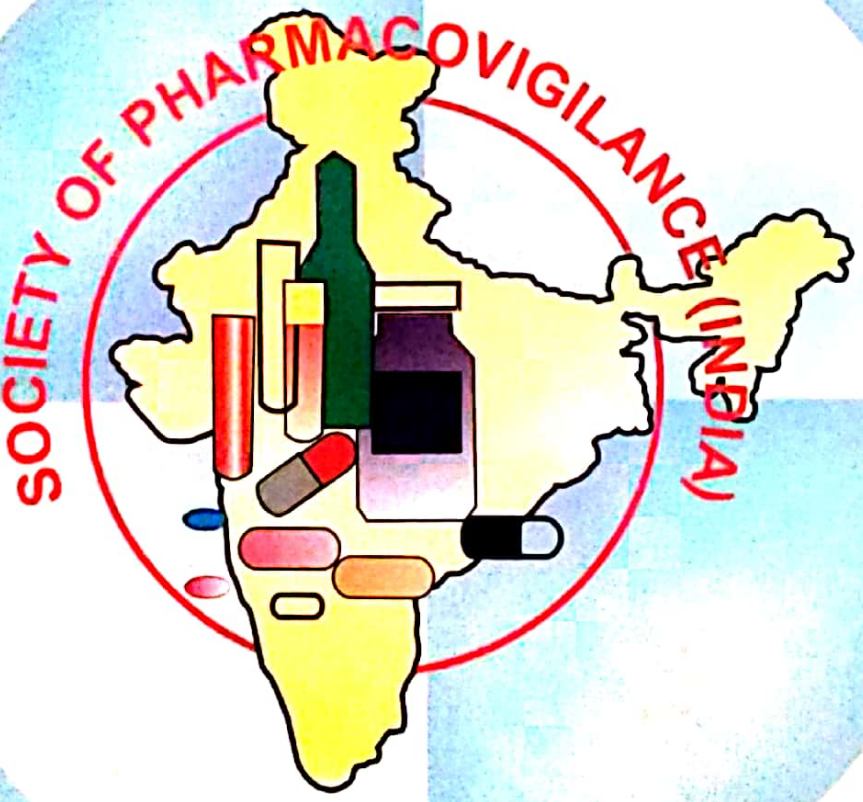
Journal of Pharmacovigilance & Drug Safety

VOLUME 6 NUMBER 1 JANUARY - MARCH 2009



ISSN 0972 -8899

Official Publication of
Society of Pharmacovigilance, India

Editor-in-Chief
Dr. Anurag Tomar

Journal of Pharmacovigilance & Drug Safety

VOLUME 6 NUMBER 1 JANUARY - MARCH 2009

Journal of Pharmacovigilance & Drug Safety (ISSN 0972-8899) is published by the Society of Pharmacovigilance, India (SOPI). Journal is provided free of charge to Life members. For institutional library annual subscription is Rs. 1000/-. Loose issues will not be sold. For individual Rs. 500/- per annum. Manuscripts and illustrations for publication should be sent to Dr. Anurag Tomar, Editor-in Chief, Journal of Pharmacovigilance & Drug Safety, NIMS City Centre, 4, Govind Marg, Jaipur - 302 004 India. Email sopijaipur@rediffmail.com. Please refer to Instructions for Authors, for additional information concerning preparation of manuscripts for publication

Journal of Pharmacovigilance & Drug Safety

January - March 2009 Volume 6 : Number 1

Contents.....

FROM THE DESK OF EDITOR

The January 2009 issue of Journal of Pharmacovigilance Drug & Safety marks the change of guard as as I take over the baton of Editor-in-chief of this prestigious journal from Dr. R.K. Goyal. The JPVDS got a new lease of life under Dr. R.K.Goyal's expertise and has grown substantially. The new format of the journal and standard protocol of articles have all contributed significantly towards this growth.

I am aware of the immense responsibility bestowed upon me and look forward to this opportunity to continue the good work done so far by all my predecessors. It is in all our hands to keep up the quality of this journal and improve upon it progressively. The only way to do so is by undertaking more research and submitting more original articles. The contributions to the journal have started increasing, slowly but surely, and this is a good sign. I look forward to a time when I am inundated with original articles and my main problem becomes the selections of the best of them for JPVDS.

Monitoring of the safety of available drugs, medical devices and of medical errors is an important public health protection activity. For the success of any health care programme it is essential to encourage voluntary reporting of adverse events and product problems (e.g. defects) associated with drugs and medical devices. Such voluntary reporting has played a critical role in identifying adverse effects that did not emerge during clinical trials and in some studies situations of the revealed effects were so serious that drug regulatory authorities labeled warning or even withdrawn such drugs or devices.

I thank all the members of the Editorial board who helped me in reviewing the articles with their valuable suggestions and comments about the articles. I will also thank our publisher Mr. Sandeep Madaan.

Dr. Anurag Tomar
MBBS, MD (Pediatrics)
Editor in Chief

J Pharmcovig Drug Safety 2009 (January - March) 6(1) :1-4

ORIGINAL ARTICLE

Nearly Fatal Wild Honey Intoxication

AKHILESH CHANDRA JAUHARI, POOJAN SHRESHTHA, K. C. SINGHAL[1]
Department of Pharmacology, Nepal Medical College Jorpati Kathmandu, Nepal .
[1]NIMS University Rajasthan, Jaipur - 302 001

ABSTRACT

On the eve of holi festival seven medical students (four interns, one final year & two first year MBBS students) went to take dinner in a restaurant, where they ingested varying quantity of wild honey. Following which they had nearly fatal anaphylactic reaction & shock, for which they were admitted in emergency ward of the Nepal Medical College Teaching Hospital for treatment.

The symptoms varied according to the quantity of honey consumed. These included Nausea, vomiting, pain in abdomen extreme weakness, loss of consciousness, bradycardia and fall in blood pressure. All of them recovered after varying periods of symptomatic treatment along with corticosteroids, antihistamines and Dopamine and adrenaline for near anaphylaxis to two.

Soon after consumption of wild honey they started developing manifestation of toxicity related to the quantity of wild honey consumed. Two of them became serious and were taken to the intensive care of NMCTH. Emergency treatment was given to them and they recovered without any sequelae. The sequence of events in individuals, signs, symptoms and treatment in described below.

Key words: Rhododendron, grayanotoxin, Honey poisoning

Introduction

Rhododendron evergreen flowering perennial shrubs of the exercise or Health family have tough, glossy, smooth, margined evergreen leaves. The large showy flowers are in terminal clusters and have five white, pink or red petals. Some horticulture varieties have yellow or orange petals with bell shaped flowers. The genus is very widely distributed, occurring throughout most of the northern hemisphere except for dry areas, and extending into the Southern Hemisphere in south-eastern Asia and northern Australia. The highest species diversity is found in the Sino-Himalayan Mountains from central Nepal and Sikkim east to Yunnan and Sichuan, with other significant areas of diversity in the mountains of Indo-China, Korea, Japan and Taiwan. In addition, there are a significant number of tropical Rhododendron species from Southeast Asia to northern Australia, with 55 known species in Borneo and 164 in New Guinea. There are more than thirty species of Rhododendron in Nepal with dozens of varieties in all sizes. Rhododendron arboretum (Rose tree in English and Lali Guras in Vernacular) is the national flower (pink colour) of Nepal. This tree attains a height of up to 15 meters. It has largest trunk, the biggest the earliest and longest span of flowering. Lali Guras is distributed widely from 1200 m to 3600 m altitude throughout Nepal. Honey is consumed worldwide, commonly at breakfast. The ingredients of honey may vary according to source from where the bees collect and deposit in comb. In Nepal, where Rhododendron arboretum (Lali Guras) national flower of Nepal with its more than thirty species is common, honey bees visit these flowers for making honey. This honey contains Grayanotoxin, which if consumed causes dose related toxicity.

Case Report

Case1: Patient version (on personal interview): Male medical intern, aged 25 years, nearly on empty stomach he went to restaurant to take dinner. Where he consumed 8 tea spoonful of wild honey on 2/3/07 at 9.00 PM (1 TSF = 5.0 ml). He felt nausea, burning sensation in throat and epigastrium, headache, drowsiness and flushing of body followed by 3-4 episodes of Vomiting. Vomitus contained food particles & honey, along with frothy fluid, and he

become unconscious. He was shifted to emergency of Nepal Medical College Teaching Hospital. In emergency he had deep gasping, respiration palpitation, and blackout.

O/E: G.C. Fair, BP. 90/60 mm of Hg., P-60/min., SpO2 without O2 92%

Chest/P.A./CVSL: NAD

Pupils were dilated and sluggish reacting to light.

Investigation : TLC-9800 cub.mm., D.L.C. N73%, L27%, Hb. 14.0gm%, Urea 31.0mg., CR.1.4.mg/ml, Na+-139meq/ml, K+ 4.4 meq/ml., Blood group A +, Total Billirubin 0.9, Direct Billirubin).2, SGPT 16.0, SGOT 31.0, ALP 209.

INSIDE ICCU: Patient was restless with pupils dilated and sluggishly reacting to light BP 88/44mm of Hg. 0.25 ml Adrenaline 1: 1000 given by subcutaneous injection immediately, thereafter 400 mg Dopamine with 1 unit normal saline was infused. The blood pressure increased to 106/59 mm.Hg

He was treated with Normal Saline 1 unit, 2 units of RL with perinorm (metoclopramide) 10mg , Inj aciloc (Ranitidine) 50mg , Inj Avil (Pheniramine) 45.5 mg and hydrocortisone by intravenous route patient regained consciousness after 4 -5 hours and was discharged after two days. Diagnosis: Honey poisoning.

***Case2*: Patient's version (on personal interview):**

Male medical Intern, aged 24 years,. Nearly on empty stomach he went to restaurant to take dinner on 2/3/07 at 9.00 PM. Where he consumed 6.0 spoonful of wild honey (1TSF= 5 ml), after diner he felt burning sensation in throat, flushing of face & body, and walked to emergency of hospital where he was admitted. His symptoms worsened and after 10 minutes, he had dizziness, sweating, shivering, dryness of throat & mouth mild headache, nausea, and was attempting to vomit then he became unconscious. He vomited 3 times.

HOPI:C/O Ingestion of 6 tea spoonful wild honey followed by drowsiness after 1½ hours.

O/E.:

Chest/CVS/PA-NAD

Pupils dilated reacting to light.

Hb 13.0 gm%, Urea 24.0 mg/ml., CR 1.1, Na+ 139.0 mq/ml, K+ 4.4 mq/ml, Glucose (R) 88.0 mg/ml.

He was treated with i.v. fluids (normal saline & ringer lactate) and hydrocortisone, Pheniramine 45.5 mg, Raitidine 50 mg, metoclopramide 10 mg by intravenous route with oxygen inhalation. He was relieved of his symptoms and was discharged from the hospital the next day.

***Case 3.*: Patient's version (on personal interview):**

Male Medical students aged 19 yrs. Consumed about 3-4 teaspoonful of wild honey at a restaurant where he had gone to take dinner. After about 30 min. of taking dinner he felt burning sensation in throat and abdomen flushing of face and palpitation. He had two projectile vomitings. He walked to the emergency of the hospital where he was admitted.

O/E

B.P. 110/80, pulse 120/mt., pupils dilated sluggishly reacting to light. He was conscious.

He was given normal saline 1 unit, inj Perinorm (Metoclopramide) 10 mg iv, inj Aciloc (Ranitidine) 50 mg, i.v. and inj. Avil (Pheniramine) 45.5 mg iv. He was discharged from the hospital next day in the morning.

***Case 4.*: Patient's version (on personal interview):**

Male intern 26 yrs. Consumed two tea spoonful of wild honey at a restaurant after that he had dinner. After sometime he felt nausea and burning sensation in eprigatrium. He went to the emergency of the hospital. After about one hour he vomited. He was prescribed Tablet Aciloc (Ranitidine) and Gelusil suspension and was asked to go hostel and take rest.

***Case 5.*:** Male intern 27 yrs ans two others. Consumed one tea spoonful of wild honey each. They did not experience anything and did not require any treatment.

Table - 1 Adverse Reactions to Wild Honey

Amount of Honey	GI Symptoms	EYE Symptoms	CVS Symptoms	CNS Symptoms
1.0 TSF.	(-)	(-)	(-)	(-)
2.0 TSF	(+)	(+)	(-)	(-)
3.0 TSF	(++)	(++)	(+)	(-)
6 TSF	(++)	(++)	(++)	(+)
8 TSF	(+++)	(++)	(+++)	(+++)

Discussion

Seven young medical graduates consumed varying quantity of wild honey at the same time while they were taking dinner together in a restaurant. The restaurant owner warned them against consuming more than 1 tea spoonful, but they ignored. They started experiencing abnormal symptoms. They were immediately rushed to Nepal Medical College and Teaching Hospital emergency and were provided prompt medical aid. The symptoms and signs of intoxication were proportional to the quantity of wild honey consumed (Table 1). On enquiry from the restaurant owner, it was revealed that wild honey was brought from Sagarmatha, District Dolakha(South of Jari) near Lincon Bazar, Nepal, Rhododendron grows in abundance in that area.

Relatively fewer species occur in North America and Europe. Species of rhododendrons are poisonous to grazing animals too. Some Rhododendrons have a toxin called grayanotoxin in their pollen and nectar. People have been known to become ill from eating honey made by bees feeding on rhododendron and azalea flowers. Xenophon described the odd behaviour of Greek soldiers after having consumed honey in a village surrounded by Rhododendrons. Later, it was found that honey resulting from these plants have a slightly hallucinogenic and laxative effect.

Grayantoxins (glycosides) a toxin which affects the gastrointestinal and cardiovascular systems is found in rhododendrons and other plants of family ericaceae. The toxin is also known as andromedotoxin, acetylandromedol or rhodotoxin and can be found in honey made from the nectar and cause a very rare poisonous reaction called grayanotoxin poisoning, honey intoxication or Rhododendron poisoning. Several cases of grayanotoxin poisonings in humans have been documented in the 1980s. These reports come from Istanbul Turkey and Austria. In Austria poisoning resulted from the consumption of honey that was brought back from visit to Turkey. From 1984 to 1986, 16 patients were treated for honey intoxication in Turkey. The symptoms started approximately 1 hr. after 50g of honey was consumed. In an average of 24 hrs,, all of the patients recovered. The case in Austria resulted in cardiac arrhythmia, which required a temporary pacemaker to prevent further decrease in heart rate. After a few hours, pacemaker stimulation was no longer needed. This shows that with increased travel throughtout the world, the risk of grayanotoxin poisoning is possible outside the areas of Ericaceae dominated vegetation, namely, Turkey, Japan, Brazil, United States, Nepal, and British Columbia. In 1983 several British veterinarians reported a incident of grayanotoxin poisoning in goats. One of the four animals died. Post-mortem examination showed grayanotoxin in the lumen contents.

According to FDA a neurotoxin found in the nectar of certain species of rhododendron (Rhododendron spp.) and Laurel (Kalmia spp.) and in unprocessed foods produced from the nectar, such as unpasteurized honey may cause dose dependent poisoning after a latent period of few minutes to two or more hours and salivation, nausea, vomiting, both cirum oral and extremity paresthesia irregular heartbeat, fall in blood pressure, ventricular, tachycardia, extrasystoles, convulsions, are reported occasionally, loss of coordination and progressive muscular weakness. The intoxication is rarely fatal and generally lasts for no more than 24 hours. Generally the disease induces dizziness, weakness, excessive perspiration, nausea and vomiting shortly after the toxic honey is ingested. Other sympotoms that can occur are low blood pressure or shock, bradyarrhythmia (slowness of the heart beat associated with an irregularity in the heart rhythm), sinus bradycardia (a slow sinus rhythm, with a heart rate less than 60), nodal rhythm (pertaining to a node, particularly the atrioventricular node), Wolff Parkinson White syndrome (anamolous atrioventricular excitation) and complete atrioventricular block.

The grayanotoxin is a polyhydroxylated cyclic diterpene. It binds to specific sodium channels in cell membranes. The binding unit is the group II receptor site, localized on a region of the sodium channel that is involved in the voltage dependent activation and

These compounds prevent inactivation; thus, excitable cells (nerve and muscle) are maintained in a state of depolarization, during which entry of calcium into the cells may be facilitated. This action is similar to that exerted by the alkaloids of veratrum and aconite. All of the observed responses of skeletal and heart muscles, nerves and the central nervous system are related to the membrane effects.

Grayanotoxins poisoning in human is rare. However, cases of honey intoxication should be anticipated everywhere. Some may be ascribed to an increase consumption of imported honey. Others may result from the ingestion of unprocessed honey. Grayanotoxin poisoning most commonly results from the ingestion of grayanotoxin contaminated honey, although it may result from the ingestion of the leaves, flowers, and nectar of rhododendrons. Not all rhododendrons produce grayanotoxins. Rhododendron ponticum grows extensively on the mountains of the eastern black sea area of Turkey.This species has been as sociated with honey poisoning since 401 BC. A number of toxic species are native to the United States. Of particular importance are the western azalea Rhododendron occidentale found from Oregon to southern California, the California rosebay Rhododendron macrophyllum found from British Columbia to central California, and Rhododendron albiforum found from British Columbia to Oregon and in Colorado. In the eastern half of the United States grayanotoxin contaminated honey may be derived from other members of the botanical family Ericaceae, to which Rhododendron belong. Mountain Laurel (Kalmia latifolia) and sheep laurel (Kalmia angustifolia) are probably the most important sources of the toxin.

Conclusion

The increased desire of public for natural (unprocessed) foods may result in more cases of grayanotoxin poisoning. Individuals who obtain honey from farmers who may have only a few hives are at risk. The pooling of massive quantities of honey during commercial processing generally dilutes any toxic substances. Public should consume only reliable branded form of honey, obtained from reliable sources to avoid honey intoxication.

Honey from Japan, Brazil, United States of America, Nepal and Britiah Coloumbia is most likely to be contaminated with grayanotoxins. The grayanotoxins can be isolated from the suspect commodity by typical extraction procedures for naturally occurring terpenes. The toxins are identified by thin larger chromatography.

References

1. Argent, G. Rhododendrons of subgenus Vireya Royal Horticultural Society. 2006 ISBN 1 - 902896-61-0
2. Nurhayat Sutlupmar, Afife Mat and Yurdagul Satganoglu Poisoning by toxic honey in Turkey. Archives of Toxicology; 1993/ 67, 148-50 .
3. Emergency Medical Journal Oct. 2004 http://www.Emj.bmj.com (on line)
4. US.FDA/CFSAN Bad Bug Book 2007 Grayanotoxin http://www.cfsan to fda. Gov (on line)
5. Seyama I et. Al. J. Pharmacol. Exp. Ther 1981, 219, 614
6. Ohgaki T. et.al Brain Res 1987, 425, 364
7. Yakehiro. M et.al Mol. pharmacol, 2000, 58, 692

J Pharmcovig Drug Safety 2009 (January - March) 6(1) :5-9

ORIGINAL ARTICLE

A Comparative Study of Causality Assessment Scales Used in the Analysis of Spontaneously Reported Events: WHO-UMC criteria vs Naranjo Probability Scale.

M. SHARMA [1], S.K. GUPTA [2], V.B. GUPTA [3], A CHATTERJEE [4]
[1,4] B.R. Nahata College of Pharmacy, Mandsaur - 458001 [2] Institute of Clinical Research India, [4] Panacea Biotec, Ltd, New Delhi

ABSTRACT

Spontaneous adverse drug reaction (ADR) reporting has been a major source of information in pharmacovigilance. The primary purpose of spontaneous ADR reporting is to provide early warnings or "signals" of previously unrecognized drug toxicity. The methods that have been developed for the estimation of the probability that a drug caused an adverse event(s) mainly include; the WHO-UMC criteria, the Naranjo probability scale, the Kramer scale and the Karch and Lasagna scale. None of the methods have shown to produce a defined and
consistent likelihood of relationship.

