



IJCP

International Journal of Community Pharmacy
Volume 2 Number 3 September-December 2009

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Editorial

I wish all the readers a happy new year. I am very happy to announce the 62 Indian Pharmaceutical congress will be held at Manipal University during 17-19 December 2010. The focus of the 62 IPC will be on Hospital Pharmacy, Clinical Pharmacy and Community Pharmacy. Although India has established leadership in Pharmaceutical Industry, there is a need to reengineer the profession in the areas of patient safety and pharmaceutical care. There is need to popularize the fields like pharmacoeconomics and pharmacoepidemiology.

The Association community Pharmacists of India has completed its two years and is able to establish itself as a leader in promotion of patient care. It has given encouragement for many young pharmacists to realize the importance of community pharmacist in health care.

In years to come the ACPI will be able to motivate the pharmacists to indulge in patient related services, which are presently not available in India.

International Journal of Community Pharmacists has successfully completed one year. During this one year we were focused to publish quality articles and case studies. We hope that the Journal gets indexed and will reach globally to professionals across the world.

Prof N Udupa

Editor In Chief, IJCP

MESSAGE FROM ACPI

Dear Readers,

Wish you all a happy new year. The Association of community pharmacists of India conducted Annual general body meeting on 13th Jan 2010. The Audited accounts for 2007-2008, and 2008-2009 along with auditor's report were presented for approval of general body. The new resolutions passed by the general body include formation of chapters of community services and launching of case study in community pharmacy. The chapter of community services gives an opportunity for non-pharmacist to join association and help in the community services. There is no documentation regarding services of pharmaceutical care in the country. This will be first of its kind and will be managed by the separate body of the association. The association has promoted a pharmaceutical care clinic at Pune. The experience of running the pharmaceutical care clinic is awaited from the pharmacists who are running this clinic. It is very important time for all of us to rededicate our services to patients so that they can be assured a quality care and safe medication.

President,

ACPI, Manipal.

RISK OF “EVIDENCE” BASED DRUG USE THROUGH PREGNANCY RISK CATEGORY

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ABSTRACT

Evidence of drug information is usually collected from Randomized Controlled Trials and Meta Analysis. Drug information is as important as drugs. Without proper drug information a drug can not be used. The question is that the pregnancy risk categories of drugs, mainly by FDA are truly evidence based? We have many experiences in past that some evidences are made from studies which are incomplete or methodologically wrong. “Some evidences have a very short shelf life”. In this study we are discussing some serious pitfalls in the developing of evidence for pregnancy risk category and misrepresentations of the categories in real practice situations. Also we are trying to define teratogen and risk of under treatment to support the need of categorizing drugs on its pregnancy risk. Evidence formulation is never easy for drugs in pregnancy. Still monitoring the risk benefit ratio is a potential tool, even though the present category is oversimplification of facts. The final suggestion is do some serious revamping of the pregnancy risk category as its highly confusing and creating false alarms and fear in patients.

Key Words: pregnancy risk category, teratogen, evidence

INTRODUCTION

With the alterations in body’s physiology in pregnancy, it may be tough to know what the best medicinal dose in pregnancy is. Studies revealing valuable information in pregnant women are too rare. There are many ethical issues in pooling drug information through drug research in the pregnant. But it does not mean research cannot be done on pregnancy.¹

Clinical investigations generally exclude pregnant women in their study protocols. It makes the development of drug information scarce. Great caution is advocated for use of drugs of which safety in pregnant or breast feeding population is not proved. European Agency for the Evaluation of Medicinal Products (EMED), Ministry of Health, Labor and Welfare (MHLW) in Japan, Australian Drug Evaluation Committee (ADEC) and Food and Drug Administration (FDA) etc are some of the authorities which try to establish Pregnancy Risk Categories.²

One important and under recognized reason is the poor compliance of pregnant women. One of the study found that 50% of pregnant women would not take a course of drug treatment as prescribed by their doctor. Fear of harming the fetus is the main concern for mothers.³ In 1998 three patients with tuberculosis (of 114 such patients treated at Homerton Hospital) became pregnant; all three were advised by their general practitioner or midwife to stop their treatment, and two accepted a termination. In addition, two of 71 female patients receiving preventive treatment with isoniazid were advised to stop treatment after a pregnancy test gave a positive result. There is no indication for the interruption of pregnancy for those with tuberculosis and that "untreated tuberculosis represents a far greater hazard to a pregnant woman and her fetus than by treatment of the disease. When pregnant women become sick they may need to be treated with drugs or when patients with chronic disease become pregnant, they may have to continue drugs.⁴ But of the many drugs in use only a few have been shown definitively to be harmful to the fetus.⁵

TERATOGEN

Teratogen is a term that refers to any substance with the potential to cause birth defects. ¹ Teratogens are defined as agents that increase the risk of or cause a congenital anomaly to occur. These defects can be structural, functional or behavioral in nature.⁶ A medicine or other chemical or a process should result in a characteristic set of

malformations, indicating selectivity for certain target organs. It shall exert its effect at a particular stage of fetal development. And it may show a dose depended incidence.⁷

Sometimes even a single intrauterine exposure to a drug can affect the fetal structures undergoing rapid development at the time of exposure⁷ There is acute toxicity and chronic toxicity. Continued exposure to a teratogen may affect several organs and cause cumulative toxicity.⁷ People mainly blame the drugs they take as the cause of birth defects. But they occur as a result of many other factors also. Much of the birth defects happen because of unknown reason and these counts 3% of all the birth happening in United States as an example.⁸

It is really a tough situation to manage hard pathological situations with potentially teratogenic drugs.

Table No. 1; Current Categories for Drug Use in Pregnancy

Category	Description
A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities.
B	Animal studies have revealed no evidence of harm to the fetus, however, there are no adequate and well-controlled studies in pregnant women. or Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.
C	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women. or No animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.
D	Studies, adequate well-controlled or observational, in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk.
X	Studies, adequate well-controlled or observational, in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant.

