosorbide-5-mononitrate) 20 mg once daily, Tab Disprin (Acetylsalicylic acid 350 mg + Calcium carbonate 105 mg) one-fourth tablet once a day. She was also in habit of taking Isapghol & Tab Dulcolax (Bisacodyl) 5 mg off and on because of chronic constipation. Life for this patient was going well when she sustained injury after felling down. After consultation from an Orthopedic Surgeon, she was exposed to X-ray for wrist joint and found Colles fracture. For which she was advised *plaster of paris*, finger exercises and Tab Nimesulide 100 mg twice daily along with ongoing treatment. On third day, she felt chest pain (angina) for which she used Tab Sorbitrate 3-4 times a day as told to her previously to use it in emergency condition, but, the problem persisted and no improvement was noticed. By noticing no improvement, she consulted her family physician. On examination, she was found anxious and tired. She had no cyanosis, pallor or pedal edema. Jugular venous pressure was not raised, no lymphadenopathy was found, however, BP was 170/100 mmHg; respiratory rate was 20/min; pulse rate 80-90/min, regular and good volume with occasional extra beats, normal vesicular breathing with fine crepitations and no other added sounds; heart sounds were normal and no murmur; other examination revealed no hepatosplenomgaly or ascites. ECG showed changes of ischemia and extra systoles but no changes of infarction. The patient was diagnosed as a case of Unstable Angina and advised to stop suspected drug nimesulide but continue to take previous treatment. The patient then showed improvement in angina clinically. As an alternative for pain and inflammation, Tab Brufen (Ibuprofen) 400 mg thrice daily was advised by the same doctor. The patient afterwards complained no problem in relation to chest pain with Tab Brufen.

Conclusion

Naranjo ADR Probability Scale Evaluation (6), when assessed the likelihood of reaction CAI with nimesulide gave an idea about a score of 3. Hence "Use of the Naranjo ADR Probability Scale indicated a 'possible' relationship between the adverse effect (CAI) and (Nimesulide) therapy in this patient." Similarly, WHO Causality Categories (7) when evaluated also confirms its 'possible' link. In this case, the unstable angina precipitated by nimesulide appears to be due to coronary artery spasm and not due to any clot because on withdrawing the suspected drug nimesulide, there was rapid relief from angina. The coronary artery spasm seems to be related to inherit properties of nimesulide molecules and not due to prostaglandin (PG) synthesis inhibition as Brufen (a potent PG Inhibitor) did not cause the same symptoms. Alternatively, the coronary spasm may be due to an imbalance caused between COX 1 and COX 2 activities due to preferential COX 2 inhibition by nimesulide. Moreover, the inhibition of PG synthesis may adversely affect cardiovascular homeostasis (8,9). Further pharmaco-epidemiological research is needed to quantify the risk for angina pectoris attributable to the use of nimesulide and to identify patients who are particularly susceptible to the adverse cardiovascular

effects of these agents. In these patients, it may be advisable to avoid the use of nimesulide.

Nevertheless, adverse reactions on cardiovascular system with nimesulide have not yet been reported but literature review suggests the risk of cardiovascular events associated with selective COX-2 inhibitors like celecoxib and rofecoxib. The most commonly reported events were heart rate and rhythm disorders, increased BP, congestive heart failure, myocardial infarction, cerebrovascular events and thrombo-embolic events (10). A study evaluated the relative expression and immunoreactive levels of COX-1 and COX-2, in the renal cortex and medulla of rats with congestive heart failure. The same study also revealed upregulation of medullary COX-2, but not of COX-1, in rats with advanced heart failure (11). Authors believe that COX 2 may be up regulated as compensatory mechanism in advanced heart disease and the inhibition of compensatory mechanism may further deteriorate the condition.

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Amlodipine and Its Associated Adverse Symptoms

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Calcium Channel Blockers

The main use of Calcium Channel Blockers (CCBs) is in the management of angina pectoris and hypertension; some are also employed in cardiac arrhythmias. CCBs, also known as calcium antagonists, calcium-entry blockers, and slow-channel blockers, inhibit the cellular influx of calcium which is responsible for maintenance of the plateau phase of the action potential. Thus CCBs primarily affect tissues in which depolarisation is dependent upon calcium rather than sodium influx, and these include vascular smooth muscle, myocardial cells, and cells within the sino-atrial (SA) and atrioventricular (AV) nodes. The main actions of the calcium-channel blockers include dilatation of coronary and peripheral arteries and arterioles with little or no effect on venous tone, a negative inotropic action, reduction of heart rate, and slowing of AV conduction. However, the effects of individual drugs, and therefore their uses, are modified by their selectivity of action at different tissue sites and by baroreceptor reflexes.

CCBs may be classified according to their chemical structure. There are three major groups that are highly specific blockers of calcium channels.

1. Dihydropyridine CCBs (such as nifedipine) have a greater selectivity for vascular smooth muscle than for myocardium and therefore their main effect is vasodilatation. They have little or no action at the SA or AV nodes and negative inotropic activity is rarely seen at therapeutic doses. They are used for their antihypertensive and anti-anginal properties. Some dihydropyridine derivatives, for example nimodipine, cross the blood-brain barrier and are used in cerebral ischaemia.
2. Benzothiazepine CCBs (such as diltiazem) and phenylalkylamine calcium-channel blockers (such as verapamil) have less selective vasodilator activity than dihydropyridine derivatives; they have a direct effect on myocardium causing depression of SA and AV nodal conduction. They are used for their antiarrhythmic, anti-anginal, and antihypertensive properties.
3. These drugs act principally on fast T-type calcium channels unlike conventional CCBs that act on slow L-type channels. Mibefradil is an example of a T-type CCB but it is no longer used clinically due to serious interactions with a wide range of drugs.

Adverse Effects of CCBs

Following adverse events with CCBs are reported in Physician's Desk Reference (1):

Body as a Whole: Fatigue, allergic reaction, asthenia, back pain, hot flushes, malaise, pain, rigors, weight gain, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia.

Central and Peripheral Nervous System: Hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo, Insomnia,

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nervousness, anxiety, tremor and decreased libido.

Dermatologic: Flushing, hot flashes, rash, skin nodule and dermatitis.

Gastrointestinal: Anorexia, constipation, dyspepsia, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia, dry mouth, nausea, abdominal pain, constipation and esophagitis.

Metabolic and Nutritional: Hyperglycemia, thirst and hypokalemia.

Respiratory System: Dyspnéa, epistaxis and pharyngitis.