Objective: To quantitatively estimate and compare the relationship between the WHO-UMC causality assessment criteria and the Naranjo probability scale.

Methods: A non interventional observational study was carried out in India to capture suspected adverse drug reactions (ADRs) caused by Extended Release formulation of Nimesulide (Willgo®) in 'real world clinical practice'. For spontaneous reporting purpose the Suspected ADR reporting form provided by the CDSCO, Directorate General of Health Services, Government of India was used.

Results: A total of 55 suspected ADR reporting forms were received. Maximum reporting was made from the Punjab state (16). Mean time taken for the assessment using WHO-UMC criteria was 7.17± 0.51 minutes and using Naranjo probability scale was 14.6 ± 3.13 minutes. In 47% cases a disagreement in causality assessment was found (k= 0.293).

Conclusion: Consistent with the findings in the previous study (ies) a disagreement was found between the WHO-UMC Scale and the Naranjo scale. Among the two, the WHO-UMC scale is simple and less time consuming.

Introduction

Pharmacovigilance has been defined by World Health Organization (WHO) as the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug related problems [1]. Spontaneous adverse drug reaction reporting has been a major source of information in pharmacovigilance. This is achieved by voluntary participation of physicians or prescribers who voluntarily report any effect they believe to be attributable to a drug 'taken by the patient'. The primary purpose of spontaneous ADR reporting is to provide early warnings or "signals" of previously unrecognized drug toxicity. Causality assessment is the evaluation of the probability or possibility that a particular treatment is the cause of an observed adverse event. Administration of the suspected drug with other drugs is very usual andfrequent. Henceforth an important problem in the assessment of ADRs is the establishment of causal association between the suspected drug and the untoward clinical event. It becomes difficult to distinguish the adverse clinical event from the underlying disease. In a recent published review 1 on electronic searches made in MEDLINE (via PubMed), EMBASE and the Cochrane databases, 34 different causality assessment methods were found [2]. These methods were divided into three broad

categories: expert judgment / global introspection, algorithms and Bayesian approaches (probabilistic methods). WHO-UMC criteria and the Naranjo probability scale are extensively used in pharmacovigilance centers and allied departments in academia and industry. None of the methods have shown to produce a defined and consistent likelihood of relationship.

The purpose of this study was to quantitatively estimate and compare the relationship between the WHO-UMC causality assessment criteria and the Naranjo probability scale for spontaneous reports, and to measure

and compare the time taken for causality assessment by WHO-UMC causality assessment and the Naranjo probability scale.

Methods

A non-interventional observational cohort study was conducted using the technique of prescription event monitoring (PEM). The study involved voluntary participation (with no incentives attached) of 1,826 prescribers (general practitioners, physicians, orthopaedicians, general surgeons, and dentists) spread through out India (161 cities all over India). A pharmacovigilance booklet containing a prescription log sheet; suspected ADR reporting forms (generated by CDSCO, Ministry of Health and Family Welfare, Government of India); Willgo® package insert and information about pharmacovigilance program) was provided. Self-addressed business reply envelopes were provided for collection of filled suspected ADR reporting forms. Causality assessment was performed for the received filled forms. Two criteria's viz WHO-UMC criteria and Naranjos probability scale (NPS) (Table 1) were used for the assessment. Before the second assessment by Naranjos scale the forms were reorganized arbitrarily. For the purpose of minimizing influence of learning a provision was kept for a gap of 4 weeks between the two assessments made by the assessors. Data was recorded for the time taken with each of the scale. Cohen's kappa test was used for comparing the rate of disagreement between the raters.

WHO-UMC causality assessment criteria [3]

Certain : A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Probable / Likely : A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration

of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.

Possible : A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Conditional/ Unclassified: A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.

Unassessible/ Unclassifiable : A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

Table 1 : Naranjo probability scale (4)

Question	Yes	No	Don't know
Are there previous conclusion reports on this reaction?	+1	0	0
Did the adverse event appear after the suspect drug was administered?	+2	-1	0
Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
Did the adverse event reappear when drug was re administered?	+2	-1	0
Are there alternate causes [other than the suspected drug] that could solely have caused the reaction?	-1	+2	0
Did the event reappear when a placebo was given?	-1	+1	0
Was the drug detected in the blood [or other fluids] in a concentration known to be toxic?	+1	0	0
Was the adverse event more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure (Past history of any similar reaction to the same or similar drugs)?	+1	0	0
Was the adverse event confirmed by objective evidence?	+1	0	0

Results

A total of 55 suspected adverse drug reaction reporting forms were received by a total of 33 prescribers during the one year pharmacovigilance programme. Eighty one suspected adverse events were reported on these forms. Maximum reporting was made from the Punjab state (16). Majority of the adverse events which involved the gastrointestinal disorders (34) followed by skin and subcutaneous disorders (18), general disorders (12), nervous system disorders (8), ear and labyrinth disorders (4), and vascular disorders (1) were 'expected'. Four 'unexpected' adverse events were also reported during the study period. The suspected adverse reaction reporting forms were randomly selected and assessed using WHO-UMC causality assessment scale and NPS. The mean time taken by the assessors using different scales was 7.17 ± 0.5 minutes for WHO-UMC scale and 14.6 ± 3.13 minutes for NPS. The causal relationship between the drug and the event is shown in table 4. The causal relationship was certain in 9% cases, probable in 20% cases followed by possible in 36% cases and unlikely in other 9% of cases. In 26% of cases the relationship was 'conditional' as more data was essential for a proper assessment. A total of 5% of the cases were reported as certain when assessed by the NPS (Table 2). The causality was assessed as 'probable' and 'possible' in 11% and 84% of the cases respectively.

Table 2 : Comparison between WHO - UMC criteria and naranjo probility Scale (n=55).

Category	WHO-UMC	Naranjo Probability Scale
Certain	5 (9%)	3 (5%)
Probable	11 (20%)	6 (11%)
Possible	20 (36%)	46 (84%)
Unlikely	5 (9%)	NA
Conditional / Unclassified	14 (26%)	NA

The assessment for the existence of disagreement between the drug and the adverse event in the forms received was 47% (n=26). As shown in table 3 there were 10 suspected adverse drug reaction reporting forms where the probability was lower by WHO-UMC scale (in 5 cases from 'probable' (WHO-UMC) to 'possible' (NPS) ; in 5 cases from 'certain' (WHO-UMC) to "possible' (NPS)). There were 16 reports where probability was higher by WHO-UMC scale (in 2 cases from 'unlikely' (WHO-UMC) to 'possible' (NPS); in 14 cases (WHO-UMC) from 'conditional' to 'possible' (NPS)

Table 3 :Disagreements in WHO-UMC criteria and Naranjo Probability Scale

	Total number of disagreements = 26	
1	**Reports where probability was lower by WHO-UMC scale**	**10**
	Probable (WHO-UMC) to Possible (NPS)	5
	Certain (WHO-UMC) to Possible (NPS)	5
	Reports where probability was higher by WHO-UMC scale	**16**
2	Unlikely (WHO-UMC) to Possible (NPS)	2
	Conditional (WHO-UMC) to Possible (NPS)	14

Discussion and Conclusion

In post approval phase spontaneous reports play a major role in the identification of rare and serious drug related adverse events. Establishing a causal relation ship between the drug and the event is important in the understanding of adverse drug reactions and safety signals.Based on the causal relationship ADRs have been classified as definite, probable, possible or with a doubtful association to the suspected drug [5]. As different causal assessment scales are available for the assessment of adverse drug events, we carried out a comparative study for the analysis of spontaneously reported events through WHO-UMC criteria and Naranjo Probability scale.

In the present study the probability pattern reported as 'possible', probable, and certain was expected since in a spontaneous reporting system cases are reported only when the physician already suspects drug causation for the adverse event.

The results of the study showed the existence of disagreement in 26 (47%) suspected adverse event reporting forms. In 16 cases probability was higher on Naranjo probability scale when compared to WHO-UMC scale. Of these the probability had an increment from conditional to possible in 14 cases and unlikely to possible in 2 cases. Among the remaining 10 cases probability was higher on WHO-UMC scale.

Causality assessment methods differ in many respects but share certain common features. The presence of confounding factors, including underlying diseases and concomitant drugs was one of the most important factor to be considered in the evaluation of the causality assessment. Differently from WHO-UMC scale, in the Naranjo probability method question 5 asks if alternate causes (other than the drug) are present, looking for a relationship between the pharmacological treatment and the event (table i). Additionally, Naranjo probability method requires additional information in relation to placebo, previous similar reports, antagonist administration, dose severity relationship, confirmation of past history of exposure by either a laboratory test or direct clinical investigation. Other studies [6, 7] have also attributed question 5 to be a major reason of disparity/ disagreement between the rators. As confirmed from the other study [8] the disagreement could have been because of the difference in the knowledge, experience and training of the assessors (interrator variability and intrarator variability) as one of the assessors was post graduate in clinical pharmacology with a teaching experience of 5 years in academic setting and the other assessor was a post graduate in pharmacy with 7 years of experience in pharmacovigilance in an industrial setting.

The existence of disagreement between the assessors when two different scales were used has been documented in previous studies [4, 10]. One of the study concluded that though the Kramer scale was more complex than the Naranjo scale, both of these scales were reliable and gave similar conclusions regarding the ADR probability [11]. In the present study the time required by the WHO-UMC scale was less i. e 7.17 ± 0.5 minutes as compared to Naranjo probability scale 14.6 ± 3.13 minutes. One of the recently published study has also documented that WHO-UMC scale is less time consuming [7]. In confirmation with other studies [12, 13], where the assessors have agreed only on 50% of cases, our study shows the existence of disagreement ($k=0.293$) between the two causality assessment methods.

Reference

1. http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/index.htm
2. Agbabiaka TB, Savovic J, Ernst E. Methods for causality assessment of adverse drug reactions: a systematic review. Drug Safety. 2008; 31 (1): 21-37.
3. www.who-umc.org.
4. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981 Aug; 30 (2 :239-45.
5. Seidl, L.G., Thornton, G.F., Smith, J.W. & Cluff, L.E. Studies on the epidemiology of adverse drug reactions. 3. Reactions in patients on a general medical service. Bull.Johns Hopkins Hospital. 119, 299-315.
6. T.A. Hutchison, J.M.Leventhal, M.S.Kramer, F.E.Karch, A.G.Lipman and A.R. Feinstein, An algorithm for the operational assessment of adverse drug reactions II.Demonstration of reproducibility and validity, J. Am. Med. Assoc.242 (1979),633-638.
7. H.S.Rehan, Deepti Chopra and Ashish Kumar Kakkar. Causality assessment of spontaneously reported adverse drug events: Comparison of WHO-UMC criteria and Naranjo probability scale. International Journal of Risk & Safety in Medicine 19 (2007) 223-227.
8. R.H. Meyboon, Y.A. Hekster, A.C. Egberts, F.W. Gribnau and I.R. Edwards, Causal or casual? The role of causality assessment in pharmacovigilance, Drug Safety. 17 (1997), 374-389.
9. Schmidt LG, Dirschedl P, Grohmann R, Scherer J, Wunderlich O, Müller-Oerlinghausen B..Consistency of assessment of adverse drug reactions in psychiatric hospitals: a comparison of an algorithmic and an empirical approach. Eur J Clin Pharmacol. 1986;30(2):199-204.
10. U.Busto, C.A.U. Naranjo and E.M. Selers, Comparison of two recently published algorithms for assessing the probability of adverse drug reactions, Br.J.Clin Pharm. 13(1982), 223-227.
11. Koch-weser J,Sellers EM,Zacest R. The ambiguity of adverse drug reactions. Eur J Clin Pharmacol 1977; 11:75-8.
12. Karch FE, Smith CL, Kerzner B, Mazzullo JM, Weintraub M,Lasagna L. Adverse drug reactions a matter of opinion. Clin Pharmacol Ther 1976;19489-92

J Pharmcovig Drug Safety 2009 (January - March) 6(1) :10-12

ORIGINAL ARTICLE

Adverse Reactions to Antimicrobials in a Teritary Care Hospital

K BHUVANA, N SARALA, T N KUMAR
Department of Pharmacology, Sri Devaraj Urs Medical College, Kolar, 563101

Introduction

Adverse drug reactions (ADRs) are unwanted consequences of antimicrobial therapy. These reactions can be common but not serious, serious and common, serious, but rare. The reactions will have an important implication on the patient and also the treating physician. Most of the ADRs related to antimicrobials are preventable. Therefore the awareness of these reactions will help us to decrease the occurrence and reduce the patients stay at the hospital and also the cost for the patients. Literature search has shown very few studies. This study will help the clinicians to know the safety profiles of the antimicrobials selected for the hospital antimicrobial formulary and for the patients. Hence the present study was carried out.

Methods

A prospective study was carried out by the department of Pharmacology from January 2006 to August 2006. The details of the patients manifesting with reactions to antimicrobials were collected both from inpatient and outpatient departments of R.L.Jalappa hospital attached to Sri Devaraj Urs Medical College. The parameters included number of patients receiving antimicrobials, their age groups, sex, indications for antimicrobials, type of reaction and the outcome of these reactions. The causality assessment of the ADRs was done as per the directions provided by WHO collaborating centre.

Results

During this 8 months period, 94,852 antimicrobial agents were prescribed. Of these, 31 patients presented with ADRs which accounts to 0.03%. Age distribution is as follows: 16% in pediatrics (0-18years), 80% in adults (19-60years) and 3% in geriatric (>60years) age groups. Males were 12 in number and females 19. Table 1 shows the antimicrobial agents causing both systemic and cutaneous ADRs.

Table 1 Number of patients affected by antimicrobial agents.

Antimicrobial agents	Number of patients
Fluoroquinolones	11
INH	5
Cephalosporins	5
Ampicillin+Cloxacillin	2
Macrolides	2
Amoxicillin	1
Tetracycline	1
Quinine	1
Cotrimoxazole	1
Dapsone	1
Fluconazole	1

The most common indications for the use of these antimicrobials were upper respiratory tract infection followed by fever, urinary tract infection, tuberculosis, bacterial diarrhea, typhoid, leprosy, cerebral malaria, esophageal candidiasis. In the present study we observed both cutaneous and systemic ADRs, which contributed to 77% and 23% respectively. Table 2 shows the type of systemic and cutaneous ADRs and also represents the antimicrobial agents implicated in that reaction.

2 patients presented with vasculitis which subsided by the 4th day and erythema multiforme due to INH subsided by 5 days. The patient with SJS had a hospital stay of 6 days. The lesions subsided gradually and patient was discharged on the 7th day. Insomnia due to ofloxacin subsided when the drug was stopped and alternate drug was given to the patient. INH induced increase in liver enzymes reverted to normal levels when the patient came for follow up after a period of 1 month. One patient had received fluconazole 150mg orally twice daily for a period of 3 days following which patient had bradycardia and ECG showed prolonged QT interval. The drug was stopped and ECG taken subsequently on the 2nd day was normal.

Table 2

Type of reactions	Antimicrobial agents implicated	Number of patients	Percentage
Cutaneous ADRs		**24**	
Maculopapular rash(19)	Fluoroquinolones	24	61
	Cefixime	8	
	Macrolides	4	
	Amoxicillin	2	
	Tetracycline	1	
	Quinine	1	
	Ampicillin+Cloxacillin	1	
Vasculitis (2)	INH	1	7
	Ampicillin+Cloxacillin	1	
Stevens-Johnson Syndrome (SJS) (1)	Ceftazidime	1	3
Erythema Multiforme	Cotrimoxazole	1	
Drug induced photo aggravated melanoderma	INH	1	3
	Dapsone	1	3
Systemic ADRs		7	
Insomnia	Ofloxacin	3	10
Altered Liver function tests	INH	2	7
Increased SGOT/SGPT	INH	1	3
Prolonged QT interval	Fluconazole	1	3

Discussion

Adverse drug reactions in hospitalized patients contribute to 10-20%, 0.3-0.5% of hospital admissions are due to ADRs and deaths in hospitalized patients due to ADRs accounts to 0.24-2.9%. [1] These reactions are common in patients receiving multi drug therapy either because of drug interaction or because of drug-disease interactions. Adverse drug reactions due to antimicrobials can be a result of exaggerated response to the known pharmacological effect, immunological reaction to the drug or its metabolite and idiosyncratic reactions due to the drug [2]

In our study, ADRs due to antimicrobials contributed to 0.03% and we observed both cutaneous and systemic ADRs. 77% of patients had cutaneous reactions, other studies has shown 44.2% [3] and 42.6%. [4] The onset of reaction ranged from few hours to 5 days except in case of INH, the manifestation occurred after 10 days of therapy. The commonest type of reaction in our study was maculopapular rash contributing to 61% which was similar to another study.[5] This subsided by 3 days after stopping the drug. Fluoroquinolones being the commonest cause, followed by cefexime, whereas earlier studies have implicated penicillins and sulphonamides. This change in trend could be due to indiscriminate use of flouroquinolones. Vasculitis which is type III hypersensitivity reaction occurred 3 days after ceftazidime and ampicillin+cloxacillin and subsided 4 days after dechallenge.

SJS was seen in 3% of patients who received cotrimoxazole for urinary tract infection, manifested after 2 days of therapy and subsided 6 days after the drug was discintinued. Earlier study[3] has shown 3.62% contribution. Erythema multiforme occurred in one patient who had received INH for the tubercular osteomyelitis involving the right tibia and the reaction required 5 days to subside. 10% of adverse drug reactions was contributed by ofloxacin causing insomnia. This could be due to the frequent use of the quinolones and insomnia being one of the most common central nervous system adverse effects caused by ofloxacin (4.7%)[6] INH known for its hepatic side effects altered the values of liver function tests in 7% of cases and increased SGOT and SGPT

levels in 3% of patients. Fluconazole was administered for the treatment of oral and esophageal candidiasis and it was detected to have caused bradycardia and prolonged QT interval in the patient and the features disappeared when the drug was withdrawn.

Conclusion

In our study antimicrobials contributed to both cutaneous and systemic ADRs. Cutaneous ADRs were more common followed by systemic.

We observed 11 cases of ADRs were due to fluroquinolones implicating widespread and perhaps indiscriminate us similar to other studies[7-11] and use of sulphonamides has been reduced. Fluoroquinolones contributed to 42% of maculopapular rash which subsided in 2-3 days. Interestingly, systemic unwanted effect observed was insomnia due to ofloxacin. Majority of the reactions were probably due to the drug. Thus a study on the adverse drug reactions caused by antimicrobials both old and new needs to be analysed regularly.

References

1. Grahame-smith DG, Aronson JK. Adverse reactions to drugs. In:Grahame-Smith DG,Aronson JK editors. Clinicalpharmacology and drug therapy. 3rdEdition.New Oxford University Press;NewYork:2002;89-104.
2. Gleckman RA, Borrego F. Adverse reactions to antibiotics. JPGM1997;101(4):97-108.
3. SharmaVK, Sethuraman G, Kumar G. Cutaneous Adverse Drug Reactions Patterns to Antimicrobial Drugs in North India. JAPI 1998;46(12):1012-5.
4. SharmaVK, Sethuraman G, Kumar G. Cutaneous adverse drug reactions: Clinical pattern and causative agents- a 6 year series from Chandigarh, India. JPGM 2001; 47(2):95-99.
5. Mani MZ, Mathew M. A study of 218 drugeruptions.Ind JDermatol Venerol Leprol 1983; 49:109-117.
6. Fish DN. Fluroquinole Adverse effects and drug interactions.Pharmacotherapy 2001;21 (10s) :253s-272s
7. Than TCK, Allen G, Hayes D, etal. Possible association between toxic epidermal necrolysis and Ciprofloxacin. Lancet 1991; 338:522
8. Stubbings J, Sheehan-Dare R, Waltons. Cutaneous vasculitis due to ciprofloxacin. BMJ 1992;305:29
9. Imrie K, Gold W, Salit I, etal. Ciprofloxacin induced neutropenia and erythema multiforme. Am J Hematol 1993; 43(2):159-60
10. Alonso MD. Mixed eruptions caused by ciprofloxacin with cross sensitivity to norfloxacin. Allergy 1993;48(4):296-7
11. Dhar S, Sharma VK. Fixed drug eruption due to ciprofloxacin. Br J Dermatol 1996; 134:156-8.