Examples of fetal damage caused by drugs include:

1. Phocomelia by Thalidomide.⁹
2. Chromosomal damage by LSD
3. 8th cranial nerve damage and deafness by Streptomycin
4. Congenital goiter by iodide-containing preparations
5. Impaired fetal growth by corticosteroids and antineoplastics. Many antineoplastics are embryocidal.
6. Virilism by sex hormones; creating ambiguous genitalia.
7. Bone growth and enamel formation of teeth affected by tetracyclines
8. Depression and delayed onset of respiration by pethidine.¹⁰
9. Fetal warfarin syndrome by warfarin. Teratogenic effects of warfarin is produced on early exposure of the drug i.e. mainly on the first trimester.
10. Fetal alcohol syndrome by consumption of alcohol in large amounts for prolonged periods. Moderate drinking during the second trimester increases the incidence of spontaneous abortions.^{11,12}
11. Differentiation in developing tissues are affected by vitamin A analogs (Isotretinoin)⁷

Most medical, industrial, and domestic uses of ethanol-containing products might be safe during pregnancy; women should still be made aware that they contain alcohol. It is important to use caution when prescribing ethanol-containing elixirs to pregnant women.¹³ Interestingly deficiency of some important supplements in the body also cause teratogenic like effects. Neural tube defects such as spina bifida are reduced by folic acid supplementation during pregnancy.⁷

FDA PREGNANCY RISK CATEGORY

According to FDA, since 1975 the drug labeling is required to include teratogenicity and related data on reproduction and pregnancy. Also the product must be classified under one of the five letter categories A, B, C, D and X.¹

RISK IN STAGES OF PREGNANCY

The differences in pharmacokinetic and pharmacodynamics of different trimesters of pregnancy are considered while taking treatment decisions.

Fetal age drug potency and drug dose determine a drug's teratogenic effect along with the time of exposure. It's an all or none phenomenon for drugs exposed before 20th day after fertilization. Either the drug kills the embryo or do not harm at all. The key fetal age where most of the teratogenesis do occur is in first trimester of pregnancy, especially between 14th and 56th days after fertilization. First trimester is the period of organogenesis. Drugs exposed after organogenesis is less teratogenic, but may still risk growth and normal functioning of fetal physiology.¹⁴

In contrast to first-trimester exposure to ACEIs, second- and third-trimester exposure appears to be fetotoxic, producing fetal hypocalvaria and renal defects. The cause of these defects appears to be related to fetal hypotension and reduced renal blood flow.¹⁵

By the time a woman presents to her doctor she is usually well into, or even beyond, crucial organogenesis period. Stopping a useful drug at this point is illogical and may even be harmful if the disease being treated worsens. Similarly, Even though the course of treatment was completed before conception there is the potential for harm if a teratogen is still in the body during organogenesis.¹

RISK OF CATEGORIZATION IN GENERAL

Availability of clinical literature on safety is the fundamental aspect to make an opinion. Especially the extent of availability becomes a key factor which leads to variations in drug safety level, for drugs which have partly available clinical data. Drugs may look like safer than actually it is. There is no position to grade the review level of drug information and authenticity of available data.³

Bupropion marketed for depression has been categorized as category B based on very small and limited human or animal data, which necessarily not supporting the adverse effects on pregnancy. Meanwhile the drug with extensive safety data such as fluoxetine and citalopram are labeled as category B. mainly because of available adverse data on rats. There is sound evidence on human data that fluoxetine is not increasing the risk of major congenital abnormalities. But still it is categorized as B because of adverse animal data. Considering bupropion which is not having a sound or extensive information in human or animal safety data is categorized as B. This cause a false impression in prescribers is that Bupropion is much safer than fluoxetine to be used in pregnancy. This widely causes an unnecessary switch-over of medicines. The FDA categorization is also misleading that the safety or risk of all medications in a particular category is equal. All the selective serotonin Reuptake Inhibitors are labeled as category C. but the drug information available on first trimester is very less for paroxetine and sertraline compared to fluoxetine and citalopram.¹⁶

People are confused in taking these categories as the toxicity level of drugs, as those drugs on A is least toxic and those on X is the most toxic. But in reality this categorization is meant by risk-benefit analysis of drugs in different treatment plans. Meanwhile, in general those drugs labeled as X may be equally or less toxic than those drugs labeled as C or D.

Oral contraceptive which are contraindicated in pregnancy (labeled as X) because, they have no indication at all once when pregnancy have started. And some safer of least toxic medicines may be labeled as C because there is not enough animal studies have been conducted or the available animal data suggest medium level of risk in pregnancy.¹⁷

Of course the FDA categorization is pregnancy risk is not only tool in risk assessment by a prescriber. This can be very well described by the example of Lithium. There is a better risk benefit ratio than actually represented by its D categorization when treating women with bipolar disorders.¹⁸

RISK OF UNDERTREATMENT

When the risk of a disease counts much higher value compared to a rare but proven teratogenicity of the drug. Ebstein's anomaly (a cardiovascular malformation) is associated with first trimester exposure to lithium. But the absolute risk is estimated to be 0.05% to 0.1%. And many psychologists avoid or stop using lithium in pregnant women. Alarmingly over 60% of relapse is seen within the first 6 months of discontinuation of lithium. So the priority given to make an expert opinion is misrepresented by its 'D' categorization.¹⁹

Some times the danger of untreated diseases is much higher than the danger with drugs which cannot be spared. Also it get complicated when health of mother or child who is important for the situation. Many other factors other than just the pharmacological actions of the drug are being counted to develop treatment plan. So as to avoid any teratogenic effect some doctors may prescribe a lower dose than adult dose. But in reality the pregnant women may require a higher dose than adult to get required therapeutic response.

Physicians should ensure that pregnant women with psychiatric disorders receive evidence-based information that balances the benefits of treatment against unproven adverse effects on unborn babies.