Urinary System: Micturition frequency, micturition disorder, nocturia and sexual problems such as impotence polyuria.

Cardiovascular: Arrhythmia (including ventricular tachycardia, atrial fibrillation, pulse irregularity and extrasystoles), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis, cardiac failure.

Musculoskeletal: musculoskeletal pain, Back pain, cramps, and muscle cramps, arthralgia, arthrosis and myalgia.

Psychiatric: sexual dysfunction (male and female), depersonalization, abnormal dreams, insomnia, nervousness, depression and anxiety

Skin and Appendages: erythema multiforme, angioedema, pruritus, rash including rash maculopapular and rash erythematous), skin discoloration, alopecia, urticaria, skin dryness and dermatitis.

Special Senses: abnormal vision, eye pain, conjunctivitis, diplopia and tinnitus.

Autonomic Nervous System: dry mouth, sweating increased.

Hemopoietic: leukopenia, thrombocytopenia and purpura.

Other infrequently reported events were seen in clinical trials (causal relationship unlikely) or in postmarketing experience. These included chest pain, ventricular extrasystoles, gout, neuritis, tinnitus, and alopecia. Martindale (2) described only the following side-effects as common: ankle oedema, flushing, headache, skin rash and fatigue.

Adverse Effects with Amlodipine

A study to compare in the non-blind randomised parallel, the efficiency of quadropril and amlodipine in the treatment of mild to moderate arterial hypertension was done. Both quadropril and amlodipine demonstrated a comparable antihypertensive effect although in 11 of 40 patients in the amlodipine group a dose increase was necessary and tolerability of quadropril was better. The authors also noticed some side effects significantly more often in the amlodipine group, then in the quadropril group. The main quadropril side effect was cough. Side effects observed in the amlodipine group were edemas, tachycardia, and weakness. (3). Dizziness and weakness occurred in one patient when amlopdine in a dose of 5 mg OD and 10 mg OD (after 2 weeks) was given in 20 patients with mild, moderate, and severe hypertension over a 10 week period (4). Phillips BB et al. documented a case of severe, progressive myopathy, myalgias, arthralgias, and weakness by amlodipine in a patient with benign essential hypertension (5). The safety profile of amlodipine was assessed from the

pooled data base of clinical research studies. This data base included 4227 subjects, 2495 of whom received amlodipine; the remainder received comparative agents. Amlodipine treatment was associated with a slightly higher incidence of side effects compared with placebo, but most of this difference was the result of edema, which was usually well tolerated. When compared with the beta-blockers atenolol and nadolol, amlodipine had a favorable safety profile. In particular, the incidence of severe side effects in patients receiving amlodipine was approximately half that reported for patients receiving beta-blockers. The data base comparing different calcium antagonists was small; in a study versus verapamil, edema was more common in patients receiving amlodipine, but constipation was more common in patients receiving verapamil. In a study versus diltiazem, both amlodipine and diltiazem were similarly well tolerated. Amlodipine was not associated with the deleterious effects of serum creatinine, urate, and fasting glucose, which was caused by hydrochlorothiazide, and in contrast to hydrochlorothiazide and nadolol, amlodipine was not associated with unfavorable changes in serum cholesterol and serum triglyceride levels. Amlodipine was well tolerated by elderly patients and is not contraindicated in patients with conduction abnormalities. Dosage modifications are unnecessary in renal impairment, but the dosage regimen for patients with hepatic impairment is not yet established. Amlodipine is an antihypertensive and antiischemic agent that has the combined advantages of a good safety profile with once-daily dosage and a smooth onset and long duration of action (6). Despite a therapeutic plasma concentration of amlodipine, there was no change in resting heart rate or blood pressure. Amlodipine did not cause significant change in oxygen uptake at the anaerobic threshold or at maximum exercise and there was also no change in heart rate or catecholamine responses. Although there was an awareness of peripheral vasodilatation and reports of lethargy during the active treatment period, the volunteers had no objective evidence of a decrease in cardiopulmonary performance (7).

Cases of adverse effects with Amlodipine in Aligarh

Amlodipine is used in controlling high blood pressure. The drug (like Amlopress) is commonly prescribed in Aligarh by all physicians. Thorough pharmacovigilance study conducted at some hospitals in Aligarh, adverse drug reactions of amlodipine were monitored. Out of many patients in two year study, five patients developed adverse reactions viz. weakness in limbs, lethargy, tiredness, difficulty in walking long distances and aching in limbs muscles. Two of them simultaneously developed oesophageal reflux (Table 1). In all patients BP was controlled. Dechallenge was positive in all patients. Rechallenge was not attempted. Alternative treatment was provided to all these patients after noticing the above reactions with amlodipine.

Table 1: Data of 5 patients who developed adverse reactions viz. weakness in limbs, lethargy, tiredness, difficulty in walking long distances and aching in limbs muscles

Age	Sex	Duration of Treatment	Gastro esophageal Reflux
74	M	3 Months	Present
54	M	One year	
58	M	2 Months	Present
52	F	One & half year	
54	M	15 Days	

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Are all new drugs 'healthy'?

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The race for the launch of new drugs, brands and combination drugs has resulted in nearly 50-80 new entries in the market in the year 2002 alone. Is it 'healthy' to have such a flooding of the market with new drugs? Do these new drugs really have benefits over their older congeners as most of them claim to have? To answer these questions, we need to look at two important aspects in the field of new drug marketing: safety and claims of superiority.

Safety of new drugs

The health sector is faced with the issue of safety of all new drugs. In the present system, before a new drug is introduced into the market, it is mandatory to go through different stages of laboratory and clinical trials. These are aimed at establishment of therapeutic efficacy as well as the safety profile of the new drug. The various phases of the clinical trial are (1):

Phase I trials test the drug on a sample of 25-50 healthy volunteers to establish its safety. Phase II trials test 50-300 patients for the drug's therapeutic effect. In Phase III trials, between 250 and 1,000 patients participate in a randomized clinical trial comparing the drug with a placebo to confirm the drug's efficacy. Phase IV 'trials' are post-marketing surveillance of the drug's safety in the general population and can cover between 2,000 and 10,000 people.

From these figures, one can see that the number of people actually exposed to the drug in the first three phases are few (a maximum of 1,350). If there are no serious adverse effects at this point, the drug is approved for marketing.