J Pharmcovig Drug Safety 2009 (January - March) 6(1) :13-18

ORIGINAL ARTICLE

Need of Effective Communication For Pharmacovigilance Of Herbal Drugs

YOGESH MURTI, VIJAY SHARMA, KAMLA PATHAK AND DEVENDER PATHAK
Rajiv Academy for Pharmacy, NH 2, P.O. Chattikkara, Mathura 281001,

ABSTRACT

From prehistoric times, herbal medicine has been used by various communities and civilizations throughout the world. This trend continues to the present day. The increasing recognition of herbal products generates a great need to develop pharmacovigilance (safety monitoring) systems for herbal medicines. In everyday practice to identify previously unrecognized adverse effects or changes in the patterns of adverse effects, providing information to healthcare professionals and patients to optimize safe and effective use of herbal drugs and monitoring the impact of any action taken, World Health Organization (WHO) has set specific guidelines for the assessment of the safety, efficacy and quality of herbal medicines. The major problem in pharmacovigilance of herbal drugs is lack of communication. Transparent communication is essential to overcome these problems and ensure that all players collaborate to meet the goal of the safe and effective use of herbal drugs. Communication related to the awareness of the ill effects or the awareness related to encounter the symptoms exhibited by the medicines taken by the consumer should be thoroughly discussed by the health professionals to the patients is essential for the effective and safe therapy and better treatment too. The development of effective communication needs to be adequately resourced. It is likely that this most important part of the safety monitoring programme for herbal medicines will require proportionately greater resources than in the case for other medicines.

Introduction

Herbal medicines are widely used in health-care in both developed and developing countries. However, in recent years, there have been several high-profile herbal safety concerns that have an impact on the public health, and therefore the increasing recognition, generates a need to develop pharmacovigilance (safety monitoring) systems for herbal medicines. Pharmacovigilance for herbal medicines is, in many respects, in its infancy and monitoring the safety of herbal medicines presents unique challenges in everyday practice to identify previously unrecognized adverse effects or changes in the patterns of adverse effects, providing information to healthcare professionals and patients to optimize safe and effective use of herbal drugs and monitoring the impact of any action taken [1].

Information from many sources is used for pharmacovigilance. These include spontaneous adverse drug reaction (ADR) reporting schemes, clinical and epidemiological studies, worldwide published medical literature, information from pharmaceutical companies, information from worldwide regulatory authorities and morbidity and mortality databases. Information from all these sources has been carefully screened. It may identify unexpected side effects or indicate that certain side effects occur more commonly than previously believed or that some patients are more susceptible to some problems than others.

The major problem in pharmacovigilance of herbal drugs is lack of communication by which the consumers are getting incomplete or no information regarding the product they are using for the treatment of diseases and also from the patient to health professionals regarding adverse effects, experienced by the patient by using herbal drugs.

Communication related to the awareness of the ill effects or the awareness related to encounter the symptoms exhibited by the medicines taken by the consumer should be thoroughly discussed by the health professionals to the patients is essential for the effective and safe therapy and better treatment too.

Accidental incidences need to be highlighted by patients or they must come into the limelight which will only be possible by an effective communication to the health professionals. Communication among health professionals and patients both to warn about adverse effects from herbal drugs and to provide feedback of information is an important aspect of pharmacovigilance. Some other advance modes of communication can also be employed which may surely fill the gap of lapses generated between the patient and correct information regarding the safe use of herbal drugs and their results. These modes play an important role where the active communication is not possible. These modes are-

- Patient Information Leaflets (PILs) and Summaries of Product Characteristics (SPCs) for medicines are updated when new safety issues are identified.
- For urgent warnings about drug hazards, letters are sent to all doctors and pharmacists by post or electronic cascade.
- The regular drug safety bulletin, 'Drug Safety Update', produced by the MHRA and CHM aimed at all healthcare professionals.
- Fact sheets are produced for major safety issues for both healthcare professionals and patients.
- Safety alerts are published on the MHRA website [2].

Aims of Pharmacovigilance of herbal drugs

The specific aims of pharmacovigilance of herbal drugs are to improve patient care and safety in relation to the use of herbal drugs, improve public health and safety in relation to the use of herbal drugs, contribute to the assessment of benefit, harm, effectiveness and risk of herbal drugs, encouraging their safe, rational and more effective (including cost-effective) use, promote understanding, education and clinical training in pharmacovigilance of herbal drugs and its effective communication to the public [3].

However good the science, the evaluation of ADR data, and signal detection may be, they are of little use unless the messages reach intended audiences - doctors, patients, nurses, pharmacists, the general public - and many more. Preventing injury to patients requires top class communications. This module will focus on the skills and practice ofuse, promote understanding, education and clinical training in pharmacovigilance of herbal drugs and its effective communication to the public [3].

However good the science, the evaluation of ADR data, and signal detection may be, they are of little use unless the messages reach intended audiences - doctors, patients, nurses, pharmacists, the general public - and many more. Preventing injury to patients requires top class communications. This module will focus on the skills and practice of effective communications for pharmacovigilance professionals. Main elements are listed below, but some time will be spent on topics chosen by participants and directly relevant to problems in their own countries.

- Moden communications: what are the secrets of success ?
- The challenge of communicating drug safety messages to all audiences
- Developing an ADR reporting culture
- Influencing prescribing practice to avoid ADRs and encourage rational therapy
- Crisis management in pharmacovigilance
- Working with journalists and the media
- Holding effective meetings
- Practical workshops to develop skills [4]

Need of pharmacovigilance of herbal drugs

For the past several decades, herbal medicines have been increasingly consumed by people without prescription. They are traditionally considered as harmless since they belong to natural sources. Herbal formulations which have reached widespread acceptability as therapeutic agents are such as antidiabetics, anti-arthritics, aphrodisiacs, hepatoprotectives, cough remedies, memory enhancers and adoptogens. However, with a more efficient case reporting of adverse drug reactions, the hazards of herbal medicines as self prescriptions have been well recorded. In this regard the World Health Organization (WHO) has set specific guidelines for

the assessment of the safety, efficacy and quality of herbal medicines. The purpose of pharmacovigilance is to detect, assess and understand, and to prevent the adverse effects or any other possible drug-related problems, which is not only confined to chemical drugs, but extended to herbal, traditional and complementary medicines, biologicals, vaccines, blood products and medical devices. Herbal pharmacovigilance should be implemented and authorities should record apart from existing information on various aspects of the single herb and/or compound herbal formulations on concomitant use with

chemical drugs, adverse drug reaction, delayed or acute toxic effects, allergies etc. Most over-the-counter herbal products like ginseng have drawn great public attention but there is several case reports mentioned in the literature of adverse drug reactions of herbal drugs which are generally considered safe [5].

Need of effective communication for pharmacovigilance of herbal drugs

Pharmacovigilance is a field where communication is paramount. Information, such as single case reports, is transferred from health professionals to National Regulatory Administrations and between administrations and industry. The cumulation of reports may be used for information purposes, and to assist in the identification of possible signals. These are then assessed by the analysis of individual and aggregate cases, the latter being exchanged between administrations for multinational analysis at the European level. Once a decision has been made on a possible alert, the decisions and the reasons thereof must be transmitted to administrations and to other correspondents, such as health professionals, the pharmaceutical industry and WHO [6]. The communication cycle at various levels is depicted in Figure1

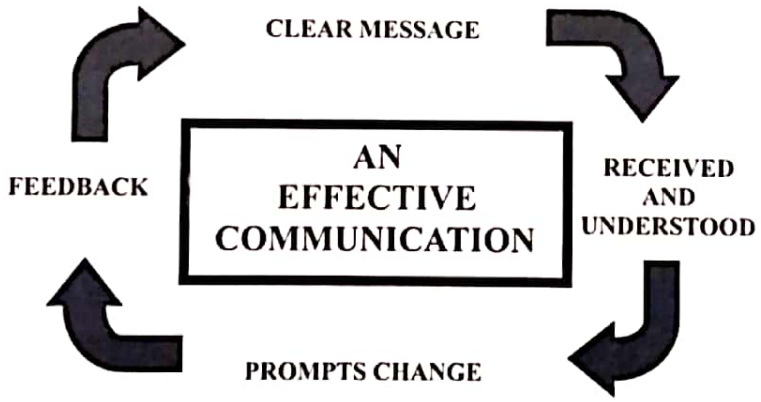


Figure 1 Levels of effective Communication cycle

Communication challenges:

There are some challenges in effective communication-

- The importance of ADRs and reporting them
- Information about benefit-harm and effectiveness-risk
- Encouraging rational drug use/compliance
- Communicating uncertainty
- Dealing with traditional beliefs and practices
- Involving patients
- Preventing or resolving crises

Actually the heart of good communications is understanding your audiences and tailoring messages precisely to them [7].

Principles of Effective Communications [8]:

- Be clear about your purpose
- Know your audience: empathy
- Choose appropriate methods
- Present message attractively
- Make benefits clear
- Repeat message
- Seek feedback

Importance of communication in pharmacovigilance of herbal drug

When medicines works well and there are no problems it is rarely news. However, a serious adverse drug reaction can be news; handling such issues is important as the public may get a wrong impression of a safe drug with a very good risk/benefit, due to a very rare adverse affects. Hence, the importance of communication in pharmacovigilance of herbal drugs; this is not limited to the general public but should also be extended to decision makers in health as well as the profession [9].

The successful safety monitoring of herbal drugs depends on good communication. There are many barriers to be broken down if all the players in this field are to be involved. There is distrust between some and ignorance of the work and function of different groups. The need of effective communication for pharmacovigilance of herbal drugs is due to:

- Known risks not communicated to prescribers/consumers
- Minimal effect of 'Dear Dr'- letters
- How to influence medical practice
- How to interact with/use media
- Crisis management and
- Challenges but few solutions [10]

Transparent communication is essential to overcome these problems and ensure that all players collaborate to meet the goal of the safe and effective use of herbal drugs.

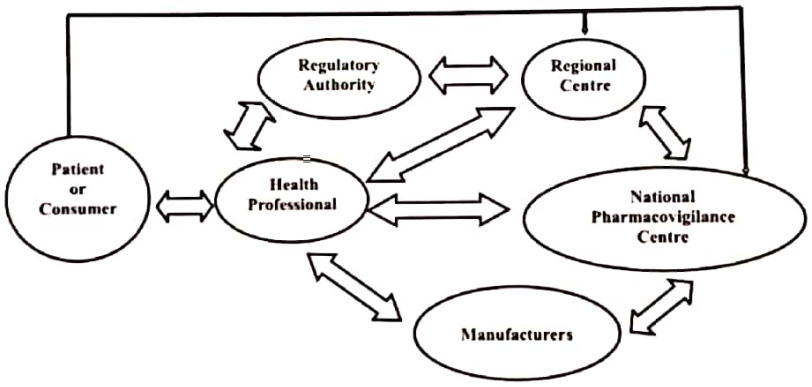


Figure : 2 Flow chart showing paths for effective communication for Pharmacovigilance of Herbal Drugs.

National pharmacovigilance centers should ensure that manufacturers receive timely information so that they can take appropriate action regarding their products. Effective communication of the results of monitoring is also essential so that pharmacovigilance activities can have a positive impact on the health of the people. If there is no national pharmacovigilance centre, consideration should be given to designating other relevant organizations, such as the national regulatory authority, poisons centers, drug information centers and consumer complaints authorities as the focal point.

Communication should be established at various levels, among -

- The national pharmacovigilance centre and health professionals
- The National Pharmacovigilance centre and providers of herbal medicines
- Health professionals and providers of Herbal Medicines, and consumers and patients
- Providers of Herbal Medicines and those for other Medicines
- The National Pharmacovigilance Centre and consumers
- The National Pharmacovigilance Centre and the Regulatory Authority
- The National Pharmacovigilance Centre and such centers in other countries, within the region or in other regions
- The National Pharmacovigilance Centre and UMC
- The National Pharmacovigilance Centre and the

mass mediaThe development of effective communication needs to be adequately resourced. It is likely that this most important part of the safety monitoring programmes for herbal drugs will require proportionately greater resources than in the case for other medicines.

Risk communication

Communication strategies should be established to reach effectively at all relevant target audiences, such as providers of herbal drugs, other health professionals,manufacturers and patients/consumers. Communication of safety information is a shared responsibility between national pharmacovigilance centers, national regulatory agencies, manufacturers and health professionals. Defferent risk communication vehicles can be considered, including-

- Adverse reaction bulletins or articles distributed in reputable journals
- Public advisories or warnings
- "Dear Health Professional" letters.

Various methods of information dissemination can be considered, such as:

- Internet posting
- Direct mass mailing to providers of herbal medicines and health professionals
- Briefings to the mass media
- Briefings to patient/consumer associations
- Education sessions at health professional society meetings.

In order to reach consumers and the wide range of providers of herbal medicines successfully, messages should be tailored to suit the recipients, including translation into local languages where appropriate [11].

Monitoring, evaluating and communicating drug safety is a public-health activity with profound implications that depend on the integrity and collective responsibility of all parties - consumers, health professionals, researchers, academia, media, pharmaceutical industry, drug regulators, governments and international organizations - working together. High scientific, ethical and professional standards and a moral code should govern this activity. The inherent uncertainty of the risks and benefits of herbal drugs needs to be acknowledged and explained. Decisions and actions that are based on this uncertainty should be informed by scientific and clinical considerations and should take into account social realities and circumstances.

Flaws in drug safety communication at all levels of society can lead to mistrust, misinformation and misguided actions resulting in harm and the creation of a climate where drug safety data may be hidden, withheld, or ignored.

Fact should be distinguished from speculation and hypothesis, and actions taken should reflect the needs of those affected and the care they require. These actions call for systems and legislation, nationally and internationally, that ensure full and open exchange of information, and effective standards of evaluation. These standards will ensure that risks and benefits can be assessed, explained and acted upon openly and in a spirit that promotes general confidence and trust.

The following statements set forth the basic requirements for this to happen:

1. Drug safety information must serve the health of the public. Such information should be ethically and effectively communicated in terms of both content and method. Facts, hypotheses and conclusions should be distinguished, uncertainty acknowledged, and information provided in ways that meet both general and individual needs.
2. Education in the appropriate use of drugs, including interpretation of safety information, is essential for the public at large, as well as for patients and health-care providers. Such education requires special commitment and resources. Drug information directed to the public in whatever form should be balanced with respect to risks and benefits.
3. All the evidence needed to assess and understand risks and benefits must be openly available. Constraints on communication parties, which hinder their ability to meet this goal must be recognized and overcome.
4. Every country needs a system with independent

expertise to ensure that safety information on all available drugs is adequately collected, impartially evaluated, and made accessible to all. Adequate nonpartisan financing must be available to support the system. Exchange of data and evaluations among countries must be encouraged and supported.

5. A strong basis for drug safety monitoring has been laid over a long period, although sometimes in response to disasters. Innovation in this field now needs to ensure that emergent problems are promptly recognized and efficiently dealt with, and that information and solutions are effectively communicated [12].

Conclusion

Pharmacovigilance has moved on from passive to active. It has a much broader remit in adverse drug reaction monitoring, patient safety, building systems and communicating. There are now opportunities for the developing world countries to engage in pharmacovigilance of herbal drugs. It is of utmost impotarnce that the monitoring, evaluating and communicating drug safety should be a collective responsibility of - consumers, health professionals, researchers, academia, media, pharmaceutical industry, drug regulators, governments and international organizations. The working should be of high scientific, ethical and professional standards and a moral code should govern this activity.

References

1. http://www.iss.it/binary/farm2/cont/pharmacovigilance%20herbal%20medicines%20meeting.1141397039.pdf
2. http://www.mhra.gov.uk/Safetyinformation/Howwemonitort hesafetyofproducts/Medicines/Pharmacovigilance/index.htm
3. http://www.pharmacovigilance.co.in/pharmacovigilance. html
4. http://www.who-umc.org/graphics/9714.pd.
5. http://www.akademiai.com/content/gq3757853221t4752/
6. http://www3.interscience.wiley.com/journal/112229710/ abstract
7. http://www.connmed.com.ar/instituciones2/aafhospitalaria.
8. http://healthtech.who.int/pq/trainingresources/pq_pres/pharmacovigilance/updatepresentations/19a_communications.ppt
9. http://www.fda.moph.go.th/apr//Global/pharmacovigilance.pdf
10. http://www.connmed.com./instituciones2/aafhospitalaria.org.ar/capacitacion/5congreso/presentaciones/47.ppt
11. http://www.who.int/medicinedocs/index/assoc/s7148e/s714 8e.pdf
12. http://www.umc.products.com

J Pharmcovig Drug Safety 2009 (January - March) 6(1) :19-21

ORIGINAL ARTICLE

Drug Utilization Pattern in the Outdoor Patient Department of a Government Dental Teaching Institute of Jamnagar city

A SUKHLECHA, SC HOTCHANDANI, HR TRIVEDI
Department of Pharmacology, M P Shah Medical College, Jamnagar - 361 008

Aim

1. To record and analyze the morbidity pattern at the outdoor unit of a Dental teaching institute
2. To study drug utilization pattern in relation to morbidity using the WHO basic drug indicators (Core and Complementary)
3. To analyze the prescriptions and assess their rationality
4. Make an attempt to provide an Essential Drug List for Dental teaching institutes based on the data collected

Methods

Data sources: Data was collected in the form of prescriptions written in from Oral Diagnosis out-door patient department because all the patients reported here initially. Prescription auditing was done from them. Review of literature was done from previous similar studies from library, internet etc.

Development of Protocol : An appropriate protocol was developed and performa for rationality of drug usage was used. The protocol and performa were approved by the institutional ethics committee. Permission from the Dean of the Dental institute was also taken.The study was carried out in the period of April- September 2006. Our study was cross-sectional (randomized).[1,2] The sample size was as per WHO (atleast 600 encounters in a cross-sectional survey). [3,4,5]

Inclusion criteria: Prescriptions of patients in age group of 15-50 years of either sex who had come with complaints for the first time in OPD were included (first encounter), For calculation of morbidity pattern all prescriptions which contained diagnosis were included.

Exclusion criteria:Prescriptions were excluded if: Handwriting couldn't be deciphered, cases referred from other hospitals, They contained drug belonging to Ayurveda or any other disciplines of medicine.

Core drug use indicators:[3,4,5] Prescribing indicators

Average number of drugs per encounter, Percentage of drugs prescribed by generic name, Percentage of encounters with an antibiotic prescribed, Percentage of encounters with an injection prescribed, Percentage of drugs prescribed from Essential drug list or formulary

Complementary drug use indicators

Average drug cost per encounter, Percentage of drug costs spent on antibiotics, Percentage of drug costs spent on injections

Study of rationality was done by a 30-point score system:[6]

Main drug (out of 20 points)	
Choice of drug (out of 10 points)	
First choice drug is used	
10 Second choice drug is used	06
Third choice drug is used	
(or used as placebo)	03
Wrong drug is used	00
Dose (out of 10 points)	
Correct formulation, strength, dose, duration	10
Inadequate dose/ excessive dose	05
Totally wrong dose	00
Correctness of complementary drug (out of 10 points)	
Choice of drug (out of 10 points)	
First choice drug is used	05
Second choice drug is used	03

(or used as placebo)	1.5
Wrong drug is used	00

Dose of complementary drug (out of 5 points)

Correct formulation, strength, dose, duration	05
Inadequate dose/ excessive dose	2.5
Totally wrong dose	00

Negative points were given for the use of :

Unnecessary drug (-5 for each drug), Irrational drugs (-5 for each drug), Hazardous drugs (-10 for each drug), Unnecessary injections (-5 for each injection)

When wrong drug was used as main drug in the prescription, zero points were assigned out of 20, but the same drug was not considered again in the column for unnecessary drug.The prescriptions were also analyzed for **FDCs (Fixed Dose Combinations)**

Prescription costs were calculated using the latest editions of MIMS (Monthly Index of Medical Specialties) [7]. Wherever drug prices were not available in the above books, prices were confirmed from pharmacies. For government supply drugs, the lowest price was taken into consideration.