It is well known that women of childbearing age often suffer from major depression, which is most prevalent among people between 25 and 44 years old. A growing body of literature suggests that the risk of adverse effects of untreated depression in pregnancy is high.¹⁵

RISK OF EVIDENCE LEVEL

Most drug information of safety is developed from animal studies and uncontrolled studies in human i.e. mainly by post marketing surveillance.

Interventional therapeutic trials with suspected teratogens are not ethical. So it may take many years of experience and help of pregnancy registry may be needed to link specific drug with certain defects. Animal data can be partly useful to suspect a drug as a teratogen. In general, one of the main reasons for adverse effect of a drug is its dose. Normally in animal studies the dose used is more than normal human dose. Any drug may be toxic at a higher dose. But sometimes animal data is the only source of information about safety of drugs in early stages of pregnancy. Teratogenic effect is not only depending on the nature of chemical but also its dose and duration of its exposure to fetus. These teratogens can also work indirectly for example reducing uterine blood flow and causing risk of growth of the fetus. In addition it may result in severe uterine hypertonia.²⁰

Pregnancy registries are sponsored mostly by pharmaceutical companies. These registries are like a drug profile of certain patients through pregnancy. They closely follow women taking certain drug until the end of their pregnancy. Researchers follow pregnancy registries in preparing the safety data of drugs during pregnancy for mother and baby. Finding out the precise dose required in pregnant is not well supported by evidence, much studies has to be done. Clinical pharmacokinetic data of drugs changes from adult to pregnant, in between 3 trimesters of pregnancy of even closer periods. Much information about basic physiological changes, absorption, metabolism, distribution and elimination of drugs are needed to be known.

Attenuated live virus vaccines pose theoretical danger of contracting fetal infection, e.g. Rubella vaccine. Varicella live virus vaccines etc. are contraindicated during pregnancy. But these vaccines are proved to be safe in neonates. All the killed vaccines are reserved for situations of potential fetal or maternal infection risks. Meanwhile Influenza vaccine is recommended for all pregnant women in after first trimester during influenza season.^{20, 21}

Thirteen randomized trials on mild to moderate chronic hypertension during pregnancy, but all were small and most were unblinded. Few women were given treatment in their first trimester. Eleven different drugs or drug combinations were studied; data on any one drug were very limited. Definitions of chronic hypertension and outcomes such as preeclampsia and growth retardation differed from trial to trial.²²

Guidelines and clinical practice for the use of antipsychotic drugs in women with non-affective disorders during pregnancy are not based on evidence from randomized controlled trials. For obvious ethical reasons there are few randomized and placebo controlled clinical trials designed to evaluate the safety and efficacy of drugs in pregnancy. Exceptions to this rule include studies of aspirin in the prevention of pre-eclampsia. Aspirin can cause minor neonatal hemorrhage when used in analgesic doses within a few days before delivery. This effect has not been seen in trials of low dose aspirin. Corticosteroids have a reputation for being teratogenic. There is no evidence for this in humans, although in high doses corticosteroids cause oral clefts in rodents. Corticosteroids have been used in thousands of pregnant women for treatment of autoimmune diseases, severe asthma, and inflammatory bowel disease and after organ transplantation with no evidence of an excess occurrence of fetal abnormality. In contrast to the steroids used to accelerate lung maturity corticosteroids are metabolized in the placenta, and there is no evidence that they influence the fetal endocrine system.²³

Paracetamol (Acetaminophen), Penicillins, Cephalosporins, antacids, and steroid and bronchodilator inhalers should be considered safe. The results of animal experiments are showing that, when used in recommended doses, the new SSRIs do not appear to increase the risk of congenital malformations.⁵

CONCLUSION

The present pregnancy risk category is causing lot of misrepresentations and confusions in patients. The use of the category is limited to the public because of its limitations and false alarms. FDA Pregnancy Risk Category is oversimplification of facts. Those women are suffering with life threatening diseases are advised to take the investigational agents if there is no other good treatment options are available. The investigational agent may be teratogenic but benefits to mother's life are counted with more priority. Case-control studies can be powerful epidemiologic tools for investigating suspected associations between fairly common antenatal exposures and rare pregnancy outcomes. A revised system of pregnancy risk categorization is the need of the hour. Evaluating the risk benefit ratio is a good logic but it should not be the only principle in categorizing the pregnancy risk of drugs. Under treatment of pregnant populations is equally hazardous.

REFERENCE

1. Meadows Michelle, Pregnancy And Drug Dilemma, FDA Consumer Magazine, USFDA, May- June, 2001
2. Addis A, Sharabi S, Bonati M. Risk Classification Systems For Drug Use During Pregnancy: Are They A Reliable Source Of Information, Drug Saf., 2000; 23(3):245-53.
3. Rubin Peter, Drug Treatment during Pregnancy, Fortnightly Review, BMJ, November 1998; 317:1503-1506.
4. Letters, Pregnancy Does Not Mean That Patients With Tuberculosis Must Stop Treatment, BMJ, May 1999; (318):1286.
5. Einarson Adrienne, Selby Peter and Koren Gideon, Abrupt Discontinuation of Psychotropic Drugs during Pregnancy: Fear of Teratogenic Risk And Impact Of Counseling, J Psychiatry Neurosci 2001; 26(1):44-8.
6. Buck Marcia L and Kelsey Julie J, Drug Use in Special Patient Population; Pediatric, Pregnant, Geriatric, Shargel Leon et. al., Comprehensive Pharmacy Review, Lippincott Williams and Wilkins, New Delhi, 2007; (6):752-753.
7. Lake DF, Briggs AD and Akporiaye ET, Thalidomide, Koren G, Teratogenic Drug Actions, Katzung G. Bertram, Basic and Clinical Pharmacology, McGraw-Hill, New Delhi, 2007;10th ed.: 918, 973
8. Kumar V, Cotran R S And Robbins S L, Pediatric Diseases, Robbins Basic Pathology, Elsevier, New Delhi, 2005; 7th Ed.: 241
9. Das K K V and Thomas M, Thalidomide, Das K K V Text Book of Medicine. Jaypee Publishers, New Delhi 2008; 5th Ed.: 1059
10. Park K, Preventive Medicine In Obstetrics, Pediatrics And Geriatrics, Park's Text Book Of Preventive And Social Medicine, M/S Banarsidas Bhanot Publishers, Jabalpur (India) 2007; (19): 418.