Is a number of 1,350 enough to detect a rare adverse effect? Let us examine this issue by looking at the following situation: In a case where the adverse drug reaction to a particular drug has an incidence of 1 in 1,000 (occurs in 1 patient out of 1,000 treated), we would need to screen a minimum number of 3,600 patients for the confirmation of its absence (2).

As 3,600 people are usually not involved in the first three phases of a clinical trial, it is possible that a drug with a rare but fatal adverse reaction could be used by the general population. The process of monitoring for safety should thus continue. This monitoring is done in Phase IV, termed as 'post-marketing surveillance'. The spectrum of adverse effects of any drug range from the common (detected during these trials and documented), to the rare (unidentified in early studies and yet important). It is these rare side-effects, usually undocumented in trial settings, which may subsequently have serious consequences for the population taking that drug. This makes the post-marketing surveillance an even more important tool to get the entire spectrum of the drug's activity.

It takes some time before such large numbers of patients get treated and observed. Thus, we see a delay of many years before such significant reactions are reported. The risk of 1 in 1,000 went undetected for 3-7 years in the following instances: pulmonary embolism due to oral

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Courtesy: <http://www.issuesinmedicalethics.org/121di015.html>

contraceptives, halothane-induced jaundice, lincomycin-induced colitis (2).

In many occasions, the incidence of a potentially fatal adverse reaction may be smaller than this. This therefore means that it may be even more difficult to detect them in the population and would need a larger number of patients on the drug, and a more intensive surveillance programme.

There are a few other issues to be highlighted regarding post-marketing surveillance. The first issue, that of who conducts the surveillance and who are the subjects, is an important one with respect to its credibility. In most of the cases, these are conducted by pharmaceutical companies, and therefore the issue of potential bias comes into play. The other aspect is that the surveillance done in western countries for adverse effects is often extrapolated to the Indian population. Considering the genetic differences as well as diet and nutrition, the extrapolation of such reports may not give the true picture in the Indian setting.

Claims of superiority

Post-marketing surveillance is not only about reporting adverse effects. It is also done to see the performance of these drugs as compared to the existing ones. Often, doctors are exposed to various claims of pharmaceutical companies that their drug is 'superior' to existing drugs, with the standard phrase being 'the initial results are very promising'. Hence, it is essential to consider the factors affecting the feedback from the case reports of patients receiving any new drug. One of the most important factors emerges when post-marketing surveillance is subject to an effect called the Weber Effect (3). This phenomenon, first described by Dr Peter Weber, denotes the combined effects of rapid increase in the use of, and interest in, a new drug, leading to a high rate of reporting. However, comparisons with older drugs with stable reporting can be misleading. Therefore, both the general over-reporting, for the new drug, combined with the Weber Effect, should be considered when comparing new drugs with drugs already existing in the market.

A possible solution

In the Indian scenario, general practitioners, with an outpatient base and limited facilities for adverse drug reaction (ADR) monitoring tend to be among the first ones to use these 'latest' drugs. Even the patients seem to prefer these 'new' drugs for their treatment without realising the risk that they are putting themselves through.

The solution to most of the above problems associated with the use of new drugs can be derived from the example of the policies of the Japanese health ministry (4). In their set-up, the pharmaceutical companies are required to provide their product to a limited number of medical institutions for a period of three months following the launch of a product and conduct focused post-marketing surveillance. After inspection of the results of this surveillance, the companies are then allowed to expand the number of medical institutions using the product. Requiring companies to limit sales to a small number of medical institutions and collecting information in this way makes it easier to respond to adverse drug reactions of newly approved products. It needs to be examined whether this practice can be transcribed to the Indian situation.

It is imperative that the drug control authorities and other governmental agencies strengthen the post-marketing surveillance programme in India. They need to look at ways of minimising risk to the population

due to rare adverse events when new drugs are introduced into the market. Any doctor or hospital, when deciding on the use of a new drug, should objectively compare it to the existing drugs. A balanced judgement needs to be made without blindly following the tall claims of superiority made by drug manufacturers.

In conclusion, an awareness of the importance of post-marketing surveillance is the need of the hour, at all levels, whether it be the government, the health professional or the patient. An official surveillance programme needs to be initiated and subsequently evaluated. Till then the question remains, 'Are all new drugs 'healthy'?'

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Environ Ministry for post-marketing surveillance of rDNA drugs

The Genetic Engineering Approval Committee (GEAC) under Ministry of Environment and Forests, Govt. of India is likely to bring in more stringent systems for post-marketing adverse drug reaction (ADR) monitoring of recombinant drugs in the country. The regional offices of the environment ministry, on whose recommendations the revalidation of genetically modified drugs and therapeutics are considered, would soon be empowered to seek expert help from outside the ministry for monitoring any possible ADRs of such drugs that are in the market. Informed sources hinted that the GEAC is to propose such a change in view of the growing use of recombinant drugs against many life-threatening diseases in the country.

Adverse drug reactions to alternative medicines have more than doubled in three years: New WHO guidelines to promote proper use of alternative medicines

The United Nations World Health Organization (WHO) on 23rd June 2004 announced the publication of guidelines aimed at helping countries and consumers navigate the largely unregulated world of alternative medicines. The United Nations World Health Organization (WHO) announced the publication of guidelines aimed at helping countries and consumers navigate the largely unregulated world of alternative medicines.
(www.who.int/mediacentre/releases/2004/pr44/en)

Up to 80 per cent of all people in the developing world rely on traditional medicine for their primary health care, according to (http://www.who.int/en/) WHO. In wealthy countries, many people seek out various types of natural remedies on the assumption that natural means safe. But reports of adverse reactions to these treatments are on the rise. "WHO supports traditional and alternative medicines when these have demonstrated benefits for the patient and minimal risks," WHO Director-General Dr. Lee Jong-wook said. "But as more people use these medicines, governments should have the tools to ensure all stakeholders have the best information about their benefits and their risks."

However, as the use of traditional or alternative medicines increases, so do reports of adverse reactions. In China, a country where traditional therapies and products are widely used in parallel with conventional medicine, there were 9 854 known reported cases of adverse drug reactions in 2002 alone, up from 4 000 between 1990 and 1999.

Many traditional/alternative medicine products are sold over the counter. In a WHO survey of 142 countries, 99 responded that most of these products could be bought without prescription. In 39 countries, many traditional remedies were used for self-medication, bought or prepared by friends, acquaintances or the patient. These trends raise concerns over the quality of the products used, their therapeutic appropriateness for a given condition, and the lack of medical follow-up.