Observations

Prescriptions collected	900
Prescriptions containing medicines in first encounter	601
Types of medicines prescribed	27
Total number of medicines Prescribed	1766

Table 1: Morbidity pattern in dentistry

S.No.	Disease	Cases	Percentage
1.	Dental caries	180	20
2.	Periodontitis (acute and chronic)	145	16
3.	Gingivitis	91	10
4.	Pulp and periapical abscess	89	10
5.	Oral ulcers	81	9
6.	Impacted teeth	72	8
7.	Mandibular injuries and fractures	62	7
8.	Trigeminal neuralgia	36	4
9.	Oral submucous fibrosis	19	2
10.	Oral candidiasis	06	1
11.	Others	119	13
	Total	**900**	**100**

Table 2: Prescribing indicators

Sl.No.	Indicator	Value
1.	Average no. of drugs per encounter (n=601)	3%
2.	Percentage of drugs prescribed by generic name (n=27)	15%
3.	Percentage of encounters with an antibiotic prescribed(n=601)	57%
4.	Percentage of encounters with an injection prescribed (n=601)	NIL
5.	Percentage of drugs prescribed from Essential Drug List	48%

Table 3: Complementary drug use indicators

S.No.	Indicator	Value
1.	Average cost of drug per encounter	Rs. 55.50
2.	Percentage of drug costs spent on antibiotics	30%
3.	Percentage of drug costs spent on injections	NIL

Table 4: Percentage frequency of prescribed medicines (n=1766)

S.No.	Type of medicine	Cases	Percentage
1	Antibiotics	435	25
2	Analgesics	395	22
3	Mouth washes	279	16
4	Vitamin B-complex	216	12
5	Gum paints	195	11
6	Medicated pastes	91	5
7	Oral ulcer gels	81	5
8	Carbamezapine	36	2
9	Antioxidants	19	1
10	Local steroids	13	0.74
11	Antifungals	6	0.33
	Total	**1766**	**100**

Table 5: GroupWise distribution of cost of medicines (five day treatment)

S.No.	Type of medicine	Cost (Rs)	% of total cost
1.	Antibiotics	10032	30
2.	Mouth washes (100ml bottle)	8370	25
3.	Analgesics	5119	15
4.	Gum paints (10 ml bottle)	3900	12
5.	Medicated pastes (50g tube)	2639	8
6.	Oral ulcer gels(10 ml bottle)	1620	5
7.	Antifungals	495	1.5
8.	Vitamin B-complex	484	1.5
9.	Carbamezapine	270	0.8
10.	Local steroids	247	0.7
11.	Antioxidants	181	0.5
	Total	**33357**	**100**

Results

- The number of medicines per prescription was 2.9 and the average cost per prescription was Rs. 55.50
- Approximately 14.8% of the prescribed medicines were generic.
- Antibiotics were prescribed in 57% of the encounters.
- Approximately 48% of the medicines were from WHO's model list of essential medicines.
- The most commonly used drugs were antibiotics, analgesics and oro-pharyngeal preparations.
- Dxycycline, Ciprofloxacin, Ampicillin+ Cloxacillin, Metronidazole, Ciprofloxacin+ Tinidazole were the most commonly used antimicrobials.
- Ibuprofen, Ibuprofen+ Paracetamol, Nimesulide, Diclofenec+ Paracetamol, Diclofenec were most commonly used analgesics.
- The most commonly used FDC was Ibuprofen+ Paracetamol.
- The most frequent diseases were dental caries, periodontitis and gingivitis in our study group.
- About 32% of the prescriptions were prescribed rationally.

Conclusion

We recommend the following medicines to be included in the Essential Drug list of a Dental Institute: Ampicillin, Ciprofloxacin, Metronidazole,Ibuprofen, Paracetamol, Carbamezapine, Antioxidants (vitamin E), Gum paint

References

1. Greenber MS, Lick MG. In Burket's Oral Medicine: iagnosis and Treatment. Tenth ed. BC Decker Inc. Hamilton, Ontario, Canada. P.10.
2. Rehan HS, Singh C, Tripathi CD, Kela AK. Study of drug utilization pattern in dental OPD at a tertiary care teaching hospital. Indian J Dent Res 2001 Jan-Mar; 12(1): 51-6
3. WHO. How to investigate drug use in health facilities: Selected drug use indicators, Geneva, World Health Organization 1993 (WHO/ DAP/ 93.1).
4. Guide to good prescribing, a practical manual, WHO, Action Programme on Essential Drugs. 1st Indian ed. 1997.
5. The selection and use of essential medicines. Report of the WHO expert committee. WHO TRS 933, 2005.
6. Gajjar BM. Evaluation and comparison of prescribing pattern of physicians from the institute and the private sectors for rational drug therapy [dissertation]. Karamsad; Sardar Patel University, 1990.
7. Gulhati CM (editor). Monthly index of medical specialities. New Delhi, India: 2006. 25(3).

J Pharmcovig Drug Safety 2009 (January - March) 6(1) :22-26

Guiding Principles for the Formulation of a Drug Policy in the State of Jammu and Kashmir

GEER MOHAMMAD ISHAQ, M. Y. SHAH
Dept. of Pharmaceutical Sciences, University of Kashmir, Srinagar 190006

ABSTRACT

Drug services to common masses and related issues in the state of Jammu and Kashmir are regulated through Drugs and Cosmetics Act, 1940, Narcotic Drugs and Psychotropic Substances Act, 1985, Drug Prices Control Order, 1995 and J&K Pharmacy Act, 2011 (samvat). As a result of increasing complexity of pharmaceutical and healthcare services in the state in the wake of an overwhelming increase in the number of drug sale outlets, an unexpected surge in morbidity rate, greater number of people resorting to alternative systems of medicine, need for promulgation of a comprehensive drug policy in the state has become inevitable. Our basic health and pharmaceutical care needs to be guided by a strong framework of guidelines envisaged under a proper policy statement. Keeping in view our regional requirements vis-à-vis existing procedures, drug-related laws and demography of the J&K state, some guiding principles that could lay a foundation in the formulation of a comprehensive drug policy for the state of Jammu and Kashmir are suggested in the present work that has resulted out of nine years of hands-on experience plus persistent, in-depth research and analysis of various facets governing pharmaceutical trade, profession and practice in the state.

Introduction

In light of the fact that drug and pharmaceutical consumption in the state of Jammu and Kashmir has touched an all time high in the recent years, drug sale outlets have witnessed an overwhelming increase in their number across the length and breadth of the state, morbidity rate has shot up as never before, number of people resorting to alternative systems of medicine has witnessed a sea change, our policy making officials and bodies need to perceive the immediate need for a detailed drug policy in the state. This assumes importance in order to take fresh initiatives in tune with ever-changing times and trends in drug and pharmaceutical sector. So far there have been absolutely no inputs towards strengthening or for that matter even initiating indigenous manufacture of some life saving drugs within the state at the smallest possible scale. The need for radically improving the policy framework for this knowledge-based sector should not be ignored any further.

Effective quality control of drugs: Rational prescribing and use of medicines; availability of safe and effective drugs in adequate quantities particularly at govt. centres; improved procurement, storage and distribution practices for drugs and other medical supplies; quality pharmaceutical and healthcare services at hospitals; stringent enforcement of drug related laws; adequate pharmacy and health education, research and training facilities at all academic and healthcare institutions; indigenous manufacture of life-saving drugs like parenterals these are some of the essential ingredients that constitute a drug policy of any state. However, not many of these vital components of basic healthcare system are guided by any strong framework of proper guidelines envisaged under a proper policy statement in the form a robust drug policy in the state of Jammu and Kashmir. -related laws and demography of the J&K state.Though we have policy frameworks for some other areas of administration like industries, agriculture, education etc, none of the state governments has so far evinced adequate interest in framing and implementing a comprehensive drug policy for the state of Jammu and Kashmir.

At national level, Pharmaceutical Policy 2002 is currently in force throughout the country including the state of Jammu and Kashmir. However national drug policy inter-alia chiefly addresses provisions relating to import, export, pricing, investments, R&D, industrial licensing and manufacture of drugs and pharmaceuticals that are mainly national concerns rather than regional ones. Our regional priorities are

somewhat different and pertain more to areas mentioned at the outset of this write-up. Hence keeping in view our regional concerns, the state of Jammu and Kashmir calls for an immediate promulgation of a new drug policy that could address all key issues related to the availability of safe and effective drugs at affordable prices as well as to their rational prescribing, improved distribution and sale in accordance with various drug laws. Some of the guiding principles that could lay the foundation and provide the basis in formulating a drug policy for the state of Jammu and Kashmir are suggested here. These guidelines are prescribed on the basis of our regional requirements vis-à-vis existing procedures, drug-related laws and demography of the J&K state.

Drug Selection

The first step towards framing a drug policy should be to select a limited number of medicines to be used throughout the state. Basic objective of this selection shall be to ensure uninterrupted supply of drugs of right quality, in a right quantity at a right price from the right source. This will be the cornerstone of our drug policy. A list of Essential Drugs to be used at the primary health centre level and at different levels of healthcare system has to be prepared. There should also be different lists for out-patients and in-patients at various hospitals that should be revised every year by a special committee consisting of eminent experts from different hospitals in the state and other leading specialists. This has also been necessitated by the World Health Organization. Preparation of an essential drugs list as per the local requirements and with particular focus to the diseases endemic to this region shall reduce drug procurement costs, ensure better availability of life-saving drugs throughout the year in every nook and corner of the state. Thus our capital expenditure can be directed in the most profitable direction resulting in its more economic use.

Procurement, Storage and Distribution

In order to maintain supply of medicines in time, reduce investments in inventories, make effective use of capital, procure drugs at a minimum price without compromising on their quality and to avoid stock out, shortages, duplication and wastage, modern techniques of drug storage and inventory control should be introduced. Drugs existing in the list prepared as above should be procured by a centralized procurement unit which may invite tenders and order the medicines for all hospitals and medical facilities in the state. However geographical entity of the state of Jammu and Kashmir demands that there should be two such fully-computerized centralized procurement units, one at Srinagar and the other at Jammu. All ordering needs to be carried out by the two central procurement, storage and distribution stores. All drugs should be ordered by these centres. stored there and distributed to different hospitals in the state.

Scientific and modern methodology for drug storage and inventory control needs to be adopted so that the central unit is aware at any time of the different drugs available at the different hospitals and health care facilities. This would ensure that the drugs do not pass their expiry dates and any imbalances such as shortages of a particular drug at one hospital and unused stocks at another would also be identified and corrective measures taken well in time. Checks and counter-checks, such as computerized inventory systems, modern accounting procedures, and surprise checks may be initiated to ensure that losses due to illegitimate activity is kept down to the bare minimum. Training of pharmacists in store-management and improvements in monitoring systems should also form an integral part of the system.

Drug Laws Enforcement Administration

Drug control enforcement staff should be augmented and strengthened in tune with the recommendations of several committees like Hathi Committee report (1975), National Human Rights Commission Report (1999) and the report of Standing Committee on Petroleum and Chemicals (2001). There should be at least one drug inspector for every 100 sales outlets or 25 manufacturing establishments.Accordingly there should be one drug inspector available at every block level in the state. In light of the fact that there are only 103 medical blocks in the entire state, net financial implication of this augmentation is estimated to be not more than rupees 1.25 crore per annum. This much financial burden on the state exchequer should be quite bearable in the face of its potential benefits in terms of an effective drug control mechanism in the state. Good news in this direction is that strenuous

efforts of J&K Pharmacy Graduates Association initiated way back in June 2003 have ultimately borne some fruit. A detailed proposal framed by this author towards creation of 90 posts of Drug Inspectors and their subsequent placement at Medical Block level in the state, after having been duly endorsed by the Drugs Controller of the J&K state has been ultimately accepted by the Ministry of Health and Family Welfare, J&K Government. The said ministry has recently issued orders in writing towards creation of 72 posts of Drug Inspectors and 14 posts of Assistant Controllers in the state. After implementation of this order, Jammu and Kashmir will probably be the only state in India having one Drug Inspector available to masses at the Block level, who are otherwise posted one at District level in other parts of the country. Presently drugs falling under alternative systems of medicine including Ayurveda, Unani, Siddha and Homeopathy are not regulated by any legal framework so far as their sale, storage or distribution is concerned. Though provisions relating to these aspects have been outlined in the Drugs and Cosmetics Act,1940 and Rules thereunder, these provisions have not been enforced unlike other provisions relating to the drugs belonging to the allopathic system of medicine. Therefore it should be a priority for the state govt. to bring drug sale, storage and distribution of alternative systems of medicine also under the ambit of Drug and Food Control Administration and adequate powers should be vested upon the existing staff in this regard until further augmentation is made possible. Further the provisions of Drugs and Cosmetics Act, 1940 dealing with the manufacture, sale, storage and distribution of cosmetics may also be enforced to the possible extent in due course of time. This shall further strengthen the need for expansion of manpower presently available with the Drug and Food Control Organization, J&K, keeping in view their existing workload which is quite heavy at present.

Further the lack of adequate transportation, accommodation, communication and judicial assistance facilities to the available inspectorate staff is posing severe hardships in proper enforcement and efficient monitoring of drug regulatory legislations within the state and hence need immediate redressal to the maximum possible extent. It is therefore high time to revive, revamp and reconstruct our drug control administration on the pattern of states like FDA, Maharashtra so as to make drugs of best quality, safety and efficacy available to the masses at reasonable rates along with suitable counseling services by qualified pharmacists at drug distribution outlets.

Quality Control of Drugs

There is a need for an urgent augmentation of the drug testing facilities in the state in respect of equipment, technical staff and infrastructure. Modernization and up-gradation of the two existing drug-testing laboratories at Jammu and Srinagar should be taken up at war footing basis. Third generation testing equipments like HPLC, HPTLC, FTIR, UV-Spectrophotometry, NMR and Mass Spectroscopy need to be introduced in a phased manner. Continuing education programmes, training workshops etc will have to be conducted for training the existing technical staff in handling such instruments. Moreover an ever-increasing need for more extensive testing and analysis of drugs and pharmaceuticals demand more number of posts of Govt. Analysts and other skilled technical personnel for such analysis.

Annual testing load and average testing time of each laboratory should be streamlined and fixed in line with the available facilities. Both testing laboratories should be sophisticated to the extent of making them able to test all kinds of drugs including parenterals. At present, most of the parenteral products are sent to CIPL, Ghaziabad as the necessary facilities are not available here thus causing inordinate delay in initiating legal proceedings against the defaulters. Quality control cells will have to be constituted in every major hospital as part of in-house Quality Assurance system.

Drug Prices Control Mechanism

Drug prices are determined by the National Pharmaceutical Pricing Authority of India at the central level and enforced by various states including hat of J&K in accordance with the provisions of the Drug Prices Control Order of 1995. In order to enable the drug control administration staff to enforce these provisions, they have to be notified under para 21 of DPCO, 1995 as enforcement officers as envisaged under Essential Commodities Act, 1955. In the state of Jammu and Kashmir inspectorate staff is not empowered to take any legal action against any individual or dealer found charging in excess to the amount prescribed because they have not been

notified under DPCO, 1995 or the Essential Commodities Act, 1955.Under these circumstances all offences relating to excessive charging of taxes etc have to be prosecuted by the Asstt. /Deputy Controller of drugs and the field staff find themselves helpless in such cases. As such, inspectorate needs to be properly notified and necessary status needs to be accorded to them in this regard so that prompt action could be initiated in cases of exorbitant/exploitative charging of prices on drugs.

Pharmacy Education and Training

The Jammu and Kashmir Pharmacy Council has been constituted a few years ago. So far, Council has prepared the first and subsequent registers of those pharmacists who have been carrying on the business or profession of pharmacy in J&K. As a next step, it has to frame an Executive Committee and regulate pharmacy education in the state by way of enforcement of Education Regulations as provided under section 10 of the J&K Pharmacy Act 2011 (samvat). Thereunder it can prescribe the minimum standards of education required for qualification as a pharmacist and can also prescribe the nature and period of study and of practical training to be undertaken before admission to the qualifying examination for a degree or diploma in pharmacy. Further these regulations shall also lay down the subjects of examination and the standards to be attained therein apart from the equipment and facilities to be provided to students for undergoing such approved courses of study.

Once Education Regulations come into force, no person other than a diploma or a degree holder in pharmacy should be designated or registered as a pharmacist and a target date should be fixed beyond which no person other than a pharmacy degree or diploma holder can apply for a drug sale license. Drug trade should thereafter be strictly restricted to diploma or degree holders in pharmacy only. In order to cater to the requirement of qualified pharmacy personnel for such endeavour, diploma course in pharmacy may be commenced at govt. polytechnics in Jammu and Srinagar after appointing teaching staff and making other necessary facilities available for the purpose.

Just the way central Drugs and Cosmetics Act, 1940 has been enforced in the state, central Pharmacy Act of 1948 too needs to be promulgated in place of J&K Pharmacy Act 2011 (samvat). This will bring all pharmacy academic institutions of the state under the purview of the Pharmacy Council of India, help our pharmacists get registered in the Central Register and practice pharmacy profession anywhere in India. Besides it will also enable our pharmacy institutions seek financial assistance from central councils, organize and participate in their continuing education programmes, seminars etc and achieve national and international level standards in our pharmacy and health education.

After constituting its Executive Committee and enforcing Education Regulations in the state, J&K Pharmacy Council may appoint its own inspectors having prescribed qualifications, as provided under section 26 A of the Pharmacy Act, 1948 in order to inspect the premises where drugs are dispensed, to enquire whether a person who is engaged in selling, dispensing or compounding of drugs is a registered pharmacist, to investigate complaints regarding contravention of the Act and to institute prosecutions against the offenders. This initiative shall help our society get rid of drug delivery and distribution at the hands of unqualified, unregistered and unscrupulous people.

Rational prescribing and use of Drugs

A State Pharmaceutical Trust may be set up to monitor the drug prescribing practices of physicians and evaluate their appropriateness with an intention to guide the medical professionals for achieving the aim of rational prescribing. Such a Trust may also be levied with the task of monitoring the standard practices in drug promotion and use, clearly identifying those that are acceptable and prohibit those which are unethical or against the consumers' interests.Such a measure is indispensable for accomplishing the goal of ethical prescribing and rational use of drugs since at present there are no legalities in place to regulate these vital issues of healthcare resulting into irregularities like polypharmacy i.e., unnecessarily heavy prescriptions and other gratifying drug promotional practices that are widely debated every now and then in the media. To make certain that drugs on the essential list are

prescribed, a series of workshops on rational use of drugs should be held throughout the state for all categories of persons involved in prescribing, dispensing and administering of drugs.