11. Brunton L L And Parker K L, Teratogenic Effects: Fetal Alcohol Syndrome, Goodman And Gilman's Manual Of Pharmacology And Therapeutics, Mc Graw Hill New Delhi 2008; 11th ed.: 382
12. Buck Marcia L and Kelsey Julie J, Drug Use in Special Patient Population; Pediatric, Pregnant, Geriatric, Shargel Leon et. al., Comprehensive Pharmacy Review, Lippincott Williams and Wilkins, New Delhi, 2007; (6): 752-753.
13. Garcia-Bournissen Facundo, Finkelstein Yaron, Rezvani Massoud, and Koren Gideon, Exposure To Alcohol-Containing Medications During Pregnancy, Can Fam Physician. 2006; 52(9): 1067–1068.
14. Block J H, Protein Binding, Block J H And Beale J M Jr. Wilson And Gisvold's Textbook Of Organic Medicinal And Pharmaceutical Chemistry, Lippincott Williams And Wilkins, Philadelphia 2004; 11th Ed.: 6
15. Kulin Nathalie A., Pastuszak Anne, Sage Suzanne R., Schick-Boschetto Betsy, Spivey Glenda, Feldkamp Marcia, Ormond Kelly, Matsui Doreen, Stein-Schechman Amy K., Cook Lola, Brochu Joanne, Rieder Michael and Koren Gideon, Pregnancy Outcome Following Maternal Use Of The New Selective Serotonin Reuptake Inhibitors JAMA. 1998; 279: 609-610.
16. Savithiri Ratnapalan, Gideon Koren, Taking ACE inhibitors during pregnancy:Is it safe, Canadian Family Physician 2002; 48:1047-9.
17. Wells B G, Dipiro J T, Scheringhammer T L And Hamilton C W, Pregnancy, Pharmacotherapy Handbook, Mc Graw Hill, New Delhi, 2005; 6th Ed.: 722
18. Newport D. Jeffrey, Viguera Adele C., Beach Aquila J., Ritchie James C., Cohen Lee S. And Stowe Zachary N., Lithium Placental Passage And Obstetrical Outcome: Implications For Clinical Management During Late Pregnancy, Am J Psychiatry 2005; 162:2162-2170
19. Cohen L. S., Friedman J. M., Jefferson J. W., Johnson E. M. And Weiner M. L, A Reevaluation Of Risk Of In Utero Exposure To Lithium JAMA, 1994; 271 (2):146-150
20. Illinois Teratogen Information Service, <http://www.fetal-exposure.org/> (retrieved on 18/04/09)
21. National Toxicology Program Center For The Evaluation Of Risks To Human Reproduction (CERHR), <http://cerhr.niehs.nih.gov/> (retrieved on 18/04/09)
22. Rodrigues P A, Kumaran A K S G, Rahman H, Prabha S G And Lavanya S, Drug Prescribing Pattern In AMaternity Care Unit, Ind. J Of Hosp. Pharm. 2008; 45:153-157
23. Jochen Theis, Acetylsalicylic acid (ASA) and nonsteroidal anti-inflammatory drugs (NSAIDS) during pregnancy http://www.motherisk.org/women/updatesDetail.jsp?content_id=135 (retrieved on 18/04/09)

IMPLICATIONS OF E-COMMERCE IN HEALTH CARE SYSTEM

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INTRODUCTION

E-commerce or Electronic commerce is the buying and selling of goods and services on the Internet, especially the World Wide Web. E-commerce activities have registered exponential growth in the past few years and have encompassed almost all sectors of the economy. Because of it the world market place has undergone a rapid transformation in terms of knowledge and services. It has actually broken the physical and the geographical barriers and given a new dimension to business transactions and developed new business models. Health Care sector is an important constituent of the world economy and e-commerce has struck formidable roots into this sector as well. The old concept of “brick and mortar” pharmacy which was limited by geographic location i.e. the patients in a particular area go to the pharmacy to pick up a wide range of medication, has given way to “brick and click” pharmacy. This new model of pharmacy combines the traditional retail operation with internet based B2C services. Any form of business transaction in which the parties interact electronically rather than physical exchange or direct physical contact is representative of e-commerce concept.

There are multiple ways in which a pharmacy can present itself on the internet and provide a platform for drug information services worldwide. Worldwide, more and more people are using the Internet and a pharmacy specific Internet site¹ can serve as a “Welcome Wagon,” providing information about the pharmacy’s hours, staff, location, and services. Wide range of products can be offered like pharmaceutical products and non pharmaceutical products like cosmetics, dietary products etc. It can also provide a channel for patients to request information about particular disease or drug or refills for physicians to prescribe and to assist patients with drug- related problems or to place an order with the wholesaler. Several manufacturers have their own web pages with brand name as part of the URL, which connects directly to them for that specific product through any search engine, such as Google or Yahoo.

Networking² is very essential as it facilitates collaboration, links and participation at global level without caring about time and distance. In this online world with a global market space, the online pharmacies target specific problems and focus on patient groups relating to diabetes, hypertension, chronic pain, etc. They serve as effective intermediaries in the information supply chain for pharmaceutical products and alter the basis of competition by disintegrating inefficient and error prone steps in this supply chain⁶³, reconfiguring the information supply channels, personalizing⁷⁴ and delivering the information thus gaining new efficiencies. Online pharmacies will share drug information with the customers i.e. building a net which is an added competitive advantage over traditional system. The pharmacist being a part of healthcare team can help patients by providing drug related information, side effects, dosage schedule, adverse effects, drug interactions, patient counseling through the use of e-mail, chat rooms, forums, videoconferencing. etc. E-commerce is an ideal tool for people to receive personalized tailored information about their disease status and relevant medicines in the comfort of their homes and it provides more anonymity than face-to-face interactions with health care professionals, which is particularly relevant when asking embarrassing questions.