Accessible, easy to understand information is key to guiding consumers in their choices. The guidelines provide simple, easy to follow tips on issues to look out for and a brief checklist of basic questions which may be used to help facilitate proper use of traditional and alternative medicine. Advice

is provided to government authorities on preparing easy-to-access information and on working with the mass media to sensitize and educate the population. In addition, suggestions are given for several health system structures and processes needed to promote proper use of traditional and alternative medicines. While the guidelines cannot compensate for poor products or inappropriate practices, they can help govts educate consumers on how to maximize the benefits and minimize the risks of traditional medicines. For more details go to UN News Centre at www.un.org/news

Alternative therapies - documented benefits and risks

Empirical and scientific evidence exists to support the benefits of acupuncture, manual therapies and several medicinal plants for chronic or mild conditions. For instance, the effectiveness of acupuncture, a popular treatment for relieving pain, has been demonstrated both through numerous clinical trials and laboratory experiments. As a result, 90% of pain clinics in the United Kingdom and 70% in Germany include acupuncture as a form of treatment. Equally, some medicinal plants have shown efficacy for life-threatening conditions; medicine combinations containing the Chinese herb Artemisia annua are now considered amongst the most effective remedies against malaria. However, there have been many cases of consumers unknowingly using suspect or counterfeit products; choosing inappropriate therapies in self-care; as well as several reports of unintentional overdose.

Similarly, there have been reports of consumers being injured by unqualified practitioners. For example, a study performed by the National Research Institute on Complementary and Alternative Medicine in Norway reported cases of pneumothorax caused by unqualified acupuncturists. In addition, there have been reports of paralysis caused by unqualified manual therapists.

Another potential risk is that patients do not inform their doctors about their use of traditional and complementary medicines. For instance, Ginkgo biloba is a popularly used herbal medicine worldwide whose main function is to prevent vascular disease and to increase blood circulation. The WHO Uppsala Monitoring Centre reported some cases of excess bleeding during a surgical operation. If the patient had informed the doctor about the use of the medicine this could have been avoided.

The development of the guidelines was carried out with the financial and technical support of the Regional Govt of Lombardy, in collaboration with the State University of Milan. The guidelines are based on evidence and experiences collected from 102 countries representing all WHO regions.

Summary of highlights: Policies Govts. could put in place

1. Make sure that sufficient information is provided to consumers on the efficacy and safety of products as well as contraindications.
2. Set up the right channels for consumers to report adverse drug reactions and make those channels known.
3. Organize communication campaigns to equip consumers with the ability to discern the quality of the service they receive.
4. Ensure that practitioners are appropriately qualified and registered.
5. Encourage interaction between traditional & conventional practitioners.

6. Provide insurance for non-conventional therapies and products whose evidence base is sound.
7. Health system structures and processes that would help promote better quality and safety.
8. Development of quality standards and treatment guidelines to ensure uniformity within a particular health system.
9. Standardization of training and knowledge requirements for practitioners to promote the credibility of traditional or alternative practices and enhance consumer trust Collaboration between conventional and traditional or complementary care providers to improve results of treatment but also promote health sector reform Organization of traditional or alternative medicine practitioners to provide better structures for self-control mechanisms.

Questions consumers should ask

1. Is the therapy suitable for his/her disease or condition?
2. Does the therapy have the potential to prevent, alleviate and/or cure symptoms or in other ways contribute to improved health and well-being for the consumer?
3. Is the therapy or herbal medicines provided by a qualified traditional medicine / complementary & alternative medicine practitioner (TM/CAM) or health care practitioner with adequate training background, good skills and knowledge, preferably registered and certified?
4. Are the herbal medicinal products or materials of assured quality and what are the contraindications and precautions of the products or materials?
5. Are the therapies or herbal medicinal products available at a competitive price?

Forthcoming Conferences on Pharmacovigilance

4th Annual Conference of Society of Pharmacovigilance, India
22-23 January 2005, Bareilly, India
Organisers / Contact: Department of Pharmacy, MJP Ruhelkhand University, Tilbit Road, Bareilly, India
Tel: +91-581-2523745 / 2527900

Compliance in Pharmacovigilance
8-9 July 2004, London, UK
Organizers / Contact: DSRU.
Tel: +44(0)23 8040 8621.
Fax: +44(0)23 8040 8605.
Email: jan.phillips@dsru.org

World Conference on Dosing of Anti-infective
September 6 to 11, 2004, Numberg-Heroldsberg, Germany
Organizers / Contact: Conference Secretariat, WCDA c/o IBMP, Paul-Ehrlich-Str. 19, 90562.
E-mail: mail@ehrlich2004.org
Web: www.ehrlich2004.org

20th Intl. Conf. on Pharmacoepidemiology & Therapeutic Risk Management
22 – 25 August 2004, Bordeaux, France
Organizers / Contact: International Society of Pharmacoepidemiology. Tel: +1 (301) 718 6500
Fax: +1 (301) 656 0989
E-mail: ispe@paimgmt.com

ISoP Annual Scientific Meeting
6-8 October 2004, Dublin, Ireland
Organizers / Contact: ISoP Administration.
Tel/Fax: +44 (0)20 8286 1888
Web: www.isoponline.org

II Congreso Internacional de Farmacologia & Terapeutica
12–15 October 2004, Havana, Cuba
Organizers / Contact: Cubatour SA. Fax: +53 7-336471.
E-mail: opc_eventos@cbtevent.cbt.tur.cu

Risk Benefit Assessment in Pharmacovigilance
13-14 October 2004, Southampton, UK
Organizers / Contact: DSRU.
Tel: +44(0)23 8040 8621.
Fax: +44(0)23 8040 8605.
Email: jan.phillips@dsru.org

Medical Approach in Diagnosis and Management of ADRs 2004
14-15 October 2004, Paris, France
Organizers / Contact: DIA.
Tel: +41 61 225 5151.
E-mail: diaeurope@diaeurope.org
www.diahome.org

Workshop on Case Narrative Writing for Reporting Adverse Events
11-12 November 2004, Southampton, UK
Organizers / Contact: DSRU.
Tel: +44(0)23 8040 8621.
Fax: +44(0)23 8040 8605.
Email: jan.phillips@dsru.org

V Jornadas de Farmacovigilancia
12-13 November 2004, Barcelona, Spain
Organizers / Contact: Institut Catala Farmacologia. Tel: +34-93 428 3029
Fax: +34-93 489 4109. E-mail: xp@icf.uab.es