Drug Information Services

The need for a reliable local source of drug information within each hospital is of paramount importance in rendering effective clinical care to the patients.For specialized information on different aspects of drugs, it is proposed to set up a computerized Drug Information Centre in the state. The main aim of this centre would be to instantaneously furnish complete, practical and unbiased information on all drug related queries like indications, contra-indications, dosage, adverse reactions, special precautions, drug and food interactions, brands available, toxicities etc.
Such a centre should be well-equipped with all necessary reference texts, journals, reprints, databases, CDs, fax, e-mail services etc. Computerization and networking of such a centre shall make its connectivity and up-linking possible with other reputed and well-established Drug Information C. .res of the country and the world, thus making information on recent developments in drug discoveries, newer treatment approaches etc easily accessible to our medical professionals.

Hospital Pharmacy Services

Guidelines put forth by the Medical Council of India with regards requirement of qualified pharmacists in hospitals need to be implemented. They have prescribed a minimum of three qualified pharmacists for every 50 bed-hospital or less, 5 for 51-100 bed hospital, 8 for 100-200, 10 for 200-300 and a minimum of 15 qualified pharmacists for 300-500 bed hospitals. National Human Rights Commission in its report on hospital pharmacy services submitted in January, 1999 has also recommended that, "every hospital should organize the pharmaceutical activities in regard to purchase, storage, testing, compounding, dispensing and distribution of drugs under the charge of a competent and experienced persons possessing at least degree in pharmacy". In accordance with these guidelines and the recommendations made vide Hathi Committee Report (1975), it is necessary that the requirements as per MCI guidelines be fulfilled and necessary mechanism devised. It is only professionally trained and legally qualified pharmacy personnel who apart from the physicians and nurses should counsel and disseminate information to patients on matters like indications of the drug, its contra-indications, adverse effects, precautions, dosage etc and could also play their legitimate and pivotal role in procurement, testing, storage and dispensing of standard quality drugs in every hospital and primary health centre.

Indigenous Manufacture of Drugs

In order to economize our drug budget, minimize our expenditure on some of the hospital pharmaceutical supplies and make quality drugs available at affordable prices at our primary, secondary as well as tertiary care hospitals, it will be apt to frame a detailed proposal in consultation with Industries department for the establishment of a govt.-owned pharmaceutical manufacturing unit in the state. There is no dearth of technical manpower in our state for efficient management of such an enterprise. Services of pharmacy graduates can be effectively utilized for this purpose too. Alternatively, in tune with Hathi Committee recommendations and considering the large scale consumption of I.V. fluids in hospitals, manufacture of I.V. fluids and tablets could be initiated in all major hospitals of the state.

Monitoring and Evaluation of the Policy

Ministry of Health and Family Welfare may frame a committee that would monitor and evaluate the drug policy once it is formulated and would also supervise its implementation and conduct regular, periodic revisions whenever and wherever required. This committee may also observe its performance in relation to projected activities and point out specifications demanding amendment and improvement from time to time.
The primary function of this document is to serve as a guide for the development and provision of quality pharmaceutical services in government health institutions as well as in private sector. The afore-mentioned objectives serve as a collective statement of goals to be achieved in our healthcare system. Transforming these goals into realities will require dedicated efforts on part of the govt., healthcare professionals as well as common consumers. On the contrary, continued absence of a comprehensive drug policy will freeze all opportunities of progress and development in our drug control and delivery mechanism.

J Pharmcovig Drug Safety 2009 (January - March) 6(1) :27-31

Detecting ADR/Signals from routine investigations in patients undergoing treatment in a medical ward of a hospital : A 3 month study

ZAHRA HASHEMI, PIPASHA BISWAS[1], SZ RAHMAN[2]
Ibn Sinâ Academy of Medieval Medicine & Sciences, Aligarh, 202002
1Symogen U.K. Marlow, Buckinghamshire SL7 1JW, United Kingdom.
2Department of Pharmacology, Jawaharlal Nehru Medical College, AMU, Aligarh, 202002

Introduction

ADR from routine investigations are defined as those Adverse Drug Reactions, which are found serendipitously on routine investigations. These routine investigations such as LFT, RFT, Haemogram on follow up patients after drug therapy may suggest either improvement or deterioration of the patient's condition. Deterioration may effect as ADR. These ADRs may then be reported as Signal from routine investigations.

There have been many reports concerning drug errors published in the medical literature including drug usage [1-3], prescribing practices [3-6] and poor system design in medical practice [7-8] which can result in occurrence of adverse drug events [9-10]. Andrews et al. [11] found that for each day in hospital the likelihood of experiencing an adverse event increased about 6%. Other studies conducted by the Harvard Medical Practice [12-13] reported medications to be the single most common cause of adverse events in hospitalized patients (19%). These ADRs could be found either on clinical examinations or by routine investigations of patients undergoing treatment in a medical ward or on OPD visit.

Drug errors increase cost, significantly prolong hospital stay and increase the risk of death almost 2-fold [14]. Several easily identifiable factors associated with a large proportion of medical prescribing errors include inadequate knowledge regarding drug therapy, patient factors related to drug therapy, such as age, impaired renal function and drug allergy; need for calculation of drug doses, specialized dosage formulation characteristics and medication prescribing nomenclature. Drug errors in hospitalized patients can be dangerous and inevitable events, not just unhappy accidents that cannot be predicted. In an era of constrained resources, drug errors are costly, but can be prevented in many instances including on routine investigations [15-23].

Methods

In the present cohort study, investigations of 110 patients were reviewed in clinical wards of the Jawaharlal Nehru Medical College Hospital, Aligarh Muslim University, Aligarh, India.

Observation

Out of 110 patients' investigations that were reviewed, 9 ADRs were found from the routine investigations in patients undergoing treatment in a medical ward of a hospital during the 3 months study period (9.9.2008 - 10.12.2008). Following is the brief description of the 9 cases.

Case 1: Gatifloxacin associated Purpura

A 70 yr old COPD patient developed severe adverse reaction purpura at inguinal skin area after Gatifloxacin

A 70 yr old male, HIV negative was diagnosed a case of COPD with acute exacerbation. He was prescribed Inj Aminophyllin, inhaled Beclomethasone (600 ug), Salbutamol (800 ug) and Gatifloxacin (200ml/400mg) ½ once daily over 1hr. After fourth dose of Gatifloxacin, he developed bluish discoloration of inguinal skin area of thigh and scrotum, with mild pruritis and burning sensation. On examination, non palpable purpura was present in the above mentioned area, it did not blanch on pressure. local temperature was not raised and painful.

Following investigations were then later on done: Hemogram, renal function test, liver function test, ABG, platelet count, BT, CT. All suggested investigations were within normal limit. X-ray was suggestive of COPD. Patient was treated with topical corticosteroid cream and systemic steroid (oral predisonolone in a dose of 40 mg once a day). In addition, he was advised to take local emollient and antihistamine H1 (Fexofadine) in a dose of 180 mg once a day for 7 days. The purpura persisted for 15 days, but it was no longer pruritic and decreased slightly. The patient on follow up was then later on found asymptomatic.

The patient might have developed the purpura due to Gatifloxacin.

Case 2: Nimesulide induced Hepatitis in a child of 4 years

Nimesulide (4-nitro-2 phenoxymethane sulphonamide) causing severe life threatening adverse events such as hepatoxicity.

A 4 years old male child, with fever for the last 8 days associated with rigors and chills only. The patient was given a prophylactic treatment by a pediatrician for paratyphoid as Ofloxacin (syrup Zenflox Forte) in a dose of 1-1/4 spoonful twice daily for 10 days. In addition, the patient was also advised the syrup Crocef 100 mg twice daily and Nimuselide (syrup Nimica 50) in a dose of 1-1/4 spoonful (5ml). On second day, Enzymes (Syrup Gastrium) for 6 weeks and Multivitamins + Iron (Elixir Nigoadine) 1-1/4 spoonful thrice daily were added.

The above drugs were advised after following investigations Haemogram and Widal Test. The Widal Test was positive.

15 days later the patient felt weakness and was diagnosed as a case of jaundice. Following investigation was then done: S. Bilirubin (8.70mg/dl); SGOT/AST (293 U/L); SGPT/ALT (785 U/L) and Alkaline Phosphatase (22KAV); Australian Antigen [Hbs Ag] and Malaria Parasite (ELISA negative).

Patient had no history of jaundice in the past, no history of contact, no history of blood transfusion or antitubercular treatment or any other drug. Family history showed no history of contact with jaundiced. Immunization status showed no history of receiving Hepatitis B vaccines. Other examination showed the pulse rate as 110/min; respiratory rate as 26 per minutes. On systemic examination, chest bilaterally was clear, on per abdominal examination, no tendernesss, however, spleen was palpable but no hepatomegaly was there. No abnormality was detected during CVS and CNS examination, icterus present, the liver was found three fingers enlarged and firm, spleen was also palpable; other systems were normal on examination.

The patient might have developed the serious hepatic adverse reaction due to Nimesulide.

Case3: Cutaneous Adverse Drug Reaction with Ciprofloxacin

A 46 yr old female was diagnosed with PUO with high fever. She was then prescribed Ciprofloxacin 500 mg daily. However, after four hours she developed itching and burning sensation all over the body with reddish brown confluent erythema along with urticaria. The confluent erythema and urticaria was then started after 2 days. Following investigations were done Blood Urea (58 mg%), Blood Sugar (222mg%), Serum Creatinine (2.3mg%), SGOT (15KAV/dl), SGPT (10 KAV/dl), Alkaline Phosphatase (20 KAV/dl), Serum Bilirubin (0.8 mg%).

Patient was asked to discontinue the drug and was treated with dexamethasone I/M (Dexona amp) once daily for 5 days, Tab Levorid once daily for seven days and cream Fucibet three times daily for seven days. The patient might have developed severe ADR due to Ciprofloxacin with no previous drug reaction.

Case 4: Artemether induced severe headache

Arthemether given to a patient of 45 years who was suffering from Malaria in a dose of 80 200 mg (3.2 mg/kg IM as 1st dose and 1.6 mg/kg IM after 12-24 hrs). Thirty minutes later the patient developed severe bitemporal headache associated with bifacial pain radiating towards jaws and neck on both sides.

On clinical investigation nothing was indicated for the causation of headache. The medicine was discontinued but headache lasted for 5 days due to Artemether.

Case 5: Suspected Cotrimoxazole Hypersensitivity A 20 yr old male patient was taking Tablet Septran 40/200 (Cotrimoxazole + Sulmethaxazole) for LRTI and developed discharging, non-healing ulcers on penis for 8-9 days. In addition, the concomitent medicine were Tab B-complex and Tab Crocin.

Investigation: Patient was stopped medication and prescribed Candy wain cream locally twice daily, and cream Genotypic locally twice daily, with tab eltoxin 500 mg thrice daily. Patient improved after 9 days of discontinuation and ulcers healed by time.

Case 6: Suspected Alprazolam Induced Dermatitis

A 40 year old male having Acid Pepsin disease with HITV developed after 18 hours urticated & erythematous papules on chest, back and legs. On treatment with Alprozolam from date 11-4-2000 to 14-4-2000.

The drug was discontinued and reintroduced, which again with same pattern of reaction appeared

Tab Alprozalam (0.2 mg) one tablet at night with concomitant drugs as below

Tab Enras 5mg; Syp Mucagel was given 3 teaspoonful six hourly. Tab Domestal 10 mg half tab twice daily.

Tab Enalapril was given 50 mg once daily Tab Capomiz 20, Tab Domperidone (10 mg) half tablet twice daily. Tab Pepcid(0.1mg) before sleep.

All drugs were stopped and tab Ataspan (Flexofenidine), 180 mg once at night from dates 13-4-2000 to 17-4-2000 was given and the reaction subsided after 4 days.

All the above drugs were reintroduced and no reaction was observed. On reintroduction of tablet Depid (Alprozolam 0.2mg), same skin reaction appeared and final assessment is that Alprozalam is the causative drug for dermatitis.

Case7: Mild Icteric Tinge of the Sclera on Chloroquine treatment for Malaria.

A 20 year old male reported at OPD with a typical history of malaria viz high grade fever with rigors for 3 days, was admitted. On examination there was no other positive findings on clinical examination.

He was given 4 tablets of chloroquine phosphate at time of admission, another 2 tablets in evening and 2 more in the morning and the condition of patient started deteriorating after the last dose of chloriquine, patient developed mild icteric of the sclera with yellow coloured urine.

Jaundice deepened and patient within the next 2 days went into acute renal shut down and expired on the 5th day of the admission.

Following investigations were done: Hemoglobin (7 gm %), Serum biliburin (4 mg%). Urine examination revealed presence of urobilinogen and absence of biliburin. The causative for excessive haemolyis in the patient is due to haemolytic origin of the jaundice. The excessive haemolysis could have been due to deficiency of enzyme Glucose 6 phosphate dehdrogenase (G6PD), however no test was done to diagnose this deficiency as it was suspected when the patient went into acute renal shutdown. This is rare case of chloroquine toxicity.

Case8: Ampicillin induced Steven Johnson syndrome.

Case Report:A 40 year old female reported with mild fever and cough with mild mucoid expectoration, On examination reveled occasional scattered crepitations in the chest.

Following investigations were done: Haemoglobin (8 gm%), Total leucocyte count (11,00/cu mm), Differential Leucocyte Count (p78 L22).

She was advised to take cap Ampicillin 250 mg orally every 6 hours. On fourth day of therapy, she returned to hospital with fever, malaise, headache, redness of the eyes and a generalized erythematous rash, with papular lesions and scattered thickened hyperpigmented plagues. Ampicillin was withdrawn following marked improvement in the condition of patient. Drug used for treatment were Erythromycin 500mg 6 hourly, prednisolone 60 mg once daily in divided doses and condy wash and G.V.Paint for local application.

Steven Johnson syndrome is well established occurring with Beta lactam Antibiotics, Ampicillin belongs to same group, on stopping this drug the patient recovered.

Case 9: Subacute bacterial Endocarditis

A 28 year old male of rheumatic heart disease with mitral stenosis was reported for fever and sore throat. He was admitted with suspicion of subacute bacterial endocarditis and was advised streptomycin (1 gram + 10 lacs) intramuscularly daily, patient started showing increase in temperature in the evening, on stopping the injection for four days the spikes of fever disappeared, on starting the drug again patient revealed again spike in temperature

On investigation and clinical examination, it was revealed mild pallor. The spleen was not palpable and there was no microscopic haematuria, blood culture was sterile.

In this case dechallenge was positive, rechallenge was also positive since the injection contained two components, namely streptomycin and penicillin, and rechallenge was not tried with individual drugs, it was difficult to incriminate only one component as either of them could have been responsible for the reaction.

Analysis of ADRs

Naranjo causality assessment algorithm scale [24] was used to assess the causality of drug's reactions.

Discussion

Adverse drug events (ADEs) contribute significantly to patient morbidity and mortality as well as to cost for healthcare providers and society. While, at one hand routine investigations help in detecting ADRs of common issue, but on the other hand, the number of diagnostic and therapeutic procedures carried out daily puts the hospitalised patient at an extremely high risk for ADEs. ADEs occurring during hospitalisation

may result from the special clinical situation of hospitalised patients;high degree of severity of diseases (e.g., renal failure, necessity of intensive care) specific drugs and other interventional administered only in hospitals. Such type of study where we do monitoring of ADRs on the basis of routine investigations help in removing the factor of biasness, which is common in other forms of reporting such as spontaneous ADR reporting. Only few studies are done wherein it was showed that routine investigations during treatment can play an important role in detecting ADRs /Signals. However, most of the studies are done where we can see that investigations were done from patients of ADRs.

Conclusion

The study to detect ADRs has added to the evidence base on routine investigations in patients undergoing treatment in a medical ward of a hospital and has identified where additional research could be focused. There is a paucity of published research to evaluate ADRs on routine investigations for suspected ADRs. However, there is now substantial experience, from several countries in which investigations are done and that reactions are then identified. None of the countries with investigations based reporting systems has reported that there is no need of doing investigation to detect ADRs. Investigation based ADR reporting appear to contribute a relatively small percentage of total reports. Therefore, it is concluded that the routine investigations should now be considered by many pharmacovigilant experts together with robust evaluation of process and outcomes.

Annotation: The above study is a part of the project report for the partial approval of the Certificate Course in Pharmacovigilance and Pharmacoepidemiology, Symogen India Pvt. Ltd., New Delhi during September to December, 2008

References

1. Lesar TS, Lomaestro BM, Pohl H. Medication prescribing errors in a teaching hospital. A 9-year experience. Arch Intern Med 1997; 157:1569-76.
2. Folli HL, Poole RL, Benitz WE, Russo JC. Medication error prevention by clinical pharmacists in two children's hospitals. Pediatrics 1987, 79:718-22.
3. Lesar TS, Briceland LL Delcoure K, et al. Medication prescribing errors in a teaching hospital. JAMA 1990,263:2329-34.
4. Peterson CD, Goldberg DE. Pharmacy coordinated process for evaluating physician drug prescribing. AmJHosp Pharm 1989; 46:1787-91.
5. Thorn DB, Sexton MG, Lemay AP, Sarigianis JS, Melita DD, Gustafson NJ. Effect of a cancer chemotherapy prescription form on prescription completeness. Am J Hosp Pharm 1989; 46:1802-6.
6. Lacasa C, Cot R, Martinez J, Polo C, Andreu C, Serrais J, Sala P. Medication errors in a general hospital. Environ Health Perspect 1998;4:35-40.
7. Leape LL, Lawthers AG, Brennan TA, Johnson WG. Preventing medical injury. Qual Rev Bull 1993;19:144-9.
8. Leape LL. Error in medicine. JAMA 1994; 272:1851-7.
9. Bates DW, Gullen D, Laird N. et al. Incidence of adverse drug events and potential adverse drug events: implications for prevention. JAMA 1995; 274: 29-34.
10. Leape LL, Bates DW, Cullen DJ, et al. System Analysis of adverse drug events. JAMA 1995; 274:35-43.
11. Andrews LB, Stocking C, Krizec T, Gotlieb L, et al. An alternative strategy for studying adverse events in medical care. Lancet 1997; 349:309-13.
12. Brennan TA, Leape LL, Laird N, et al. Incidence of adverse effects and negligence in hospitalized patients: results of the Harvard Medical Practice Study. I. N Engl J Med 1991; 324:370-6.
13. Leape LL, Brennan TA, Laird N, et al. The nature of adverse events in hospitalized patients: Results of the Harvard Medical Practice Study. II. N Engl J Med 1991; 324:377-84.
14. Classen DC, Pestotnik SL, Evans RS, et al. Adverse drug events in hospitalized patients. Excess length of stay, extra costs and attributable mortality. JAMA1997;277:301-6.15

15. Lesar TS, Briceland L, Stein DS. Factors related to errors in medication prescribing. JAMA 1997; 277:312-7.
16. Stephens D. Insurer looks at the pharmacist's cost control function. Am Druggist 1991; 203:62.
17. Dobie RL, Rascati KL. Documenting the value of pharmacist interventions. Am Pharmacy 1994;34:50-4.
18. Porsius AJ, Van Den Brick G. Quality assessment of drug therapy: Criteria and protocols. Pharm Weekbl.1991;126/49-50:1275-82.
19. Bates DW, Spell N, Cullen DJ, et al. The cost of adverse drug events in hospitalized patients. Adverse drug events prevention study group. JAMA 1997; 277;307-1
20. Rupp MT. Value of community pharmacists' interventions to correct prescribing errors. Ann Pharmacother 1992; 26;1580-4.
21. Vincer MJ, Murrey JM, Yull A, Allen AC, Evane JR, Stineon DA. Drug error and incidence in a neonatal care unit: a quality assurance activity. Am J D C 1989;143:740-87.
22. O'Donnell J. Pharmacy malpractice: An avoidable hospital cost. Perspect Pharmacol 1984;1:1-12.
23. Hartwig SC, Denger SD, Schneider PJ. Severity indexed, incident report based medication error reporting program. Am J Hosp Pharm 1991;48:2611-6.
24. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981; 30: 239-45.