The importance of internet as information source and distribution channel can not be underestimated as technology is the critical foundation of any e- Commerce venture. There are number of options available ranging from Open Source like OS-Commerce to IBM Web sphere Commerce, a licensed software or managed e-Commerce services arrangement. It should be kept in mind that we should consider investing in robust site analytics software like Omniture or Google Analytics and a parametric based search solution so that customers can easily find what they are looking for. NOVARTIS has formed a partnership with Jeeves Solutions to optimise use of branded internet services. Google is now the top online searching tool for healthcare. PhRMA has launched an online database to promote access to free medicine for eligible US patients. E-commerce venture can be successful only if it is built with good technology and has good marketing strategies for their consumers because without a good marketing strategy no e-commerce venture can survive. Fast growing fields of online communication are listed here:

1)**e-marketing & sales:** Use of internet in marketing of sale of pharmaceutical products through internet.

2)**e-detailing:** Constitutes a useful marketing strategy that is possibly not being used to its best effect in healthcare. Actually E-detailing is via interactive online software, internet⁵ conferencing, medical portals etc. e-detailing always differs from the traditional “push” model of sales promotion, this may probably suit prescribers better.

3)**e-prescribing:** It is Using internet for prescribing of drugs. Prescription writing constitutes one of the largest paper based process in healthcare. e-prescribing plays an increasingly important role in pharmaceuticals also Like CAFÉ Rx- made a new alliance to promote and facilitate e-prescribing in US. Prescription counseling initiatives, for example the Primary Care Question Answering Service of the National Library for Health⁶ (NLH) and ATTRACT⁷, are also proliferating.

RESULT AND CONCLUSION

Before we look at the factors that will drive an explosive growth in e-Commerce, it is important to look at why e-commerce hasn't taken off so far in India. The most basic reason is that most Indian consumers still don't see enough value propositions in shopping online because they have heard a lot of horror stories about not receiving the right products, not receiving products in time, notwithstanding the issues related to cumbersome returns and cancellation processes when shopping online. Online security is an important concern among the consumers therefore Companies need to have strong internet marketing strategies for them. On the other hand, we can't fully blame the online retailers because they have to rely on third party vendors, logistics partners who still haven't achieved enough scale and the level of technology automation to consistently meet the desired service levels. These issues really point to the lack of a mature eco system across the e-commerce value chain.

BIBLIOGRAPHY

1. Anderson C ;The Internet and its implication for pharmacy; Int Pharm J 2001; 15:17-19.
2. Butler, D;Science in the web age: joint efforts; Nature; 2005;438:548–9.
3. Felkey B. Threats and opportunities of the Internet for pharmacy practice. Int Pharm J 2000;14(1) : 11-13.
4. Zehnder S, Beutler M, Bruppacher R, Hersberger K. Drug information sources used by patients in Switzerland: an in-pharmacy-survey on the use of drug information sources with special focus on new information technologies. J Soc Adm Pharm 2003; 20(5): 156-165.
5. Docherty N; Cyber retailing in U.K.;Int J Retail Distribution Mangement 1990;27:22-36.
6. National Library for Health. Primary Care Question Answering Service. [2 April 2006]. <http://www.clinicalanswers.nhs.uk>.
7. ATTRACT. [2 April 2006]. <http://www.attract.wales.nhs.uk/index.cfm>

EVALUATION OF DRUGS UTILIZATION ESPECIALLY ANTIMICROBIAL AGENTS IN INPATIENT DEPARTMENT OF TERTIARY CARE HOSPITAL

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ABSTRACT

Objective: To determine prescribing pattern of drugs specially antibiotics in prophylaxis, empirical & directed therapy. **Methodology:** A prospective analysis of inpatient records was carried out at tertiary care hospital for five months. **Results:** In the first phase 416 patients were surveyed for antimicrobial use pattern study and in the second phase 100 patients were surveyed for surgical prophylaxis study. A total of 332(79.80%) patients received antibiotics. 132(39.75%) and 200(60.24%) patients received antimicrobials for surgical prophylaxis and as empirical therapy respectively. Out of 200 patients, 101 (50.5%) patient's specimens were sent for culture. 21(22.7%) patients had positive culture reports and 18(19.8%) patients received antimicrobials as per culture sensitivity reports. 75% patients received more than a single dose of antibiotic in operation of less than 4 hours. 60% patients received same antibiotic pre and postoperatively. 15% and 7% patients received fluoroquinolones & cefazolin respectively. **Conclusion:** Although there are no gold standards for the extent of use of antimicrobials in in-patient settings. High (79.8%) antimicrobials usage, average numbers of drugs per encounter, percentage of encounters with an antibiotic prescribed. and non compliance with the Standard treatment guidelines (STG's) for antibiotic usage in surgical prophylaxis was observed therefore the study findings called for a review of antimicrobial prescribing practices.

Keywords: Antimicrobials, Prescribing pattern, surgical prophylaxis

INTRODUCTION

One of the most pressing problems for public health providers and administrators in many countries is to ensure rational use of drugs¹. The present definition of rational use was agreed at an international conference in Kenya in 1985. According to WHO: "Patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community"².

Problems of irrational use of drugs leads to insufficient therapeutic effect, adverse drug reactions, preventable side effects, interactions from medicines, increasing resistance of bacterial pathogens to antimicrobial medicines. There are Strategies or interventions to promote RUD which are educational strategies which aim to inform & persuade users, managerial strategies which aim to structure & guide decisions made by users & Regulatory strategies which aim to restrict or limit the decisions of users.^{2,3}. There are several well-established tools to measure the type and degree of irrational use of drugs. These are:

Focused DUE (Drug Use Evaluation) is an ongoing, systematic process designed to maintain the appropriate and effective use of drugs⁴. It involves a comprehensive review of patients' prescription and medication data before, during, and after dispensing to ensure appropriate medication decision making and positive patient outcomes^{2,3}. Different type of DUE studies are there which consists of Prospective - evaluation of a patient's drug therapy before medication is dispensed. Concurrent ongoing monitoring of drug therapy during the course of treatment. Retrospective - review of drug therapy after the patient has received the medication.

