JOURNAL OF CLINICAL AND DIAGNOSTIC RESEARCH

How to cite this article:
MUDIGANTY SSP,DANG A,RATABOLI PV.CRIPPLED PHARMACO VIGILANCE: A QUALM OF MEDICAL PROFESSION!!. Journal of Clinical and Diagnostic Research [serial online] 2008 October [cited: 2008 October 6]; 2:1110-1118.
Available from
http://www.jcdr.net/back_issues.asp?issn=0973-709x&year=2008&month=October&volume=2&issue=5&page=1110-1118 & id=274

REVIEW

Crippled Pharmacovigilance: A Qualm of Medical Profession!!

MUDIGANTY S S P*, DANG A,RATABOLI PV*****

ABSTRACT

Drug prescribing is the most essential practice of medical professionals. A single drug to be marketed has to undergo rigorous processes and drug trials before it is labelled as safe for use in humans. However, all the adverse effects and toxicities cannot be elicited in the limited number of volunteers used in the phased trial. A lot of dangerous rare toxicities come to light only when drugs are marketed and prescribed to thousands of people. Drug regulatory bodies should be aware of these facts and take prompt initiatives to withdraw their sale. Similarly useless and irrational combinations flow the markets without any additional benefits to the patient. This review is an attempt to create awareness about drugs that are no longer used due to lack of safety, those once banned but reintroduced, those that are still used despite toxicities and doubtful efficacy and drugs surrounded by controversies.

Key words

Drug market, banned drugs, bannable drugs, drug toxicity, controversial drugs.

*Intern
Goa medical College,
Bambolim, Goa.

**M.B.B.S
Post Graduate student
Dept. of Pharmacology
Goa Medical College

***M.D. (Pharmacology)
Assistant Professor
Dept. of Pharmacology
Goa Medical College

Corresponding Author:
Dr. Dang A
Room no. 8, ground floor
Residents hostel (GARD)
Goa medical college
Bambolim, Goa-403202
Mobile no. 09764001983
E-mail address: dramit_gmc@rediffmail.com

Introduction

Drugs have become an integral part of medical practice. Presently there are drugs galore available for prescribing by doctors. World drug market has become a cornucopia of drugs[1]. The list of available drugs to select from is inexhaustible. Number of these drugs are known to cause hazardous effects in humans, but are still used. Others have been withdrawn voluntarily by some manufacturers.

Clioquinols were once "hot selling" name in the world market. These drugs were however reported to cause SMON (subacute myelo optic neuropathy)[2]. Dr. Olle Hanson was a Swedish pediatric neurologist, who actively opposed the use of clioqinols. In opposition to the sale of Mexaform and Enterovioform in the third world countries, over 3000 doctors in Finland, Denmark, Norway, Sweden abhorred the products of Ciba-Geigy. The company suffered huge losses and ultimately withdrew the drugs[3].

An award has been named in honour of Dr. Olle Hanson for people of developing countries actively working in the field of rational drug use. The first Indian recipient of this award is Dr. Mira Shiva.

International Scenario: A Timeline Of Events[4]

1901 - The vaccine event: Children who were administered Diphtheria vaccine died of tetanus. This was because the horse sera that was used to prepare the anti-toxin was contaminated with tetanus toxin.

1902 - The Biologics Control act: is passed to ensure purity and safety of serums, vaccines, and similar products used to prevent or treat diseases in humans.

1906 - The food and drugs act: It prohibits interstate commerce in misbranded and adulterated foods, drinks and drugs.

1937 - Cough syrup incidence: Elixir of Sulfanilamide, containing the poisonous solvent diethylene glycol, kills 107 people, many of whom were children, dramatizing the need to establish drug safety before marketing and to enact the pending food and drug law.

1938 - The Federal Food, Drug and Cosmetics (FDC) Act: This was revision of food and drugs act, 1906 which now also includes cosmetics and therapeutic devices.

1955 - The Cutter incidence[5] : Over 250 polio cases were reported due to the use of two contaminated polio vaccine lots. The vaccine contained live active virus instead of the inactive virus because of a supposedly insignificant change in process. This highlighted the importance of process validation.

1961 - Thalidomide disaster: Thalidomide was a drug introduced for sleeping disorders. But when used for treatment of morning sickness in pregnant women it caused severe damage to the foetus. Over 12,000 babies were born with phocomelia (without limbs).

1962 - Kefauver-Harris drug amendments: These were to ensure the safety and efficacy of a drug before it is marketed. In testing a new drug the manufacturer must seek informed consent from the subjects. Nowadays the regulators insist that the drug before being tested on humans, must undergo reproductive studies in 2 or 3 animal species.

1968 - Drug Efficacy Study Implementation (DESI): Formed by FDA to implement recommendations of the National Academy of Sciences investigation of effectiveness of drugs first marketed between 1938 and 1962.

1972 - Over-the-Counter Drug Review: It was started to enhance the safety, effectiveness and appropriate labeling of drugs sold without prescription.

1982 - Tylenol tampering: Deaths resulted due to cyanide poisoning when over-the-counter tylenol was consumed. This occurred due to the tampering on store shelves. Now regulations lay stress on 'tampering-resistant packaging'.

1987 - New guidelines and establishments: To monitor vaccine safety, the NIH (National Institute of Health) established the division of Biologics Control. Today, it's the Centre for Biologics Evaluation and Research (CBER), now part of FDA.

1989 - L-Tryptophan event: There were 38 deaths and hundreds of less severe reactions due to consumption of a dietary supplement, L-tryptophan which contained a harmful byproduct in excess of normal.

2004 - FDA bans dietary supplements: As they contained ephedrine alkaloids and caused increased number of adverse events.