J Pharmcovig Drug Safety 2009 (January - March) 6(1) :32-34

ORIGINAL ARTICLE

Study of Adverse Drug Reactions Due to Antiretrovirals

SHAZIA PARVEEN, HAROON.S. KHAN, ANJUM PERVEZ, JAMEEL AHMAD.
Department of Medicine and Pharmacology1, JN Medical College & Hospital, AMU Aligarh-202002

ABSTRACT

Objective: To study the adverse drug reactions of antiretroviral drugs Zidovudine (AZT) & Stavudine (d4T) in HIV positive patients.

Methods and Results: In the present study, adverse drug reactions (ADRs) due to the drugs, AZT & d4T were studied. 300 patients on antiretroviral drugs were studied prospectively of which 212 patients were on AZT based regimen and 88 on d4T based regimen. All the patients attending to the ART centre were investigated along with base line investigations including haemogram, Renal function test, Blood sugar, Liver function test, lipid profile, VDRL, HBsAg, anti HCV and CD4 cell count. These patients were evaluated initially at 15 days and then every month. Haemoglobin and LFT were done at 15th day follow up and also Serum lactate and amylase levels if required. On AZT based regimen, anemia was the commonest ADR followed by nail and tongue pigmentation, fever and myopathy. On d4T based regimen peripheral neuropathy was the commonest ADR followed by lipid dystrophy and lactic acidosis.

Conclusions: Although AZT can cause life threatening anemia but with proper initial monitoring this can be prevented but on the other hand, d4T causes long term ADRs and need monitoring for long term metabolic effects, so AZT is a better option for starting ART.

Key words: Zidovudine, Stavudine, Antiretroviral, Adverse Reaction, Peripheral neuropathy, d4T, CD4, NNRTI

Introduction

The first line antiretroviral therapy include the combination of nucleoside reverse transcriptase inhibitor (NRTI) and nonnucleoside reverse transcriptase inhibitor (NNRTI). Stavudine, Lamuvidine,and zidovudine belong to NRTI while nevirapine and efavirenz belong to NNRTI. Either d4T or AZT is given along with lamuvidine with one NNRTI. The NRTI group of drugs causes long term toxicities due to impairment of synthesis of mitochondrial enzymes that generate the ATP. The ADRs are myopathy, neuropathy, hepatic impairment, lactic acidosis, lipid dystrophy, myelosuppresson which further causes anemia and granulocytopenia1,8.

AZT causes myelosupression that leads anemia and granulocytopenia, it can also causes myalgia, nail and tongue pigmentation2 .Anemia due AZT may be so severe that it may require hospital admission and blood transfusion3.

d4T causes long term side effects like peripheral neuropathy and lipid dystrophy4. Both peripheral neuropathy and lipid dystrophy may be so severe that it may need change of treatment. It occurs in patients having low CD4 counts5,7,9.

It is more distressing to females as it causes increase in breast and abdominal fat and loss of buccal fat while men present with fat loss at the site of in limbs and buttock 6 d4T may also cause pancreatitis which were asked to bring the drug bottles with them and may require hospitalization.

Lactic acidosis may occur due to NRTI, it is rare but if it occurs, it is life threatening and need stoppage of drug.

AZT is superior to d4T because its active triphosphate is only a weak inhibitor of gamma polymerase, although d4T is cheaper but it causes long term metabolic and morphologic ADRs.

Methods

The study was carried out at ART centre, Department of Medicine, JNMCH Aligarh. 300 patients on ART were included. History of patients illness including

past history of ART intake was taken in detail and counseling was done regarding the drugs and disease. Examination of the patient was done. Each patient used to undergo investigation such as Haemoglobin, general blood picture(GBP), Total leukocyte count (TLC), Differential leukocyte count(DLC), ESR, Urine routine and Microscopy, VDRL, HBsAg, anti HCV, lipid profile, RFT, BS, LFT, CD4 count and X-ray and USG, if needed. Patient who have previous history of ART were followed up monthly basis, CD4 counts were done 6 monthly or as required. Patient newly started on ART were followed at 15Th day (haemoglobin and LFT were done) and then monthly. Serum lactate levels and serum amylase were done whenever indicated. On every visit to ART centre, patient was counseled about drug adherence, they pills were counted by the counselor and staff nurse.

Table 1 ADRs ON AZT Regimen

	No patients	%
Anemia	21	47.7%
Nail & Tongue pigmentation	11	25%
Fever	11	25%
Myalgia	1	2.27%

Table 2 ADRs ON d4T Regimen

	No patients	%
Peripheral neuropathy	11	61.1%
Lipodystrophy	5	27.77%
Lactic acidosis	2	2.27%

Results

Out of 212 patients on AZT, 44 (20.75%) patients developed adverse drug reactions. Out of 88 patients on d4T, 18 (20.45%) patients developed adverse reactions.

As shown in table-1 most common ADR due to AZT was anemia in 21 patients (47.7%), followed by nail or tongue hyper-pigmentation in 11 patients (25%), fever in 11 patients (25%) while myalgia (2.27%). Severe anemia (Hb% <5g%) was observed in 9 patients who needed blood transfusion. 2 out of 9 patients died due to complications caused by severe anemia. As shown in table-2 most common ADRs due to d4T was peripheral neuropathy in11 patients (61.1%), lipodystrophy in 5 patients (27.77%) and lactic acidosis in 2 patients (2.27%).Change of therapy was required in 2 cases of peripheral neuropathy and 2 cases of lipid dystrophy on d4T.

Discussion

The incidence of ADRs due to AZT and d4T were almost equal 20.75% and 20.45% respectively. d4T causes long term metabolic effects, its peripheral neuropathy is so much distressing that need change of drug, similarly lipid dystrophy is very much distressing to females with regard to cosmetic issues. In the study done by Dournon et al2. AZT induced anemia was 16.15% which is much less to our study 47.7%. Van Leeuwen et3 al. reported severe anemia in 34% of cases while in the present study it was 20.4%.

Nail and tongue pigmentation are the less common ADRs causing not much harm to the patient. In the study done by Hforett- Smith et al4 d4T induced peripheral neuropathy was 24% while in the present study it was 61.1%. In the study done by Hforett - Smith et al and Saint Marc T et al.10. lipid dystrophy was 16% and 63% respectively while in the present study it was 27.7%. Although AZT can cause life threatening anemia but with proper initial monitoring this can be prevented but d4T causes long term ADRs and need monitoring for long term metabolic effects also lactic acidosis can be life threatening, so AZT may be a better option as NRTI.

References

1. Carr A, Cooper DA, Adverse effects of antiretroviral therapy. Lancet 2000;356:1423-30.

2. Dournon E, Matheron S, Rozenbaum W, Gharakhanian S, Michon C, Girard PM, et al. Effects of zidovudine in 365 consecutive patients. AIDS or AIDS-related complex. Lancet 1988;2:1297-302.
3. Van Leeuwen R, van den Hurk PJ, J Obsis GJ, Van der Wouw PA, Reiss P, Eeftinck Schattenkerk JK, et al. Failure to maintain high treatment regimens during long term use of Zidovudine in patients with symptomatic HIV-1 infections. Genitourin Med 1990;66:418-22.
4. Hforett-Smith, Reynolds L. D4T once daily 2 year Follow up . lipodystrophy and peripheral neuropathy and antiretroviral activity 43rd annual Int Conf. on Anti micro and chemo, Chicago; Sept 14-17, 2003.
5. Moyle GJ, Sadler M. Peripheral neuropathy with nucleoside antiretrovirals: Risk factors, incidence and Management. Drug Saf 1998;19:481-94.
6. Ofotukun I, Pomeroy C. Sex difference in adverse reaction to antiretroviral treatment. Top HIV Med 2003;11:55-9.
7. McComsey GA,Ward DJ,Hessenthaler SM,SensionMG, Shalet P, Lonergan JT, FisherRL, WilliamVC,Hernandez JE,Trial to assess the Regression of hyperlactetatemia and to Evaluate the regression of established \Lipodystrophy in HIV 1 positive Subjects (TARHEEL;ESS40010) Study Team. Improvement in lipoatrophy associated with highly active antiretroviral herapy in human immunodeficiency virus nfected patients switched from stavudine to abacavir or zidovudine: the results of TARHEE study.Clin infect dis .2004; 38(2):263-70.
8. C laurent, A Bourgeoiss , E Mpoudi-Ngole, and others.Tolerability and effectiveness of First line Regimens combining Nevirapine and Lamuvidine Plus Zidovudine or Stavudine in Cameroon. AIDS Research and Human Retrovirus 24(3):393-400, 2008.
9. Bogner JR, Vielhauer ,BeckmanRA,et al. Staavudineversus Zidovudine and the development of lipodystrophy. J Acquir Immuno Deficiecysyndrome 2001;27:23744.
10. Saint-MarcT,Partisani M, Poizet-Martin I, Bruno F,Rouviere O, Lang JM et al.A syndrome of peripheral fat wasting(lipodystrophy) in patients receiving long term nucleoside analogue therapy. AIDS 1999;13:1659-67.

J Pharmcovig Drug Safety 2009 (January - March) 6(1) :35-37

ORIGINAL ARTICLE

Adverse Drug Reactions in Dermotology and a Growing Need for Pharmacovigilance

S. SHAHANI, S. NERLEKAR, A. DESAI, P. UIKE
Dept. of Pharmacology, LTMMC, Sion, Mumbai - 22

ABSTRACT

Objective: Adverse Reactions in Skin are becoming an increasingly common incidence mainly due to unscrupulous prescription by physicians or unnecessary abuse by patients. Adding to this is the increasing number of OTC preparations that the patient receives even for minor ailments.

Methods: This article was aimed at finding the incidence of various ADRs encountered in dermatology. In our study of spontaneous ADR reporting conducted for a period of 2 years we reported a total of 211 cases.

Results: Out of that 38.38% were of maculopapular rash followed by urticaria and Fixed Drug Eruption. In all the cases reported antibiotics (46.19 %) followed by NSAIDS (24.69%) formed the major portion as the offending group, while paracetamol was the most common offending drug. Of the recorded ADRs 68.72% were of moderate severity, 16.11% were serious and 3 deaths due to TEN were reported.

Conclusion: This study highlights the importance of pharmacovigilance and a need to stress the importance of avoiding indiscriminate drug use.

Introduction

Drugs are like double edged swords. Though believed to be safe and efficacious, are associated with unwanted adverse effects. It has been estimated that ADRs account for 6.7% of the hospitalizations with a fatality rate of 0.32%1. Thus ADRs are the 4th leading cause of deathhaving a significant effect on morbidity and mortality. Hence safe use of medicines is of utmost importance for doctors, nurses, pharmacists, the pharmaceutical industry, and the public.

Majority of these reactions and are self limiting, except few severe and potentially life threatening situations like Steven Johnson and Toxic epidermal necrolysis (TEN). However it has been noted that one third to as high as one half of ADRs, are preventable2. Cutaneous ADRs are most common among the various adverse reactions caused by the drugs. Any skin disorder can be imitated, induced, or aggravated by drugs. The incidence of cutaneous drug reactions varies from 15 to 30% 3. Present study was conducted to analyze the pattern of dermatological Adverse Drug Reaction.

Methods

This was a spontaneous Adverse Drug Reaction reporting study conducted for a period of 2 years by the Dept of Pharmacology in coordination with the other departments. The protocol design was approved by the institutional ethics committee. In the present study, reports of hypersensitivity reactions in the inpatients and outpatient were recorded. The patterns of hypersensitive reactions were evaluated. Causality assessment was done by using Naranjo's scale and severity was also assessed using Hartwig et al. scale 4,5. The outcome was observer till the patient followed up or completely recovered which ever was earlier.

Results

Data of 211 patients presented with various hypersensitive reactions was analyzed. Out of the 211 cases 107 were males and 99 were female patients.

Table 1 shows various types of ADRs involving the skin.

ADR	Male	Female	Total	Percentage	Offending drug
Maculopapular rash	49	29	78	36.96%	Antibiotics (46.91 %) NSAIDS (24.69 %) Others (28.4%)
Urticaria	17	21	38	18.00%	Antibiotics (38.46 %) NSAIDS (33.33%) Others (28.21%)
Fixed Drug Reactions	15	23	38	18.00%	Antibiotics (46.15 %) NSAIDS (41.02%) Others (12.83%)
TEN & SJ Syndrome	16	13	29	13.74%	Antibiotics (42.85 %) NSAIDS (28.57%)
Photosensitivity	4	4	8	3.79%	Antibiotics (37.5%) Others (62.5%)
Hyper pigmentation	4	6	10	4.73%	Antibiotics (50%) Others (50%)
Anaphylaxis	5	0	5	2.36%	Antibiotics
Allergic dermatitis	2	3	5	2 36%	Gloves, Adhesive

Table 2 shows the severity of ADR on analysis using Hartwig et al scale.

Severity	Incidence (number of patients)	Percentage
Mild	13	6.16%
Moderate	145	68.72%
Severe	19	9%
Serious	34	16.11%
Death	3	1.45%

Most frequently reported cutaneous drug reactions were for antibiotics in 91 (43.12%) cases, followed by NSAIDS in 62(29.38%) cases, antiepileptic drugs in 15 (7%) cases, and antiretroviral in 11 (6%) cases. Some of the other drug classes involved were antipsychotic lamotrigine and ayurvedic medicines etc.

On causality assessment we observed 66.35% of the ARDs as possible and 33.64% as probable category. No ADR could be put in category of definite as no rechallenge test was done. Most of the patients recovered from the hypersensitive reactions, and in about 2% recovery was incomplete till the came for follow up. The fate of about 5 % of patients was not known as they did no come for follow up, while 3 deaths were reported, either due to the direct or indirect effect of the SJ syndrome and Toxic Epidermal Necrolysis.

Discussion

In the present study the most common ADR observed were maculopapular rashes 81 (38.38%) cases, which is similar to studies carried out by Kushwaha et al., S Ghosh and Naina et al.6,7 , followed by 38 (18.00%) cases of urticaria and fixed drug eruption each. Our study revealed NSAIDS and Antibiotics as the most by Bern et al., Faich et al. and Bigby et al.8,9 shows similar results, antibiotics as the most frequent cause of adverse skin reactions reported in their spontaneous surveillance or hospital incidence system.We found the most common offending drug was responsible for maximum number of ADRs was paracetamol (36) followed by septran(19) amoxicillin(13),unlike the previous studies conducted by Bigby et al.10 which documented that penicillins and aminopenicillins had the highest incidence of cutaneous ADRs. This was due to change in prescription pattern seen with time. In the study conducted by Naldi et al.11 acetaminophen was ranked 8th amongst common analgesics, to cause cutaneous reactions. We could confirm the causative drug in 40.75% of cases as in majority of the patients the drug was dispensed by prescribing physician and no written prescription was given to them. However our study showed maximum number of hypersensitivity reactions to acetaminophen. This may be related to the common prescribing pattern and self-medication habits among the local population.This shows the growing need for increasing the awareness of Pharmacovigilance amongst the medical fraternity.

References

1. Lazarou J, Pomeranz B, Corey PN. Incidence of adverse drug reactions in hospitalized patients: A meta-analysis of prospective studies. JAMA 1998;279:12001205.
2. Barbara, S.M., In: Shargel, L., Eds., Comprehensive Pharmacy Review, 4th Edn., Lippincott Williams & Wilkins, London, 2001, 416.
3. Boston collaborative Drug Surveillance Program, Int. J. Epidemiol., 1973, 2, 167.
4. Hartwig, S.C., Siege, l.J. and Schneider, P. J., Amer. J.Hosp. Pharm., 1992, 49, 2229.
5. Naranjo, C. A., Busto, U., Sellers, E. M., Clin. Pharmacol. Ther., 1981, 30, 239.
6. Kushwaha, K.P., Verma, R.B., Singh, Y.D. and Rathi, A.K., Indian J. Pediatr., 1994, 61, 357.
6. Kushwaha, K.P., Verma, R.B., Singh, Y.D. and Rathi, A.K., Indian J. Pediatr., 1994, 61, 357.
7. Naina, H.H., Philip, A.N. and Dennis, P.W., In: Dipiro, T.J., Eds., Pharmacotherapy; A Pathophysiologic Approach, 4th Edn., Appleton and Lange, Stamford, Cannecticut, 1999, 1505.
8. Bern, J.I., Mann, R.D. and Rawlins, M.D., Brit. Med. J., 1998, 296, 1319.
9. Faich, G.A., Knapp, D., Dreis, M. and Turner, W., J. Amer. Med. Assoc., 1987, 257, 2068.
10. Bigby, M., Jick, S., Jick, H. and Arndt, K.A., J. Amer. Med. Assoc., 1986, 256, 3358.
11. Naina, H.H., Philip, A.N. and Dennis, P.W., In: Dipiro, T.J., Eds., Pharmacotherapy; A Pathophysiologic Approach, 4th Edn., Appleton and Lange, Stamford, Cannecticut, 1999, 1505

J Pharmcovig Drug Safety 2009 (January - March) 6(1) :38-40

Intellectual Property Rights

JITENDER SINGH, PARUL GROVER, DHARAM PAL PATHAK

Lord Shiva College of pharmacy, Near Civil Hospital, SIRSA - 125055,
1Delhi Institute of Pharmaceutical Sciences and Drug Research, Delhi - 110017

Introduction

IPR is a general term covering patents, copyrights, trademarks, industrial design, geographical indication, protection of layout design of integrated circuits and protection of undisclosed information. IPR has many practical advantages in industrial fields and provides protection for their innovative work.

Key Words: IPR, Patent, Biotechnology

Intellectual property rights are "legal rights which result from intellectual activity in the Industrial, Scientific, Literary and artistic fields". Intellectual property is a legal definition of ideas, innovations, artistic works and other commercially viable product created out of one's own mental process. Intellectual property is also known as secret recipe. Not every idea inside a person's mind can be considered intellectual property. There is usually a commercial viability angle which needs proper protection to prevent theft of the idea or outright copyright infringement. Intellectual property may or may not belong to the original inventor or composer; however Individual scientists working for pharmaceutical companies or private laboratory may invent a formula for a new drug but the actual Intellectual property rights may be held by the company or the laboratory as a whole. Often when a company acquires another company, it receives intellectual property rights as well as the building and the equipment.

IPR is a general term covering patents, copyrights trademarks, industrial design, geographical indication, protection of layout design of integrated circuits and protection of undisclosed information.

Generally speaking intellectual property laws aims to safeguarding creator and the producer of intellectual goods and services by granting them time limited right to control the use of those production.

Intellectual property right are negative rights in that they allow their owner to stop others doing something rather than giving them rights to do something that they could not otherwise do. Like any other term of property or business asset, they can be licensed, bought, sold, rented or hired.

Characteristics of IPR

- Intellectual property is economically valuable information.
- Intellectual property right is the legally entorceable power to exclude other from using the information & to set the term on which it can be used.
- Trips prescribe uniform minimum standards and periods for which protection should be granted to intellectual property rights.
- Most favoured nation and national treatment.

Principles

- Paris convention on industrial patents; Berne convents on copyrights; Rome convention and treaty property in respect of integrated circuit.
- Non-discrimination against foreigners and non-discrimination between foreign nationals.
- The concept of exhaustion of rights.
- The concept of jurisdiction across.
- Dispute settlement does not come in to play so long as Most Favoured Nation and national treatment.

Creation of IPR

A very simple creation on IPR without determining its importance and use by the public will not do any good. Such an IPR will not have value and will only remain in paper.

It should be noted that importance of IPR has dual objectives namely

(i) The creator getting source benefit, financial or otherwise, for the intellectual input and

(ii) The society getting the benefit of IPR created.

The responsibility of the state in giving protection to such an IPR to balance the right and obligation of above said two parties in such two ways that are not misused or abused.