Defined Daily Dose (DDD) Methodology can be used to compare drug consumption among institutions, regions and countries^{2,3}.

ABC Analysis is the analysis of annual consumption of medicine & their cost in order to determine which items account for greatest proportion of the budget

Surgical Prophylaxis

Surgical Site Infections (SSI): Surgical Site Infections are the most common nosocomial infections in surgical patients and lead to prolonged hospital stay, readmissions to the hospital, Antibiotic resistance and increased morbidity and mortality. For many procedures, perioperative antimicrobial prophylaxis has proven to be effective in reducing the incidence of SSI⁵. Moreover; incorrect timing of prophylaxis reduces its efficacy. Therefore, the quality of prophylaxis is important⁵. Although drug utilization among outpatients is frequently monitored in many countries (Some countries like Czech Republic had established special institutions for this purpose)⁶, studies on inpatients are rare & incomplete⁷. This type of data are rarely available for hospitals affiliated to universities, which makes interpretation of data difficult⁸.

METHODOLOGY

Study Design

The present study was a prospective study which was conducted at Indira Gandhi Memorial hospital. The Protocol (Proforma) was prepared as per World Health Organization (WHO)¹⁷ recommended drug use indicators (Prescribing & facility indicators) based guidelines and was approved by the Institutional Human Ethical Committee of R.C.Patel Institute of Pharmaceutical Education & Research, Shirpur.

Project Duration & Sample Size: This prospective study was carried out over a period of 5 months in which patients were enrolled from June'08 to October'08.

In the first phase of the study, 416 patients of either sex were taken for antimicrobial use pattern study for 4 months.

In the second phase of the study, 100 patients of either sex were taken to evaluate antibiotic use for surgical prophylaxis for 01 month.

Inclusion & Exclusion Criteria

- Patients admitted in 1st, 2nd (ICU), 3rd, 4th and 5th floor were included.
- Patients from emergency & outpatient department were excluded from the study.

Collection of data

- **Antimicrobial use pattern study:** The format for the collection of the data was prepared as per WHO based guidelines which involved patient as well as medication information such as name, dose, frequency, route etc. And patient information such as name, age, sex. Information like specimen which includes blood/pus/urine/sputum/CSF sent for the culture or not, organism/s grown (if any), culture sensitivity report, sensitivity pattern, disease diagnosed & duration of treatment.
- **Surgical prophylaxis survey:** Patient's name, age, sex, identification number, date of admission & date of discharge, type of surgery, whether the antimicrobial administered or not?. If yes then name of all antimicrobials before & after surgery & at the time of discharge of patient. Dose frequency and timing of antimicrobials (preferentially timing of first doses) and duration of antimicrobials was considered.

3.7 Statistical Consideration:

The results for prescribing and facility indicators were calculated as percentage as applicable.

RESULTS

I. Antimicrobial Use pattern study:

The average age of the patients was 59 years. Average duration of stay in the hospital was 5 days. The overall population of sex categorization study was found to be 49.75% of males (n= 207) and 50.25 % of females. The details of the age wise distribution are given in Table No. (1). The details of the specialty wise distribution of patients are given in Table No. (2). The evaluation of the pattern of medication use showed that total number of drugs prescribed during the study were 1421. Total number of patients who received antibiotics during the study period were 332(79.80%). Out of 332 patients, 132(39.75%) patients received antimicrobials for surgical prophylaxis and rest of 200(60.24%) patients received antimicrobials as empirical therapy. Out of 200(60.24%) patients who

received antimicrobials, a total of 101 patient's (50.5%) specimen was sent for culture. Out of these, 91(45.5%) reports were received, 10(9.9%) patients were discharged on 2nd day therefore culture reports were not available. Out of these 91 patients, 21(22.7%) patients had positive culture reports and 18(19.8%) patients received antimicrobials as per the culture sensitivity reports. The details of the medication use are given in Table No. (3)

II. Antimicrobial use for surgical prophylaxis:

A total 100 patients were taken for surgical prophylaxis, out of them 18 & 16 patients were from Orthopedics & General surgery speciality respectively, 9 from neurosurgery. The details of the distribution are given in Table No (4).

In 75% of the cases, more than a single dose of antibiotic was used in operation which lasted for less than 4 hours. In 60% patients, antibiotic given before surgery was continued postoperatively & prescribed at the time of discharge also. 7% of patients received cefazolin & fluoroquinolones were used in 15% cases. 08 patients received single dose of antibiotic. 80 patients received more than one antibiotics. Minimum number of antibiotic/s prescribed to a patient was 01 and maximum numbers was 04. The details of the distribution are given in Table No. (5). Cefuroxime was the most commonly prescribed antibiotic. A total of 41% patients received cefuroxime during the study period. The details are given in Table No (6).

Overall, Surgical Prophylaxis was used for 94.1 % of the 13 selected procedures. The details of procedure wise use of antimicrobials for different surgical procedures with their mean duration are given in Table No (7).

DISCUSSION

The present study was performed to study the prevalence of irrationality & inappropriate use of medicines in inpatient department.

As compared with the prevalence of antimicrobial use in present study (79.8%), Shrishyla reported antimicrobial use of 56% & other Indian Studies report figures of 20% to 67%⁹. Gaash B. (2005) evaluate antimicrobial use in some of the developing countries like Pakistan, Nepal, Indonesia and reported antimicrobial use of 76%, 50.2% & 43% respectively¹⁰.

In the present study, out of 332 (79.80%) patients who received antimicrobials, 101(50.5%) patients were received definite therapy, however previous studies shows a lower rate of 29%, 27% & 57.8% in inpatient settings.