Data Safety Monitoring Boards & Data Review Committees
24 November 2004, London, UK
Organizers / Contact: DSRU.
Tel: +44(0)23 8040 8621.
Fax: +44(0)23 8040 8605.
Email: jan.phillips@dsru.org

Hot Topics in Pharmacovigilance
29-30 November 2004, Paris, France
Organizers / Contact: DIA.
Tel: +41 61 225 5151.
E-mail: diaeurope@diaeurope.org
www.diahome.org

Pharmacovigilance training course - The Study of Adverse Drug Reactions' in association with the UMC.
8-19 November 2004, Canberra, Australia
Organizers / Contact: The national Pharmacovigilance centre, Therapeutic Goods administration, Australia

The 10th International training course 'Pharmacovigilance - The Study of Adverse Drug Reactions'
23 May to 3 June 2005, Uppsala, Sweden
Organizers / Contact: Uppsala, Sweden

3rd Annual Conference of Society of Pharmacovigi.ance, India – A Report

The third national conference of Society of Pharmacovigilance, India was held under the president-ship of Prof. K. C. Singhal at Hotel Howard Park Plaza during 11-13 December 2003. The organizing secretary was Dr. Sandeep Agarwal, a renowned oncologist of Agra

In 1998, an idea was mooted out during the International Workshop on Adverse Drug Reaction Monitoring to establish Pharmacovigilance as a distinct and influential clinical discipline in India. To give shape to this idea, a meeting of interested scientists took place at Lucknow at the time of the annual conference of Indian Pharmacological Society. Some decisions were taken at the meeting and as a follow up, action application was submitted under the Societies Registration Act XXI of 1860. Prof. K. C. Singhal of Aligarh drafted the Memorandum of Association for the Society of Pharmacovigilance, India (SOPI). The first meeting of the society was held in 1999 at Agra. At present, SOPI is the only single national society in the entire world which is associated with International Society of Pharmacovigilance - ISoP (Earlier European Society for Pharmacovigilance). In addition to the office bearers and executive members, the society is a component of 160 life-members.

In spite of the fact that Pharmacovigilance is a new discipline in India, even then 75 participants registered themselves for the 3rd Annual Conference as delegates including 13 foreign delegates: Prof. Ralph Edward (Sweden), Prof. Chris J van Boxtel (Holland), Prof. Peter I Folb (South Africa), Prof. John Autian (USA), Dr. Alex Dodoo (Ghana), Dr. P. Galappathy (Sri Lanka), Dr. P. C. Nani Ijeoma (Nigeria), Prof. Roy Jobson (South Africa), Mrs. Marje Jobson (South Africa), Prof. M. Arifulla (UAE), Dr. Rajen Mishra (South Africa), Dr. Ms. Cecilia Biriell (Sweden) and Mr. Geoffrey Bowring (Sweden). Inaugural Session was started with "Welcome Address" by the Vice-Chancellor of Agra University followed by Presidential Address by Prof. K. C. Singhal. The chief guest Prof. Ralph Edwards (Director, WHO Collaborating Centre for ADR Monitoring, Uppsala, Sweden) delivered the inaugural address, while Prof. John Autian (Dean Emeritus and former vice chancellor, University of Tenesses, Memphis, USA) released the souvenir.

Prof. K. C. Singhal in his presidential address emphasized on the need of concerted efforts for organized activities of Pharmacovigilance. Monitoring is needed for adverse drug reactions (ADR), medical devices, drug abuse, counterfeit drugs and for medical errors. He informed that 85,000 pharmaceutical formulations in India poses even greater problem in monitoring ADR. Large number of drugs available in the market is unethical and is being promoted by industry and drug control regulators. Prescription drugs are available without prescription, responsible for drug-induced reactions. He emphasized the need to dissociate the hazards caused from the abuse factors from the medical negligence and to revamp laws and judicial panel for alleged negligence against physicians. Prof. John Autian emphasized that ADR Monitoring Center and Poison Centres should jointly be established in every medical institution and the findings and observations be published in newsletters and journals. Prof. Edwards emphasized the need for rational drug therapy, approaching poor population for providing effective medical care, conducting research and finding usefulness of TCMs in comparison with drugs of modern systems of medicine.

The John Autian Oration was delivered by Prof. Chris J van Boxtel who spoke on Artemisia and Artemisin: a story about toxicity (published recently in Uppsala Report 25, April 2004). Other deliberations of the conference were held in many sessions including symposium on vaccine safety (sponsored by Serum Institute of India). Prof Peter Folb spoke on vaccine and immunization. Other eminent speakers were Dr. M. P. Bansal (CMO, Aligarh), Dr. Subodh Bhardwaj (Pune) and Dr. Rakesh Bhatia (Agra). It brought together officials from national governments and international organizations like WHO ollaborating Centre for International Drug Monitoring, academia, research institutes, public

health and private pharmaceutical industries and others to discuss possible mechanisms for global cooperation in raising the importance of Pharmacovigilance, and increasing the transparency of such efforts, as well as fulfilling global obligations to facilitate technology transfer. During the meeting, possible legal frameworks to enhancing global cooperation on ADR Monitoring were discussed. Overall, the deliberations aroused interest in participants and very useful discussions took place especially with experts from WHO. The discussions were held in a friendly and healthy environment.

Pharmacovigilance is a new and emerging discipline. It is relatively more new to India. Limited number of physicians, pharmacists and faculty members in medical colleges has awareness about the methodologies and activities in the field of Pharmacovigilance. Pharmacovigilance activities should be carried out in coordinated manner under the auspices of Government agencies, apex hospitals and Society of Pharmacovigilance, India. Collaboration should be sought from WHO Centre for Adverse Drug Reaction Monitoring Uppsala, Sweden at levels other than National Centres to facilitate ADR monitoring and reporting. ADR Monitoring and other aspects of Pharmacovigilance should form a part of curriculum for medical undergraduate students, pharmacy and postgraduate medical students (MD/MS).

Regional Centres should be established for Pharmacovigilance activities. The main activities of these centres should be ADR Monitoring, Error Monitoring, Poison Information and to promote Rational Drug Therapy. General practitioners and specialists in private practice be involved in Pharmacovigilance activities. Recently, Central Drugs Standard Control Organization (CDSCO), an establishment of Directorate General of Health Services, Ministry of Health & Family Welfare, has initiated a Pharmacovigilance project across the country. This project will envisage setting-up peripheral, regional and zonal Pharmacovigilance centers for spontaneous as well as drug specific adverse drug event monitoring and causality analysis.