Types of Intellectual Property (IP)

Intellectual property right can be divided into main types as shown:

Intellectual Property	Type	Provides to	Protection Time (Yr.)
Unregistered IP	Copy Right	Creative works, musical, lectures, photographs, artistic, plays, models, computer software's	50
	Layout Design	Integrated Circuits	10
	Trade Names	Product for distinctive manner	
Registered IP	Patents	Inventions that are novel, non-obvious and useful	20
	Trademarks	Distinctive marks such as words/sign or combinations	7

Practical Applications

Intellectual property rights will be helpful in fighting the expensive wars in the knowledge market that the Indian Industry will have to face in its economy with global economy.

Manpower planning for IPR protection needs priority. Hence it is essential to make IPR a compulsory subject matter in the law courses in Indian Universities.

The biotechnology industry organization advocates a strong and effective intellectual property system. Strong intellectual property protection is essential to the success and in some instances to survival, of biotechnology companies in the country. For these companies the patent system serves to encourage development of new medicines, and diagnostics for treatment and monitoring intractable disease, and agricultural product to meet global needs.

Intellectual property right gives the owner the right to exclude other from access to use their property for a certain period of time.

IPR role in industry (small & medium sized enterprises)- Along with human creativity and inventiveness, intellectual property is all around us. Every product or service that we use in our daily lives is the result of long chains of big or small innovations, such as changes in design, or improvements that make a product look or function the way it does today. By improvement in the product and its design someone can legally protect their improvements through the acquisition of IP right. The trademark on our pen is also intellectual property, and it helps the producer to market the product and develop a good reputation, and this would be the case with almost any product or services in the market place.

Almost every Small Medium Sized Enterprise (SME) has trade name or trademarks and should consider protecting them. A large number would have developed creative to original design. Many would have produced or assisted in the publication, and in the transfer of technology when IP is generated and consequently wealth is generated by the commercialization. Therefore undertaking R&D, dissemination or of copyright work. Some may have invented or improved a product or services.In all such cases, SME should consider how best to use IP system to its own benefit. IP may assist your SME in almost every aspect of your business development and competitive strategy from product development to product design, from service delivery to marketing, and from raising financial resources to experting or expanding your business aboard through licensing or franchising. The advantage of IP system is in obtaining a patent for an invention. The national patent law of each country requires full disclosure of the essential details of the invention to be protected. This information is disclosed in the document commonly known as specification. The information contained in patent specification includes information regarding the field to which the invention relates, background of the prior art knowledge on the subject, drawback connected with the said prior art, the future demands of the invention, the best mode carrying out the invention, detailed working examples of the invention based on the experiments carried out in the laboratory and claims defining the scope of protection and legal right secured. The information provided in the specification should be such that it would be

sufficient for a person having ordinary skill on the area to which the invention relates, to carry out the invention without assistance of the inventor/applicant.

The patent specification throughout the world usually has uniform structure. For the preservation of the novelty of the invention developed, the information in respect of the invention is first published in patent document, therefore 80% of the information contained in patent are not available in any other document.

The specification is therefore a valuable and unique source of information. One of the important objectives of the patent system is to disseminate the scientific & technological information contained in the document (specification) as soon as possible.

The role of IPR and transfer of technology in relation to scientific work has an important role both in R&D entering into any collaboration and in the transfer of technology the IPR will be an important component.

References

1. Minshall tim, Mills Jonna & Jenning Richard, Introduction to Intellectual Property Right, University of Cambridge Entreprenarship & Research division.
2. Subbaram, N.R. IPR Creation, development, protection, & Information disemination, New Delhi.
3. Miller Raphal, Michael. H. Davis, Intellectual Property: patent, trademarks, copyright, west wadsworth 3rd edition, 2000.
4. Michoel perelman, Intellectual Property Right, Pulgrave Macmilan, 2002.
5. Roger E. Schechter, John R Thomas. Intellectual Property, The Law of copyright, patent & trademarks, west wadsworth 2003.
6. Cornish, W.R. (1999) Intellectual Property, patent copyright, trademarks.
7. Jisc legal information services: Intellectual property right 2002.
8. Field Thomas G. Jr. Intellectual property, The Practical and legal fundamentals 2001.
9. Vaidya Vandana, Intellectual property right- "A boon to Indian Companies, 2002.
10. Mashelkar R.A., Economics of Knowledge Republic day special. 2002.
11. Subhash K Bijalam, "The innovation potential of an SME and the value of IPR", 2000.
12. Kari Sipita, "Roles of IPR is the promotion of competitiveness & development of Enterprise", 1999.
13. http://www.intellectualproperty.gov.uk.
14. www.patent.gov.uk/design

J Pharmcovig Drug Safety 2009 (January - March) 6(1) :41-44

Prebiotic and Probiotic in Pharmaceutical Industry

SHREENA GUPTA, IMRAN ZAFAR
NIMS Institute of Pharmacy, NIMS University Rajasthan, Jaipur - 302 001

Prebiotics are a category of functional food, defined as: Non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improve host health.Most potential prebiotics are carbohydrates (such as oligosaccharides), but the definition does not exclude the use of non-carbohydrates as prebiotics. The definition does not emphasize a specific bacterial group. Often, however, it is assumed that a prebiotic should increase the number and/or activity of bifidobacteria and lactic acid bacteria.

Sources

- soybeans
- Jerusalem artichokes (which contain inulin)
- raw oats,
- unrefined wheat
- unrefined barley.
- Oligosaccharide from breast milk eg: fructooligosaccharides (FOS), xylooligosaccharides (XOS), and galactooligosaccharides (GOS).

Mechanism of action (HYPOTHESIS)

- Resistance to digestion,
- Hydrolysis and fermentation by colonic microflora,
- Selective stimulation of growth of one or a limited number of bacteria in the feces (in vivo in humans).

Health benifits of Prebiotics

The major nutritional and physiologic effects of a model prebiotic, namely inulin-type fructans, concern the composition of the colonic flora, the bowel functions, calcium absorption, and possibly, lipid metabolism and reduction of the risk of colon cancer.

Classification of some Naturally Occurring and Synthetic Prebiotics and their Sources are given below in the table as Described by Rosenberg :

Sl.No	Classification	Origin /Manufacturing Procedure
I	Disaccharides	Lactose synthetic
	1 Lactulose	
	2 Lactitol	
II	Oligosaccharides	
	Fructo- oligosaccharides	Legumes, vegetables, extracts / hydrolysis of cereals.
	Soybean oligosaccharides	Extraction / hydrolysis of soy bean
	Xylo-oligosaccharides	Plant sources
	Trans Galacto-oligosaccharides	Lactose synthetic
III	Polysaccharides	
	Inulin	Extracts obtained from legumes, vegetables and cereals.
	Resistant starches	Extracts obtained from legumes, vegetables and cereals.

Probiotics

This term may be unfamiliar to many readers refers to the so-called friendly bacteria that live within the gastrointestinal tract. Probiotics are dietary supplements containing potentially beneficial bacteria or yeasts. According to the currently adopted definition by FAO/WHO, probiotics are: *'Live microorganisms which when administered in adequate amounts confer a health benefit on the host'*. Lactic acid bacteria (LAB) are the most common type of microbes used. LAB have been used in the food industry for many years, because they are able to convert sugars (including lactose) and other carbohydrates into lactic acid. This not only provides the characteristic sour taste of fermented dairy foods such as yogurt, by buffering the pH and creating fewer opportunities for spoilage organisms to grow, and lowering cholesterols in blood, hence creating huge health benefits on preventing gastrointestinal infections, hyperlipidemia, and hypertensions etc. Strains of the genera *Lactobacillus* and *Bifidobacterium*, are the most widely used probiotic bacteria

Sources:

- Natural cheese,
- Kefir
- Wheat grass,
- Yogurt,
- Buttermilk,
- Spirulina
- Chlorell

Machanism of action

The mechanism of action of the probiotic bacteria has not been studied systematically. According to some recent publications, in the aquaculture the mechanism of action of the probiotic bacteria may have several aspects.

1. Probiotic bacteria may competitively exclude the pathogenic bacteria or produce substances that inhibit the rowth of the pathogenic bacteria.
2. Provide essential nutrients to enhance the nutrition
3. Provide digestive enzymes to enhance the digestion.
4. Probiotic bacteria directly uptake or decompose the organi matter or toxic material

Pharmacoogical applications

- Managing Lactose Intolerance
- Prevention of Colon Cance
- Cholesterol Lowering
- Lowering Blood Pressure

The following claims have been attributed to strains of lactobacilli and bifidobacteria

- inhibition of potential pathogens, such as *E. coli* or *Clostridium perfringens*
- prevention of diarrhoea caused by (rota)virus or *Salmonella*
- reducing the effects of a *Candida* infection
- positive effects on cholesterol level
- prevention and/or reduction of colon cancer
- stimulation of the immune system
- production of vitamins
- increased defecation and reduced constipation
- improving the uptake of minerals, especially calcium
- digestion of lactose for lactose-intolerant persons

Lactobacillus us Acidophilus - Intestinal Health

- Aids in digestion and suppression of disease-causing bacteria.
- Aids in the prevention and treatment of diarrhea, including infectious diarrhea, particularly from rotavirus (a virus that commonly causes diarrhea in children).
- Helps in treating overgrowth of "bad" organisms in the gastrointestinal tract (a condition that tends to cause diarrhea and may occur from use of antibiotics).
- Alleviates symptoms of irritable bowel syndrome and, possibly, inflammatory bowel disease (such as Crohn's disease and ulcerative colitis).
- Prevents and/or reduces the recurrence of vaginal yeast infections, urinary tract infections, and cystitis (bladder inflammation).
- Improves lactose absorption digestion in people who are lactose intolerant
- Aids in the treatment of respiratory infections such as sinusitis, bronchitis, and pneumonia.
- Lowers risk of allergies, including asthma, hay fever, food allergies to milk, and skin reactions such as eczema.
- Helps to treat high cholesterol.
- Reduces the risk of recurring bladder tumors once this cancer has been treated.
- Other conditions under investigation for use of probiotics include colon cancer, HIV related diarrhea, and Helicobacter pylori, an organism that can lead to development of ulcers
- L. acidophilus supplementation may be especially useful for helping patients restore beneficial bacteria to the intestines after treatment with antibiotics.
- Because of its ability to reduce cholesterol levels, it can potentially reduce the risk of coronary heart disease by 6 to 10 percent.
- Infants treated with L. acidophilus may recover from bouts with diarrhea more quickly

Probiotic Organisms	Benefits
Live Yeast Culture (Saccharomyces cerevisiae)	• Provides heat and storage stability • Does not interfere or get interfered by antibiotics and feed supplement • Provides vitamins and growth factors
Bacillus coagulans (Lactobacillus sporogens)	• Provides vitamins and growth • Vegitate in upper part of gut and rapidly multiply • Product range of enzymes for better digestion and utilization of nutrients
Lactobacillus acidophilus & Streptococcus faecium	• Native gut flora • Rapidly colonize in gut • Competitive exclusion of pathogens

Dosage and Recommendation

Usage	Broiler	Layer	Breeder
Chick	0-4 weeks @ 500g / ton	0-4 weeks @ 500 g / ton	0-4 weeks @ 500 g / ton
Grower	-	500 g / ton	500 g / ton
Layer	-	250 - 500 g / ton as week a month programme after AGP for a week	1 kg / ton
Benefits	- Better growth & weight gain -Improved FCR - Improved body resistance - Reduced mortality	- Better growth - Uniform weight gain - Better egg production and shell quality	- Better fertility - Improved hatchability - Decreased egg abnormality - Decrease in depletion or cull %

Symbiotics

As probiotics are mainly active in the small intestine and prebiotics are only effective in the large intestine, the combination of the two may give a synergistic effect. Appropriate combinations of pre- and probiotics are synbiotics.

Synbiotics have also been defined as metabolites produced by ecoorgan or by synergistic action of prebiotics and probiotics e.g. short chain fatty acids, other fatty acids, amino acids, peptides, polyamines, carbohydrates, vitamins, numerous antioxidants and phytosterols, growth factors, coagulation factors, various signal_ molecules such as cytokine-like bacteriokines.

The development of functional foods is a unique opportunity to improve the quality of the food available to consumers to benefit their health and well-being. Thus, prebiotics, especially inulin-type fructans, are natural products that may receive classification as functional food ingredients with valid health claims. However, only a rigorous scientific approach producing sound data will justify such a classification, which remains a challenge for both the scientific community and for the food industry.

References

1. FAO/WHO (2001) Health and Nutritional Properties of Probiotics in Food including Powder Milk with Live Lactic Acid Bacteria. Report of a Joint FAO/WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food Including Powder Milk with Live Lactic Acid Bacteria.
2. Nichols,AndrewW.(2007)."Probiotics and athletic performance: Asystematicreview3. Current Sports Medicine Reports 6 (4): 269 - 273. Current Medicine Group LLC. doi:10.1007.
4. Tannock G (editor). (2005). Probiotics and Prebiotics: Scientific Aspects,1st ed., Caister Academic Press. ISBN 978-1-904455-01-8
5. Sanders ME. Considerations for use of probiotic bacteria to modulate human health. J Nutr. 2000;130:384S-390S. Entrez PubMed 10721912
6. Metchnikoff, E. 1907. Essais optimistes. Paris. The prolongation of life. Optimistic studies.

Translated and edited by P. Chalmers Mitchell. London: Heinemann, 1907.
7. Vaughan RB. 1965. The romantic rationalist: A study of Elie Metchnikoff. Med Hist. 9:201-15.
8. Tissier, H. 1900. Recherchers sur la flora intestinale normale et pathologique du nourisson. Thesis, University of Paris, Paris, France.
9. Nissle, A. 1918. Die antagonistische Behandlung chronischer Darmstörungen mit Colibakterien. Med Klin 1918, 2:29-30.
10. Cheplin, H.A., and L.F. Rettger, 1920. Studies on the transformation of the intestinal flora, with special reference to the implantation of Bacillus acidophilus, II. Feeding experiments of man. Proc Natl Acad Sci U S A. 1920 December; 6(12): 704705.
11. Rettger, L.F., W.N. Levy, L. Weinstein, and J.E. Weiss. 1935. Lactobacillus acidophilus and its therapeutic application. Yale University Press, New Haven.
12. Lilly, D.M, and R.H. Stillwell. 1065. Probiotics: growth-promoting factors produced by microorgansism. Science 147:747-748.
13. Fuller, R. 1989. Probiotics in man and animals. J. Appl. Bacteroil. 66:365-378.
14. Tannock, G.W. 2003. Probiotics: Time for a dose of realism. Curr. Intest. Microbiol. 4:33-42.
15. Gut Reactions programme 3
16. Wollowski I, Rechkemmer G, Pool-Zobel BL. Protective role of probiotics and prebiotics in colon cancer. Am J Clin Nutr. 2001;73:451S-455S. Entrez PubMed 11157356
17. Brady LJ, Gallaher DD, Busta FF. The role of probiotic cultures in the prevention of colon cancer. J Nutr. 2000;130:410S-414S. Entrez PubMed 10721916
18. Reid G, Jass J, Sebulsky MT, McCormick JK. Potential uses of probiotics in clinical practice. Clin Microbiol Rev. 2003;16:658-72. Entrez PubMed 14557292
19. Ouwehand AC, Salminen S, Isolauri E. Probiotics: an overview of beneficial effects. Antonie Van Leeuwenhoek. 2002;82:279-89. Entrez PubMed 12369194
20. Hatakka K, Savilahti E, Ponka A, Meurman JH, Poussa T, Nase L, Saxelin M, Korpela R. Effect of long term consumption of probiotic milk on infections in children attending day care centres: double blind, randomised trial. BMJ. 2001;322:1327 Entrez PubMed 11387176
21. Nase L, Hatakka K, Savilahti E, Saxelin M, Ponka A, Poussa T, Korpela R, Meurman JH. Effect of long-term consumption of a probiotic bacterium, Lactobacillus rhamnosus GG, in milk on dental caries and caries risk in children. Caries Res. 2001;35:412-20. Entrez PubMed 11799281

J Pharmcovig Drug Safety 2009 (January - March) 6(1) :45

Good Pharmacovigilance Practices: A Growing Need

ARUNABHA RAY, KAVITA GULATI AND SANTANU K TRIPATHI
Vallabhbhai Patel Chest Institute, University of Delhi, Delhi - 110007, and Burdwan Medical College & Hospitals, West Bengal - 713104

The goal of pharmacovigilance is to identify adverse events and identify their nature and risk potential. The phrase Good Pharmacovigilance Practice (GPVP) refers to carefully planned and executed pharmacovigilance activities to minimize toxicity and maximize beneficial effects of drugs and biologicals. GPVP of observed/recorded data involves signal identification, pharmacoepidemiological assessment, safety signal interpretation and pharmacovigilance plan development. Risk assessment is an interactive process and encompasses risk-benefit balance, development of tools to minimize risks while maintaining benefits, evaluation of these tools, and making appropriate adjustments in order to improve the risk-benefit balance. GPVP is generally based on acquisition of data from spontaneous ADR reports and several such reports may be used to develop a case series for interpretation. Good reports may be of great help in generating ADR signals and hence the quality of reporting is critical for assessing causality. A good ADR report should cover all aspects about the drug, the individual, the disease, clinical course, laboratory data, etc. At various stages of ADR examination and risk indentification/assessment, data mining (statistical evaluation) can provide additional information on the incidence/severity of the particular adverse event. Such data mining can be effectively used to augment signal detection strategies, viz. ADR patterns, time trends, drug-drug interactions, etc. The above methods may help in identifying and characterizing safety signals and could result in the further detailed investigation of the adverse event.

Safety signals so generated could be further investigated by carefully designed non-randomized observational studies/trials for assessment of safety of the compound. In addition to data mining techniques and comparing reported vs background incidence rates, preclinical data may also give an indication for the need of such observational studies. On evaluation of the safety signal, if a potential safety risk is identified, then all available safety confirmation (including preclinical data), analysis performed, should be reanalyzed or causality. The sponsors and regulatory authorities need to interact regularly and systematically at all levels of adverse event assessment in the interest of drug related safety issues for the population. A pharmacovigilance plan is an essential component of GPVP and focuses on detection of new safety risks or evaluates already existing ones. The plan describes effects beyond routine post marketing surveillance reporting and helps to enhance and expedite the acquisition of safety information. It should be based on scientific and logistic factors and could be appropriate for compounds with (a) serious safety concerns (pre- and post- approval) or (b) inadequately studied at-risk populations. The GPVP is thus a systems approach to pharmacovigilance and has been developed over the past three decades. The incorporation of state-of-the-art IT systems with the pharmacovigilance programme have given a boost to this concept. These tools may help in identifying alerts from random data and may help in visualizing those that are invisible to the naked eye. Thus drugs/biologicals safety and related public health monitoring will become more efficient and effective.