Most commonly prescribed drugs in present study are pantoprazole, ranitidine, ondansetron, diclofenac & tramadol. However similar study reported most commonly prescribed drugs as cetirizine, paracetamol, antibiotics¹³ whereas Al Faris 1999 reported fluconazole, cotrimoxazole, doxycycline, vitamins & minerals as most commonly prescribed drugs.¹² Most commonly prescribed antibiotics in present Antimicrobial use pattern study was tobramycin, ofloxacin, cefuroxime, amoxicillin + clavulanic acid, amikacin, cefoperazone + sulbactam & ceftriaxone. However Farooqi et al. 2005 reported Penicillin, 1st generation Cephalosporins and quinolones as the most commonly prescribed antibiotics¹³. Similar studies carried out by Fonseca showed Cephalosporins, amino glycosides & Penicillin as the most commonly prescribed class of antibiotics¹³.

Average number of drugs in the present study is very high (10 drugs per patient) as compared to other studies reported 3.36, 3.5, 1.5 & 2.8 respectively as the average number of drugs per patient in the inpatient department¹⁴.

In the present Antimicrobial use pattern study, 83 (25%) patients received 3 or more than 3 antimicrobials; however reported 13% patients who received 3 or more than 3 antimicrobials¹¹.

Surgical prophylaxis survey

Out of 100 cases enrolled, 75% of the cases received more than single dose of antibiotic in operations which lasted for less than 4 hours. In 60% cases, antibiotics given before surgery were continued postoperatively & prescribed at the time of discharge also. However previous study shows that 51% patients received antimicrobials preoperatively & 99.7% postoperatively or both. Cefazolin was used in 7% cases & fluoroquinolones were used in 15% cases. Tobramycin (40%), amikacin (19%) & aminoglycosides was used to a large extent, both as pre & post operatively whereas some previous studies showed a value of 62%.¹⁵ Some of the procedures does not required antibiotics viz

laparoscopic cholecystectomy, hernia repair but in present study antibiotics was prescribed for surgical prophylaxis. 08 patients received single dose of antibiotic. 80 patients received more than one antibiotic. In previous studies this percentage reduced to 75%. ¹⁵Minimum number of antibiotic/s prescribed to a patient was 01. Maximum number of antibiotic/s prescribed to a patient was 04. Similar studies in some of the European countries showed that more than 90% of surgical prophylaxis was found to be inappropriate ¹⁶.

Present study on prophylaxis showed cefuroxime, tobramycin, to be the most frequently prescribed antibiotics, however previous studies on prophylaxis showed metronidazole, ampicillin+cloxicillin, to be the most frequently prescribed antibiotics. A recent (2007) study at the Jawaharlal Lal Nehru Medical College, AMU, revealed that the most commonly prescribed drugs by general surgeons were (93%) – mostly ceftriaxone and amikacin ¹⁰.

The possible reason for difference in prevalence of antimicrobial use in different parts of India & in different countries may be the difference in the demographic characteristics of the patients, disease characteristic, and difference in sample size, pharmaceutical market among countries, prescribing patterns, and physician specialties. There is a need to look into the cases where more than 3 antibiotics were given. Further the empirical therapy needs to be rationalized, and a guideline for the use of antimicrobials needs to be revised.

Table No.1. Age group of patient admitted in inpatient department in Antimicrobial use pattern study

Age group(Years)	No. of patients	Percentage
0-14*	21	5.04
15-25	52	12.5
26-35	86	20.6
36-45	55	13.22
46-55	57	13.70
56-65	88	21.15
Above 65	57	13.70

* 3 patients were Infants

Table No.2. Number of patients from different specialties.

Specialty	No. of patients
Oncology	74
Neurology	72
Internal medicine	65
OBG	45
Orthopedics	42
General surgery	27
Urology	19
Nephrology	16
Gastroenterology	15
Cardiology	12
Pulmonary & critical care	11
Plastic surgery	10
Pediatrics	8
Total	416

Table No. 3. Drug use Pattern (n=416)

Total number of drugs prescribed during the study	1421
Average number of drugs prescribed per patient (during stay in hospital)	10 (2-29)
No. of patients received antibiotics (%)	332 (79.80%)
Average number of antibiotics per patient (during stay in hospital)	2 (1-5)
No. of patients whose specimen sent for culture (%)	101 (50.5%)
No. of patients whose culture reports received (%)	91 (45.5%)
No. of patients discharge on 2 nd day therefore culture report was no available	10(9.9%)
No. of patients with positive culture reports	21 (22.7%)
No. of patients who received antibiotics as per culture sensitivity report (%)	18 (19.8%)
No. of patients who received 10 or more than 10 Drugs	130
No. of patients who received 3 or more than 3 Antibiotics	83
No. of patients who received Antibiotics for surgical prophylaxis	132(39.7%)

Table No. 4. Number of patients from different specialties in surgical prophylaxis study.

Specialty	No. of patients
ORTHOPAEDICS	18
GENERAL SURGERY	16
OBG	14
UROLOGY	11
NEUROSURGERY	9
ENT	7
PS	5
GASTRO.	4
OPHTHALMOLOGY	4
MED. ONCOLOGY	2
ANAESTHESIA	2
PEDIATRIC SURGERY	1
NEPHROLOGY	1

Table No.5. Surgical Prophylaxis Report

Sno	Parameters taken	No. of patients	Percentage of patients
1	More than single dose of antibiotic in operation of <4 hours	75	75
2	Antibiotics continued pre and post operatively	60	60
3	No. of patients received fluoroquinolones	15	15
4	No. of patients received Cefazolin	7	7

Table No. 6. Most commonly prescribed antibiotics for Surgical Prophylaxis

SNo.	Antimicrobial used	Percentage of patients receiving antimicrobials
1.	Cefuroxime	41%
2.	Tobramycin	40%
3.	(Amoxicillin + Clavulanic acid)	25%
4.	Amikacin	19%
5.	Fluoroquinolones	15%
6.	Tinidazole	14%
7.	Metronidazole	12%
8.	Cefotaxime	11%
9.	Cefoperazone+ sulbactam	7%
10.	Cefazolin	7%
11.	Ceftizoxime	6%
12.	Azithromycin	3%

CONCLUSION

Based on base line data & lacunae in the present prescribing practice, such as high use of high antibiotics & non compliance with the Standard treatment guidelines (STG's) for antibiotic usage in surgical prophylaxis, an intervention study is warranted to further improve the current prescribing practice in hospital. There is a strong need to develop hospital antibiotic policies for its efficient use & to strictly adhere with them. This clinical data could support for treating the patients better and it would also excel in assorting confidence in the population regarding the rational use of drugs because patients have zero error expectation from the health care providers.