Overall the programme was highly educative and useful in updating knowledge of pharmacologist, pharmacists, General / Specialist practitioners, Academicians, medical teachers and consultants. It was very well organized. All delegates including foreign one were very happy and satisfied with all scientific sessions.

Following major decisions were taken during General Body Meetings on 12.12.2003:

1. The house approved the previous minutes of the 2nd Annual Meeting held at VP Chest Institute, New Delhi.
2. The house approved the Treasurer, Secretary and Editors's Report.
3. The house elected following members as the office bearers' of the society: Prof. K. C. Singhal (Aligarh) – President; Prof. N. S. Parmar (Gandhinagar) & Prof. A. Ray (Delhi) - Vice-Presidents; Dr. Sandeep Agarwal (Agra) - Gen. Secretary; Dr. Pipasha Biswas (UK) - Secretary Intl. Affairs; Dr. Govind Mohan (Agra) – Treasurer; Dr. Syed Ziaur Rahman (Aligarh) – Editor; Dr. A. K. Kela (New Delhi), Dr. Geeta Sharma (Amritsar), Dr. Barna Ganguly (Karamsad) and Dr. Anil Kumar (Rohtak) - Members, EC.
4. The fourth annual conference of SOPI will be held either at Ahmedabad or Bareilly.

A Tribute and Recollection of Professor N. S. Parmar

(Prof. N. S. Parmar was the Vice-President of the Society of Pharmacovigilance, India. During the 3rd annual conference of SOPI which was held in Agra from December 11-13, 2003, he proposed to organize the 4th annual conference in Ahmedabad. But unfortunately he died just 2 months after this announcement. His dedication for the society is exhibited when we look back the e-mails he started writing for the preparation of the 4th annual conference. Although, he won't be present during the 4th annual conference, but his presence will be felt by all of us. We are grateful to Dr. Venkat Gopal (Canada) for contributing the following obituary on our request – Editorial Staff)

It was a great shock to all of us to receive the news that Professor NS Parmar reached the Heavenly Abode on Thursday February 26, 2004 at 13.55 Hrs while delivering a lecture at the Institution he founded as its Founder Director.

I met Dr. Parmar as a student in the year 1972 who taught us the fundamentals - ABC of Pharmacology along with Professor M. N. Ghosh. I still remember when Dr. Parmar simply printed on the board - particularly every sentence of the notes on the Classification of Antihypertensive. Today, we do not use some of them (reserpine, alpha-methyl Dopa, guanethidine) while diuretics continue to stay and its importance is emphasized by major clinical trials in the world. Thus, the fundamental knowledge Dr. Parmar provided us gave us the basis to advance in our careers. I do recollect Dr. Parmar as I present my class room lectures here or when I give out my slides at invited seminars at many Universities talking about the new classes of agonists that may decrease total peripheral resistance.

It was Parmar who took on his shoulders the task of bringing the Editorial office of the Indian Journal of Pharmacology (IJP) to JIPMER and ran it efficiently with very minimal budget. While at JIPMER he carried on multi-variate roles that involved Hospital Pharmacy management to maintaining the Editorial office of the IJP. This was besides being an efficient teacher.

His work on bioflavanoids has set a new trend and currently many Pharmaceutical companies are interested in active molecules derived from these plant active principles Professor Parmar characterized in those days. Several students took up these studies in different institutions of India including Ahmedabad and have won several awards. Thus, he made a significant and a major contribution as a very good researcher.

Today, KB Institute of Pharmaceutical Education & Research (KBIPER) in Ahmedabad stands as a big edifice. As a director of KBIPER, Dr. Parmar maintained good and cordial working relationship with other institutions like LM College in the same city. Thus, one can see a man with a great vision, a successful and an able administrator. Seeing as the sudden demise, we have lost a valuable friend, a devoted colleague, an outstanding teacher, a very good scholar and an able administrator. He was an all rounder who did his very best for the Indian Pharmacological Society (IPS). A very few have done such a long-standing work of major contribution to the IPS in several capacities. He loved all and served all with humility, respect and reverence for the society.

Venkat Gopal and Urmila A Shinde
Saskatoon / Canada

Information for Authors on how to submit articles to the journal

The following editorial guidelines for the JPDS are in accordance with the fifth edition of "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" [1].

Scope of Articles

The *Journal of Pharmacovigilance & Drug Safety (JPDS)* is an official journal of Society of Pharmacovigilance, India (SOPI), peer-reviewed specialty journal that aims to advance the practice and research knowledgebase of Pharmacovigilance. The *JPDS* welcomes the submission of any original manuscript that seeks to improve the practice of drug surveillance or articulates developments and history of the profession and related fields. The *JPDS* also welcomes manuscripts that extend the knowledgebase through research in the organization, delivery, rational use, and impact of information on health care, biomedical research, and health professionals' education.

Manuscripts are reviewed for possible publication with the understanding that they have not been published, submitted, or accepted for publication elsewhere. General availability or mass distribution in an online format is considered publication. Presentation of a paper at a conference or inclusion of a preliminary report in a published proceedings are not considered to be prior publication provided that the submitted manuscript is substantially more complete than an initial report and any duplicative material is kept to a minimum. Specific cases should be referred to the editor.

Categories of Articles

The *JPDS* publishes accepted manuscripts in a variety of categories to best serve readers of the journal. The most frequent categories are described below.

Full-length paper
Manuscripts that present original hypotheses and findings or cover the topic of investigation in a comprehensive manner including a review of the relevant literature are published as full-length papers. Full-length papers must have an informative abstract of not more than 200 words using a structured abstract format for research papers and a conventional, unstructured abstract for other papers. Full-length paper submissions should be double-spaced, not to exceed 5,000 words, excluding illustrations.

Brief communication
Manuscripts that report interesting and important developments related to the practice of health sciences librarianship but do not aim to be comprehensive or research oriented in nature may be published as brief communications. Brief communication submissions should be double-spaced, not to exceed 1,250 words, excluding illustrations. An abstract is not necessary for a brief communication.

Comment and opinion
Manuscripts that are primarily editorial in nature, meet the quality standards of the *JPDS*, and cover important and timely topics are published in the comment and opinion section of the journal. Submissions should be double-spaced and no longer than 2,500 words. An abstract is not necessary for comment and opinion pieces.

Letter to the editor
Letters commenting on, questioning, or criticizing a recent *JPDS* publication, including responses from original authors, are welcomed. All letters are limited to 300 words and must be typewritten or printed, doubled-spaced, and include no more than five references.