J Pharmcovig Drug Safety 2009 (January - March) 6(1) :46

Pharmacovigilance in special settings: a case study

KAVITA GULATI, ARUNABHA RAY, V.K. VIJAYAN
Vallabhbhai Patel Chest Institute, University of Delhi, Delhi-110 007

Pharmacovigilance deals with detection, assessment and prevention of adverse drug reactions (ADR). ADRs can be a complex phenomemnon and several factors like the drug, the individual, and the disease state could contribute to its genesis. Specific and methodical ADR monitoring is the need of the hour and in the interest of national health priorities. Respiratory disorder are one of the major global causes of morbidity and mortality. Long-term drug use particularly those with low therapeutic index, polypharmacy related drug-drug/disease interactions and multiple routes of administration contributes to ADRs during therapy in respiratory diseases. Focussed ADR reporting / monitoring could be of great help and provide specific information for prevention/alleviation of such ADR related problems, thereby cutting health costs. Environmental and occupational factors may further compound this problem. The knowledge of clinical pharmacodynamics and pharmacokinetics in these specific situations are also of great importance. A study was conducted in 140 patients of obstructive airway disease (bronchial asthma and COPD) in outpatients, inpatients and ICU admissions at the Vallabhbhai Patel Chest Institute, University of Delhi. Ethical clearance was obtained and GCP guidelines followed. The pattern of ADR generation and profile were recorded as per the guidelines of the National Pharmacovigilance Programme and causality assessment was done using the Naranjo's scale. All patients received multi-drug therapy schedules by inhalation, oral or parenteral routes. Most patients received bronchodilators and/or corticosteroids, besides other forms of therapy. The results showed that 75% patients complained of one or other adverse effect. Oral steroids were associated with 25% incidence of ADRs in COPD as compared to 40% in bronchial asthma. 60% of the patients received inhaled anticholinergics out of which 25% complained of one or other ADR. Out of the 63 patients put on oral theophylline, a drug with a narrow therapeutic index, 45% complained/exhibited ADRs like anxiety, dyspepsia, muscle spasm, paresthesia, etc.). Most ADRs were moderate to tolerable, whereas some with theophylline and steroids needed dose reduction. Causality assessment showed that most ADRs were in the "probable" category (score ranging from 5 to 8 in the Narajo's scale). Such studies of focused ADR reporting and pharmacovigilance could be very helpful in reducing morbidity/mortality as well as health costs and help in rationalizing drug therapy in specific disease and/or drug related scenarios.

XXVII Annual Conference of Indian Academy of Neurosciences

December 18th - 20th, 2009

Venue: National Institute of Medical Sciences, NIMS University Rajasthan, Jaipur.
Date: 18th - 20th December, 2009.

Greetings from Pink city

Brain Disorders are not uncommon. There are many current issues and challenges in order to have better standards in research, medical service and education, and to have strategies for the future. Therefore, keeping in view of these objectives the Indian Academy of Neurosciences is holding its 27th Annual Conference at NIMS University Shobha Nagar, Jaipur-303001 from December 18-20, 2009. The conference will discuss various protective and therapeutic strategies for brain disorders. The aim of the conference is to bring together the neuroscientists , physicians, surgeons biotechnologists & researchers to discuss the advances in the field of basic and clinical neuroscience. At the meeting, the conference will present a good balance between the recent advances in basic science research and the clinical challenges that the physicians face in their clinical practices.

It is expected that about 500 delegates from various medical , dental , neurology, neurosurgery , neurosciences biotechnology, & pharmaceutical institutions of India and abroad, will attend this Conference. As it is going to be a highly educative affair, on behalf of the Indian Academy of Neurosciences we solicit an active participation of all health personnel. Your active involvement will go a long way in making this national event a grand success.

I feel pleasure to invite all of you to Jaipur. A warm reception awaits you and I eagerly look forward to welcome you and promise an academically beneficial and socially enriching experience during your stay with us. You will enjoy the scientific, cultural and social programs of the IAN in December 2009

REGISTRATION FEES

Please fill in the Registration Form and send by post to the Conference Secretariat

Category	Upto 30.9.2009	Upto 31.10.2009	Spot Registration
Delegate	Rs. 2,000/-	Rs. 2,250/-	Rs. 2,500/-
IAN Member	Rs.1,500/-	Rs. 1,750/-	Rs. 2,000/-
Corporate Delegates	Rs. 4000/-	Rs. 5000/-	Rs. 6000/-
PG Student**	Rs. 1000/-	Rs. 1250/-	Rs. 1500/-
Spouse/Accompanying Person	Rs. 750/-	Rs. 1,000/-	Rs. 1,200/-
Children (5-12 yrs)	Rs. 400/-	Rs. 400/-	Rs. 500/-

** to be certified by Head of the Department of the delegate.

Dully filled redistration forms along with DD to be sent by
Registrered Post/courier to the conference secretariat

Dr. Anurag Tomar,
Organising Secretary IAN 2009,
NIMS City Centre, 4, Govind Marg, Jaipur 302004 (Rajasthan)
Tel. No.: (0141) 2604040, 2611020
Fax No.: (0141) 2605050 Mobile No.: 09829061020
E-mail: anurag@nimsr.com; ianjaipur@rediffmail.com; sopijaipur@rediffmail.com

XXVII Annual Conference of Indian Academy of Neurosciences

December 18th – 20th, 2009

NIMS UNIVERSITY Rajasthan, Jaipur

REGISTRATION FORM

Receipt No. _____ (Office use)

Kindly use full CAPITALS for filling the form

Delegate ☐ IAN Member ☐ PG Student* ☐

Name: Prof./Dr./Mr./Ms.....

Academic Qualifications: .....

Designation: .....

Name of the Organization/Institution .....

Accompanying person/spouse name: .....

Mailing Address: .....

City: .....PIN Code..... Stat..... Country.....

E-mail:..... Phone: STD Code: .... (R) .....(O) .....

Fax:..... Mobile:.....

Type of Food Preference Vegetarian ☐ Non Vegetarian ☐

Type of Accommodation Hostel ☐ Campus Guest House ☐ Hotel ☐

Payment Details:

1. IAN Member:	Rs. .....
2. Delegate:	Rs. .....
3. Corporate Delegate	Rs. .....
4. Accomp. Person/Spouse:	Rs. .....
5. PG Student:	Rs. .....
6. Others (Accommodation):	Rs. .....
Total:	Rs. .....

For foreign delegates only

Passport No.: ..... Date and place of issue .....

Mode of payment by Demand Draft/At Par Cheque drawn in fav our of **"IAN 2009"** payable at **Jaipur.** In out station cheques please add Rs. 100 as bank collection charges.

D.D./Cheque payable at Par No..... Dated ....

Bank details: .....

Signature of Delegate Date: .....

Please mail completed Registration Form with Payment to Conference Secretariat:

Dr. Anurag Tomar, Organising Secretary IAN 2009, **NIMS City Centre,** 4, Govind Marg, Jaipur -302004 (India);
Ph.: 91-141- 2604040, 2611020; Fax: 91-141-2605050; Mobile: 9829061020
E-mail: ianjaipur@rediffmail.com; anurag@nimsr.com

* PG students should submit certificate from the Head of the Department.

N.B. Please photocopy this form, if more copies are required.

Kindly attach your visiting card with this form.

9th Annual Conference of Society of Pharmacovigilance (India)

Theme: Quality and Safety of Drugs

Pre-conference workshop on November 20th 2009

Conference on November 21st and 22nd 2009

Venue:

Rajendra Institute of Technology & Sciences

4th Mile Stone, Hisar Road, SIRSA-125055 Haryana, India

Ph: 01666-250837, 250838, 92157-47148, Fax: 01666-250840

E-mail: sopi.rits@gmail.com

Scientific Programme

Workshop & CME (Limited 40 seats)

Practical Pharmacovigilance Adverse Drug reaction Monitoring

The interested persons can send the filled workshop registration form along with a demand draft/at per cheque worth Rs. 500 - (drawn in favor of organising Secretary SOPI 2009, payable at Sirsa) to Organising Secretary, SOPI 2009, Rajendra Institute of Technology & Sciences, 4 th Milestone Hisar, Sirsa - 125055 (Haryana) India. For any quries contact Mr. Nitin Bansal, Local Coordinator , Workshop & CME, Ph.: 98122-67168, email : nitindsp@gmail.com

ORATIONS

Prof. John Autian Oration

Prof. K.C. Singhal Oration

AWARDS

Uppsala Award for Best Oral Presentation

Best Poster Presentation Award

SYMPOSIA

Safety Monitoring of Herbal Medicines

Pharmacovigilance in Clinical Practices

Pharmacovigilance in Drug Regulation

Current Scenario in Pharmacovigilance

Call for Registration & Abstract

Registration

Please fill in the registration form and send by post to the Organising Secretary, SOPI 2009, Rajendra Institute of Technology & Sciences, 4th Milestone Hisar, Sirsa-125055 (HARYANA), India, along with a demand draft/ at par cheque (drawn in favour of Organising secretary SOPI 2009, payable at Sirsa) Email: sopi.rits@gmail.com

Registration fee (Per person)	Early Registration fee by 31.10.2009	Standard fee after 31.10.09 to 19.11.09	Spot Registration
Delegate	Rs. 1200	Rs. 1400	Rs. 1600
SOPI member	Rs. 800	Rs. 1000	Rs. 1200
PG student	Rs. 500	Rs. 600	Rs. 700
Accompanying person	Rs. 800	Rs. 1000	Rs. 1200

Abstract submission

Original unpublished research articles related to Pharmacovigilance, Drug safety, Adverse drug reactions, Pharmacogenomics, Pharmacoeconomics, Clinical research, Drug discovery and Regulatory Affairs are invited for oral and or poster presentation by registered delegates.

Abstracts should be written in English, not exceeding 300 words. The abstract should include title (14 pt, Bold, Upper case, Times New Roman), Author(s) & Affiliations (12 pt, Sentence case, Arial), the name of the presenting author should be underline. The text (single spaces, 11 pt, Times New Roman) should be divided in 4 sections viz objective of the study, materials & methods, results and conclusion. The preference for consideration to include abstract in oral/poster/either session should be indicated as Header. Abstracts should be sent through email to abstractssopi@gmail.com on or before 15.10.2009

Important Dates

Early Registration	31-10-2009
Last Date for submission of Abstract	15-10-2009
Last Date for submission of Full Paper For Uppsala Award	20-10-2009
Confirmation of Abstracts	22-10-2009

NEWS AND EVENT

9th Annual Conference of Society of Pharmacovigilance (India)
Theme: Quality and Safety of Drugs

Pre-conference workshop on November 20th 2009
Conference on November 21st and 22nd 2009
Venue: Rajendra Institute of Technology & Sciences
Contact
Dr. Surinder Goyal
Organizing Secretary,
Director, Rajendra Institute of Technology & Sciences,
4th Mile Stone, Hisar Road, SIRSA-125055 Haryana, India
Ph: 01666-250837, 250838, 92157-47148, Fax: 01666-250840
E-mail: sopi.rits@gmail.com

XXVII Annual Conference of Indian Academy of Neurosciences
Date: 18th - 20th December, 2009.
Venue: National Institute of Medical Sciences, NIMS University Rajasthan, Jaipur.

Contact
Dr. Anurag Tomar,
Organising Secretary IAN 2009,
NIMS City Centre, 4, Govind Marg, Jaipur 302004 (Rajasthan)
Fax No.: (0141) 2605050 Mobile No.: 09829061020
E-mail: anurag@nimsr.com; ianjaipur@rediffmail.com

SOCIETY OF PHARMACOVIGILANCE (INDIA)
MEMBERSHIP FORM

wish to become a member of the Society of Pharmacovigilance (INDIA). I have read the constitution of the society and agree to abide by it.

1. Name :
2. Educational Qualifications :
3. **Address**
   a. Office :
   b. Residence :
4. **Contracts**

   Phone with STD code :

   Office :

   Residence :

   Mobile :

   E-mail ID :
5. Are you actively engaged in work concerning Pharmacovigilance :
6. Field of Specialisation :

Date Signature

NOTE:

(1) The admission fee of Rupees Fifty only shall be chargeable at the initial admittance to the Society. The subscription for Life membership is Rs. 2000.00/- only. Please add Rs. 80.00 for outstation cheques payable at State Bank of India, S.N. Medical College, Agra.

(2) All payments be made either in cash or a demand draft in favour of 'TREASURER, SOCIETY OF PHARMACOVIGILANCE (INDIA) and should be sent alongwith this form completely filled and mailed to the treasurer.

(Dr. GOVIND MOHAN)
Treasurer,
SOCIETY OF PHARMACOVIGILANCE (INDIA)
Department of Pharmacology
S.N. Medical College, Agra 282 002 (INDIA)

FOR OFFICE USE ONLY

Membership No.....

Cheque/DD No..... Date of Presenting.....

Bank.....

Bank Instrument in Bank..... Date of Issue.....

Treasurer

INSTRUCTIONS TO AUTHORS

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

Submission of Manuscript: Manuscripts are reviewed for possible publication with the understanding that they have not been published, submitted, or accepted for publication elsewhere. They will be reviewed for scientific content, technical importance and significance by two independent reviewers of repute. The authors may suggest reviewers, but it is not mandatory and editor has a regent not to accept it.

The Journal will entertain research papers for publication under the following categories:

Original research article
Short Communication
Reviews (including Mini reviews)
Commentary
Case reports on drug safety

Original research article should be a comprehensive description of significant findings, whereas, short communication shall be limited to 1500 words. Review articles updating current topics will be entertained normally by invitation. A commentary on any specific field covered shall be limited to 500 words without any figure or table.

Three copies of manuscripts are required to be submitted along with CD containing the electronic version using Microsoft word or any other word-processing software. The manuscript should be sent at following address:

Dr. Anurag Tomar
Editor-in-Chief, JPVDS
NIMS City Centre,
4, Govind Marg, Jaipur - 302 004
anurag@nimsr.com, sopijaipur@rediffmail.com

Preparation of the Manuscript

The manuscript should contain following sections:

Abstract: The abstract should state the purpose of the study or investigation, basic procedures (selection of study subjects or laboratory animals; observational and analytic methods), main findings (giving specific data and their statistical significance, if possible), and the principal conclusions.

The abstract should be self explanatory (limited to 200 words in one paragraph) suitable for reproduction without change. Abstract should have three sections (a) Objective (not more than 3 lines (b) Methods and Results, (c) Conclusions (not more than 3-4 lines).

Introduction: It should provide background information providing rationale of the study giving pertinent reference. Introduction should always end with objective of the study/article.

Methods: One should describe selection of the observational or experimental subjects (Patients including controls) clearly. The age, sex and other important characteristics of the subjects should be identified. The definition and relevance of race and ethnicity should be ambiguous. Authors should be particularly careful about using these categories. One should given the methods, apparatus (The manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers reduce the results. Give references to established methods including statistical methods. All drugs and chemicals used, including generic name(s) dose(s) and route(s) of administration.

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

Discussion: The discussion must interpret the results and relate them to existing knowledge on the topic in as lucid a manner as possible, avoiding repetition or duplication of information. It should not be unnecessarily lengthy.

Include the implications of the findings and their limitations, including implications for future research. Relate the observations to other relevant studies. It should always end with concluding remarks. Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not completely supported by the data. In particular, authors should avoid making statements on economic benefits and costs unless their manuscript includes economic data and analyses. Avoid claming priority and alluding to work that has not been completed. State new hypotheses when warranted, but clearly table them as such. Recommendations, when appropriate, may be included.

References: References should be numbered consecutively in the order in which they are first mentioned in the text. Identify references in text, tables and legends by Arabic numerals in parentheses. References cited only in tables or in legends to figures should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure

Standard journal article: List the first six authors followed by et al.

Vega KJ, Pina I, Krevsky B. Heart transplantation is associated with an increased risk for Pancreatobiliary disease. Ann Intern Med 1996 124(11):980-3.

More than six authors: Parkin DM, Clayton D, Black RJ, Masuyer E, Friedl HP Ivanow E, et al. Childhood leukaemia in Europe after Chernobyl:5 year follow-up. Br J Cancer 1996; 73:1006-12.

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

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

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

Tables and Figure: These should be given in the end after references section consecutively, and provided with caption. Footnotes should be identified by lower case lettrs and cited in the tables as italicized
superscripts. All tables should be cited in the text. Figure should be kept to the inimum, colored figure, halftone figure will be charged @ Rs 200 per figure.

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

Proofs and Reprints : Accepted paper's proofs will be sent to the corresponding author for verification against the original and appropriate corrections made. It will be mandatory to purchase at least 50 reprints. An order form for reprints will be sent with proofs. Please return the reprint order form with a cheque of Rs. 1000/- (India) in favour of "Editor-in-Chief, Journal of Pharmacovigilance and Drug Safety." Reprints will be posted within 15 days after printing the journal.

Issue to Consider before submitting a Manuscript
Redundant or Duplicate Publication
Redundant or duplicate publication is publication of a paper that overlaps substantially with one already published.
Readers of primary source periodicals deserve to be able to trust that what they are reading is original unless there is a clear statement that the article is being republished by the choice of the author and editor. The bases of this position are international copyright laws, ethical conduct, and cost-effective use of resources.
Most journals do not wish to receive papers on work that has already been reported in large part in a published article or is contained in another paper that has been submitted or accepted for publication elsewhere, in print or in electronic media. This policy does not preclude the journal from considering a paper that has been rejected by another journal, or a complete report that follows publication of a preliminary report such as an abstract or poster displayed for colleagues at a professional meeting. Nor does it prevent journals from considering a paper that has been presented at a scientific meeting but not published in full or that is being considered for publication in a proceedings or similar format. Press reports of scheduled meetings will not usually be regarded as breaches of this rule, but such reports should not be amplified by additional data or copies of tables and illustrations.
When submitting a paper, an author should always make a full statement to the editor about all submissions and previous reports that might be regarded as redundant or duplicate publication of the same or very similar work. The author should alert the editor if the work includes subjects about whom a previous report has been published. Any such work should be referred to and referenced in the new paper. Copies of such material should be included with the submitted paper to help the editor decide how to deal with the matter.
If redundant or duplicate publication is attempted or occurs without such notification, authors should expect editorial action to be taken. At the least, prompt rejection of the submitted manuscript should be expected. If the editor was not aware of the violations and the article has already been published, then a notice of redundant or duplicate publication will probably be published with or without the author's explanation or approval.
Preliminary release, usually to public media, of scientific information described in a paper that has been accepted but not yet published violates the policies of many journals. In a few cases, and only by arrangement with the editor, preliminary release of data may be acceptable- for example, if there is a public health emergency.

Requirements for the submission of manuscript
Double-space all parts of manuscripts.
Begin each section or component on a new page.
Review the sequence: title page, abstract and key words, text, acknowledgements, references, tables (each on separate page), and legends.
Illustration (uncounted prints) should be no large than 203x254 mm (8x10 in.).
Include permission to reproduce previously published material or to use illustrations that may identify human subjects.
Enclose transfer-of-copyright and other forms.
Submit the required number of paper copies.
Keep copies of everything submitted.

NIMS UNIVERSITY

JAIPUR, RAJASTHAN

(University established by Act of Govt. of Rajasthan under Section 2(F) of UGC Act 1956)

NIMS Believes in : " World class standards in all spheres within one's reach"

NIMS UNIVERSITY, gives an opportunity for holistic development of personality with its ambience, attitude in teaching methodology and student- teacher relationship. The location being in the backdrop of Aravali hills simulates the environment of 'Gurukul'. Further the inculcation of modern methods of teaching learning aids as well as process coupled with traditional way, the hybrid process greatly suits both students and the faculty.

Courses Offered by NIMS UNIVERSITY

• NIMS Institute of Medical Sciences & Research	MBBS
• NIMS Hospital	
• NIMS Dental College	BDS
• NIMS College of Physiotherapy	BPT, MPT, BOT
• NIMS College of Nursing	B.Sc., M.Sc.
• NIMS School of Nursing	GNM
• NIMS College of Paramedical Technology	DMLT, DOT, X-Ray Technology
• NIMS Institute of Management Studies & Computer Science	BBA, MBA
• NIMS Institute of Engineering and Technology	B. Tech
• NIMS Institute of Pharmacy	B.Pharma, M. Pharma
• NIMS Institute of Advance Sciences & Technology	M.Sc. (Micro, Biotech, Biochem.)
• NIMS School of Law	LLB
• NIMS Department of Library Science.	B.Lib., M. Lib.

- Lecture Halls
- Libraries Laboratories
- Conference Halls
- Auditorium
- Hostel Facility
- ATM Facility
- Staff Quarters
- Transport Facilities
- Canteen & Cafeteria
- Shopping
- Hospital Facility
- Sports Facilities

NIMS UNIVERSITY

JAIPUR - Rajasthan, INDIA

+91- 97847 49000 Fax No. : +91- 141- 2605050

E - mail : director@nimsr.com Web. : www.nimsuniversity.org