Table No. 7. Antibiotics used for prophylaxis according to surgical procedure.

Procedure	Most commonly used Antibiotic	Mean duration(days)
Stapled Haemorrhoidectomy	Tobramycin	2
	Metronidazole	6
	Cefotaxime	1
	Ofloxacin	2
Laparoscopic Inguinal Hernia	Tobramycin	
	Cefotaxime	2
	Cefuroxime	6
		7
Cholecystectomy Lap	Tobramycin	3
	Cefuroxime	4
	Metronidazole	7
	(Cefoperazone+ Salbactum)	7
Bilateral Total Knee Replacement	Tobramycin	2
	Cefuroxime	2
Open Reduction Internal Fixation	Cefuroxime	2
	Amikacin	5
	(Cefoperazone+ Salbactum)	2
Laparoscopic Partial Nephrectomy	Cefuroxime	6
	Metronidazole	4

Prescribing pattern of antimicrobials

Dj Stent Removal	Cefotaxime	4
	Ofloxacin	1
Urethroscopy	(Cefoperazone+ Salbactam)	2.4
	Ofloxacin	1
	Amikacin	2
Lower Segment Caesarian Section	Tinidazole	2
	Tobramycin	5
	Amoxicillin + Clavulanic	4.2
Total Abdomen Hysterectomy	Tinidazole	2
	Tobramycin	5
	Amoxicillin + Clavulanic	4.2
Craniotomy	Amikacin	1
	Cefazolin	4
	Ceftizoxime	4
Phaco Intraocular Lens	Azithromycin	2
	Amoxicillin + Clavulanic	5

ACKNOWLEDGMENTS

The authors are appreciating the co-operation of all the health care providers of Indira Gandhi Memorial Hospital and Patients who participated in this study.

REFERENCES

- 1) Bykov M, A.; Savelli, T.; Zagorski, A; January 1997, Guidelines for implementing drug utilization review programs in hospitals. Rational Pharmaceutical Management Project. Russia Rational Pharmaceutical Management Project. Arlington, Moscow, Russia, Management Sciences for Health.
- 2) World Health Organization, 2002, WHO policy perspectives on medicines-promoting rational use of medicines: core components. Geneva, Switzerland: WHO.
- 3) Holloway, K., Green, T., 2004. Drugs & therapeutic committees, a practical guide, World Health Organization; Geneva, Switzerland.

- 4) Palumbo FB, Ober J., 1995. Drug use evaluation. in Principles and practices of managed care pharmacy. Alexandria (VA): Academy of Managed Care Pharmacy. p. 51-60.
- 5) Geubbels EL, Mintjes-De Groot AJ, Van Den Berg Jmet AL, 2000 An operating surveillance system of surgical-site infections in The Netherlands: results of the Prezies national surveillance network. Preventive van Ziekenhuisinfecties door Surveillance. *Infect Control Hosp Epidemiology*; 21: 311–8.
- 6) Miljković M, Đukić LJ, 2000 Analysis of drug utilization in Serbia during the years 1996 and 1997. *Pharmacoepidemiology and Drug Safety*; 9:59-64.
- 7) Janković SM, Milovanović D, Ruzić D, Nedović D, 1998. Cardiovascular drugs utilization in cardiology department of clinical hospital center "Kragujevac" during year 1997. *Pharmaca Yugoslavia*; 36:62-5.
- 8) Hekster YA, Goris RJ., The defined daily dose per 100 bed-days as a unit of comparison and a parameter for studying antimicrobial drug use in a university hospital. A retrospective study of the effects of guidelines and audit on antimicrobial drug use. *Journal of Clinical Hospital Pharmacy* 1982; 7:251-60.
- 9) Shrishyla, M 1994. Drug utilization of antimicrobials in the in-patient setting of a tertiary hospital. *Indian Journal of Pharmacology*; 26: 282 – 287.
- 10) Gaash, B 2008-03 - 2008-04 .Irrational Use of Antibiotics *Indian Journal for the Practicing Doctor* 5.
- 11) Gul Rusher, 2009. Examining Antibiotic Use at an Education and Research Hospital in Turkey. *Turkey journal of medical science*. 39(1): 125-131.
- 12) Slobodan M. Janković, 2001 Drug utilization trends in clinical hospital center “kragujevac” from 1997 TO 1999. *Indian journal of pharmacology*; 33:2936.
- 13) Fonseca., 2004. Audit of Antibiotic Use in a Brazilian University Hospital. *The Brazilian Infectious Diseases*; 8(4):272-280.
- 14) Shanker PR, dubey AK, Rana MS., 2005 Investigation of antimicrobial use pattern in the intensive treatment unit of a teaching hospital in western Nepal. *Journal of Nepal Health & Research Council*.;65-67.
- 15) Annette H. Sohn, MD; Farah M. Parvez, MD, July 2002 Prevalence of surgical-site infections and patterns of antimicrobial use in a large tertiary-care hospital in ho Chi Minh City, Vietnam *Infection control and hospital epidemiology*; 382-85.
- 16) Harvey 1995. Therapeutic guidelines – the way ahead. Essential Drug Monitor (WHO).
- 17) Bimo, Chowdhary A, Das A, Diwan V, Kafle KK, Mabadeje B, et al. In: How to investigate drug use in health facilities (selected drug use indicator) action programme on essential drugs. WHO official publication, 1995:68.