Writing Guidelines and Editorial Style

Writing Guidelines
There are many published guidelines that can be of assistance in organizing the content and preparing a manuscript for submission to the *JPDS*. Because the peer-review evaluation examines the writing style in addition to the content, authors should take great care to submit a manuscript that is well written and adheres to applicable style guidelines. The *JPDS* follows the Vancouver style and format guidelines for scientific and medical publications

Editorial Style
The style conventions used by the *JPDS* conform to the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" prepared by the International Committee of Medical Journal Editors [International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. JAMA 1997 Mar 19; 277(11):927–34]. Authors are referred to "Uniform Requirements" and the examples below for the reference style used by the *JPDS*.

Editorial Review and Processing

Peer-Review Evaluation
Members of the Editorial Board of the *Journal of Pharmacovigilance & Drug Safety* evaluate all contributed manuscripts. The *JPDS* uses a double-blind peer-review process, in which members of the editorial board do not know the identity of the author, and the identity of manuscript reviewers is not revealed to the author. Manuscripts are reviewed by at least two members of the editorial board or by subject experts chosen by the editor. The *JPDS* aims to complete the review process and provide feedback to authors within eight weeks of submission. All submitted manuscripts are treated as confidential communication.

The editor notifies the corresponding author of acceptance, provisional acceptance requiring revision of the manuscript before publication, or rejection. The formal notification will include feedback from the review panel and suggestions for revising the manuscript if it has been accepted for publication. Reviewers are asked to examine carefully the content and style of the manuscript for relevance, originality, and importance to the aims of the *JPDS*. Reviewers evaluate the methodology used, validity of data, presence of supportable conclusions, clarity of writing style, and appropriateness of the literature review.

Manuscript Submission

Authors should submit the original manuscript along with an electronic copy to the editor (see electronic submission instructions below). A copyright license statement (see "Notice to Authors" below) must accompany each submission. Authors will be notified of acceptance, rejection, or need for revision of their manuscripts (see peer-review evaluation). The *JPDS* reserves the right to make minor editorial changes in manuscripts if these changes will not affect the meaning.

Electronic Manuscript Submission

Authors should submit an electronic copy of their manuscript, either as an email

attachment sent to the editor using any standard word-processing software, such as Microsoft Word or WordPerfect, or as a 3.5-inch diskette labeled as to software used and files submitted, included with the paper copy of the manuscript. Questions regarding other acceptable electronic formats should be directed to the editor.

Proofs

Page proofs will be sent to authors for correction of errors; alterations cannot be made at this stage. Prompt return of proofs to the editor's address is essential. Use overnight express services. Order blanks for reprints are sent to authors with the proofs and should be returned according to the instructions given.

Title Page

The first page of the manuscript should be a separate title page, giving the title, bylines, authors' email addresses and institutional affiliations, and title page footnotes described below. The title should be specific, descriptive, and concise. Bylines should include first and middle names or initials, highest degrees earned, and the authors' professional titles. Institutional affiliations should include address and zip code. All persons designated as authors should have participated sufficiently in the work to take public responsibility for the content. Title page footnotes, if needed, should indicate present addresses of the authors or acknowledgment of grant support, including grant numbers. Manuscripts based on papers presented at a meeting should include a footnote giving the date, name, and place of the meeting. Use the following symbols in the order noted for explanatory footnotes on the title page or within the text: *, †, ‡, §, **, ††, etc.

Example:

* This program was supported by Ministry of Health & FW, Govt. of India Grant no. 5-GO4-LM-01609-03 from the Department of AYUSH.

† Based on a presentation at the 3rd Annual Meeting of the SOPI, Agra, India, December 11-13, 2003.

Abstract

Full-length articles must have an informative abstract of not more than 200 words, typewritten and double-spaced, on a separate page. All acronyms must be defined.

The abstract for research papers must be structured to include objectives, methods, results, and conclusions. The structured abstract should state the purposes of the study or investigation, basic procedures (e.g., selection of subjects, analytical methods), main findings (giving specific data and their statistical significance as appropriate), and principal conclusions. It should emphasize new and important aspects of the study or observations.

Other major manuscripts that will be published as full-length papers should contain a conventional, unstructured abstract of not more than 200 words that succinctly capture the important points made by the investigation.

Organization of Manuscripts

Manuscript pages on which the text appears should be numbered consecutively. Divide full-length papers into sections, each with an appropriate, brief heading. Footnotes in the text and personal acknowledgments should be kept to a minimum. Text footnotes if needed should be typed together on a separate page, not at the bottom of the page on which they occur. Relate them to the text

by means of the symbols noted above in the instructions for the title page (e.g., *, †, etc.). Personal acknowledgments may be placed at the end of the text, but ahead of the references.

Reference Style

Number references in the order they are mentioned in the text using Arabic numerals enclosed in brackets (e.g., as reported in *JAMA* [International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. JAMA 1997 Mar 19; 277(11):927–34]). References should be listed on a separate page and double-spaced. Bibliographies unrelated to the text are generally not acceptable. Abbreviations of journal titles should conform to the style of *Index Medicus*.

List all authors or editors. Italics should not be used in references. Capitalize only the first word and proper names. Words following punctuation in the title of a work are not capitalized, unless they are a proper name. Include the full date, including month, day or season, as well and volume and issue number. If papers not yet published but accepted are included in the list of references, authors must verify acceptance when a manuscript is submitted to the *JPDS*. An abbreviated reference should include the word "forthcoming." Authors are responsible for bibliographic accuracy and must compare bibliographic citations carefully with the original publications. Papers cannot be accepted for publication unless all references conform to *JPDS* format.

Reference Style Examples

Use the reference style of the examples below that are based on the formats used by the National Library of Medicine in *Index Medicus*.

1. Weller AC. Editorial policy and the assessment of quality among medical journals. Bull Med Libr Assoc 1987 Oct; 75(4):310–6.
2. Singhal KC, Rahman SZ. Lansoprazole Induced Adverse Effects on the Skin. Indian Medical Gazette 2001 July; CXXXV (7): 223-225.
3. Day RA. How to write and publish a scientific paper. 3rd ed. Phoenix, AZ: Oryx Press, 1988.
4. Rahman SZ, Singhal KC. Problems in Pharmacovigilance of Medicinal Products of Herbal Origin & Means to Minimize Them. [Insert]. Uppsala Reports. WHO Collaborating Center for ADR monitoring, UMC, Sweden. Issue 17 January 2002: 1-4.
5. Rahman SZ, Kumar A, Singhal KC. Pharmacogenetic and Pharmacogenomic in the Sphere of Pharmacovigilance – A Review. In: Singhal KC ed, Proceedings. International Workshop on Adverse Drug Reaction Monitoring & 3rd Annual Conference of Society of Pharmacovigilance, India (SOPI), Agra; 2003 December: 95-107
6. National Library of Medicine. Medical informatics. Bethesda, MD: National Institutes of Health, 1986 Dec: 16–25. (National Library of Medicine Long Range Plan, Report of Panel 4.)
7. Rahman SZ, Khan RA, Kumar A. Experimental study of the morphine de-addiction properties of Delphinium denudatum Wall. BMC Complementary and Alternative Medicine 2002: 2 [Online] <http://www.biomedcentral.com/1472-6882/2/6>
8. Ibn Sina Academy. [Web document]. Aligarh, India: The Trust, 2004. [rev. 4 June 2004; cited 9 June 2004]. <http://www.ibnsinaacademy.com>.

Illustrations and Tables

Illustrations often help to present complex information directly pertinent to the study in

a way more easily conveyed than by text alone; however they should not be included for purely illustrative or decorative purposes. Authors may include a total of six illustrations (photographs, tables, figures) for a full-length manuscript and one for a brief communication. All graphs, charts, photographs, and so on, must be submitted in black and white for publication in the print journal. Color versions may be submitted in addition and will be used for the online version.

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Print illustrations: If photographs or figures are used, the *JPDS* requires one original copy of the material, ready to be photographed, and four xerographic copies. Submit black-and-white, high-quality glossies or camera-ready figures from a high-quality laser printer. Materials should be prepared using black ink on white paper or blue-lined coordinate paper for line drawings and graphs. Do not combine line drawings and typewritten material in one figure; lettering must be professionally or computer produced, must be very clear, and must be large enough to permit considerable reduction in size by the printer. Care must be taken to use the same scale on all graphs and charts. Photographs should have a glossy finish, with sharp contrast between black and white areas. To assist in the layout of the publication, each figure should be marked on its back indicating the figure number, author's name, and the top of the figure. Captions for illustrations should be typewritten and double-spaced on a separate sheet, with numbers corresponding to those on the illustrations.

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Tables should be typed, double-spaced, on separate sheets at the end of the file, numbered consecutively, and headed by a brief, descriptive title. Use your word processor's table commands or use a single tab between columns and a hard return between rows.

Indicate the placement of all illustrations and tables in the text with callouts. For example, "Table 1 shows the relationship of authors to their citations" or "Students preferred electronic reserves to print reserves (Table 1)."

Simultaneous submission of manuscripts

Authors may not send the same manuscript to more that one journal at the same time. If the editor learns of possible simultaneous submission, the editor reserves the right to consult with the other editor(s) who have received the paper. Further the editor may return the paper without review, or may reject it without regard to the reviews, or make this decision in discussion with the other editor(s) involved, and may decide to consider no papers from the author from the authors for a period of time, and may also

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ISSN 0972– 8899 Journal of Pharmacovigilance & Drug Safety

With a view to establish Pharmacovigilance as a distinct and influential clinical discipline in India, an idea was generated during international workshop on adverse drug reaction monitoring held in November 1998 at New Delhi. To give shape to this idea, a meeting of interested scientists under the guidance of Prof. K.C. Singhal took place at Lucknow at the time of annual conference of Indian Pharmacological Society. Some decisions were taken at the meeting and as a follow up, Society of Pharmacovigilance, India (SOPI) came into existence under the Societies Registration Act XXI of 1860.

Aims and objectives: To promote study of the use and effects of drugs in population in a rational way and determine risk benefit ratio of drugs in individual and in population; to establish Pharmacovigilance as a distinct and influential clinical specialization; to organize training programmes, workshops, seminars, conferences for promotion of pharmacovigilance and pharmacoepidemiology and publish ***Journal of Pharmacovigilance & Drug Safety***; to collaborate with similar other societies at the international level for better interaction; to establish centers for study of pharmacovigilance and pharmacoepidemiology at medical colleges and hospitals; to foster relationship with key individuals and specialists (clinicians, academics, drug control authorities, industry, journalists, and clinical specialists); to provide a forum for the exchange of information and ideas, particularly among clinicians, pharmacists, industry and regulators; to institute awards for the development of research in pharmacoepidemiology and to award fellowship to eminent scientist form amongst members of the association.

Journal of Pharmacovigilance & Drug Safety (JPDS)

The General Body of the SOPI has decided to bring out its journal and newsletter in English to provide a forum to its constituent members and outsiders for informed discussion and peer review, to facilitate dissemination of ideas and views as also to foster drug reactions to insure actualizing their experience in a confident manner.

You are requested to patronize the Journal of SOPI and obliged us with your illuminating case report on adverse drug reaction or any other matter related to pharmacovigilance. You can help us a great deal by favouring us with advertisements of your firms, business, academic establishments, corporate bodies, NGOs under your kind control or influence. You can also be generous enough to sponsor at least a few pages of the journal. But, in any case, we would greatly appreciate your valued involvement in any manner suitable to you just to encourage our aims and objectives, based on the onerous task of popularizing an important topic in India, which is still in infancy, comparable to developed countries. Your encouraging response, we are certain, will pave the way for further strengthening of research in pharmacovigilance. Your support, cooperation and active involvement in our constructive ventures will go a long way to serve the cause of adverse drug reactions monitoring and its impact in society and we shall be pleased to duly acknowledge the same praying for your continued good health and success in your own endeavors. With regards, Editor

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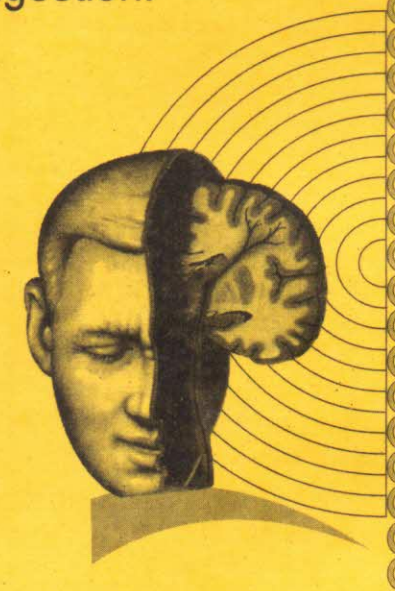

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