2005 - Formation of the Drug Safety Board: The Board will advise the Director, Center for Drug Evaluation and Research, FDA, on drug safety issues and work with the agency in communicating safety information to health professionals and patients.

Indian Scenario

India has the world's third largest medical manpower and has one of the best developed pharmaceutical industries among the developing countries, but ironically 1 out of every 5 drugs tested turns out to be sub-standard or spurious. India contributes to about 35% of Asia's counterfeit drugs[6]. In spite of having 70,000 formulations in market, we fail to have essential life saving drugs. There is uncontrolled proliferation of irrational, useless and sometimes hazardous drug products[7]. There is no source for unbiased drug information. The practices of adverse drug reaction (ADR) monitoring and post marketing surveillance (PMS) by

the drug manufacturing companies clearly falls short of the expected requirement[8]. The latest official update available states that 78 categories of drugs have been banned in India, out of which 15 are individual drugs and 63 are fixed-drug combinations[9].

Establishment Of Review Committees

1. Hathi Committee-1974[10]

It attempted to formulate an essential drugs list for the first time. It recommended drug price control measures to increase the availability of life saving and essential drugs. The Drug Price Control Order (DPCO) was started in 1979 with three different categories of drugs. Presently, there are only two categories, one which allows a profit margin of 100% and other whose prices are decontrolled. The committee recommended a gradual shift to generic names from brand names.

2. The Lentin Commission Report-1986

Fourteen deaths were reported from J. J. hospital, Mumbai in January 1986. The deaths were totally unrelated to the treatments. The deaths were caused due to the use of diethylene glycol instead of the safer propylene glycol which resulted in acute renal failure. The event was similar to the one which occurred in 1937.

3. Mashelkar Committee-2003

This committee presented a report on comprehensive examination of drug regulatory issues including the menace of spurious drugs.

Drug Product Recall (DPR)[11]

A DPR may be initiated by the Food and Drug Administration (FDA) or by the manufacturer (voluntary recall). A numerical class indicates the degree of consumer hazards associated with the product being recalled.

•**Class I**: Situation I in which there is a reasonable probability that the use of, or exposure to, a violative product will cause adverse health consequences or death.

•**Class II:** Situation in which the use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences, or where the probability of serious health consequences is remote.

•**Class III**: Situation in which the use of, or exposure to, a violative product is not likely to cause adverse health consequences.

Criteria For Banning A Drug/Drug Combination

•Harmful single ingredient preparations.

•Combinations containing harmful ingredients.

•Irrational and untested combinations.

•Food supplements and tonics with inadequate quantity of nutrients.

•Potentially harmful preparations for which safer alternatives of comparable or better efficacy and pricing are available.

Reasons For Banning A Drug/Drug Combination

A drug is introduced into the market for the benefit of consumers. FDA approves a drug only when its safety is proved. However a safe drug need not be harmless. Every drug comes with its own adverse effects. But only when the risk: benefit ratio is low that the drug is approved by FDA.

The Reasons For Banning A Drug Are:

1. Unexpected Problems

The adverse effects of drugs introduced into the market are well known. Morbidity and mortality is more due to known adverse effects rather than unknown adverse effects. Some adverse effects are rare and cannot be elicited by clinical trials which highlight the commonly encountered adverse effects. Severe drug-induced liver diseases is one of the leading causes of banning drugs but is very rare to the extent of 1:5,000 to 1:10,000 exposures or less, which is easily missed in

clinical trials and drug is introduced in the market.

2. Excess Toxicity

A drug may show toxicity only after it is introduced in the market and not at the time of clinical trials. The best example would be Cerivastatin (Baycol) which caused severe rhabdomyolysis[12].

3. Availability Of Safer Options

A drug with less adverse effects and greater or similar efficacy is preferred. Terfenadine introduced in 1985 was banned in 1998 due to its implications in causation of cardiac rhythm abnormalities. This was because fexofenadine introduced in 1997 had similar efficacy but no such adverse effects[13].

4. Harmful Interactions

Mibefradil and astemizole were introduced in the market with known dangerous interactions with 3-4 drugs each. Consequently they showed dangerous interactions with other drugs. They were withdrawn due to availability of other safer alternatives.

5. Irrational Use

The safety of thalidomide in pregnant women was not established. Still this drug was used in pregnant women, causing foetal toxicity and children were born with phocomelia. It was clearly mentioned that bromfenac sodium (NSAID) should be used only for a short time as it elevates liver enzymes when used over a long period of time. However it was used for prolonged time period and this resulted in many cases of liver failure.

6. Failure Of Other Risk Management Options

To highlight the risks associated with a particular drug FDA educates health care professionals through letters (Dear doctor letters) and labeling changes, sometimes new warnings which are placed in black box (black box warnings). Labels are attached specifically for patients mentioning adverse effects and how to detect/avoid them. Drugs are placed in 'second line' list – i.e. they are to be used only if other treatments fail. Some drugs are placed in category of restricted distribution, wherein they are made available only in certain conditions.

(Table/Fig 1) Drugs Banned In India[15]

S. no	Drug	Property	Reasons for the ban	Year of ban
1.	Amidopyrine	NSAID	Agranulocytosis and aplastic anemia	1983
2.	Phenacetin	NSAID	Renal papillary necrosis and hepatotoxicity	1983
3.	Demeclocycline/ Oxytetracycline liquid oral preparations	Antibiotics	Teeth discolouration, enamel hypoplasia, reduced mineralization, increased intracranial tension	1984
4.	Methaqualone	Narcotic, psychotropic	Abuse potential, severe toxicity	1984
5.	Methapyrilene and its salts	Hypnotic	Carcinogenicity	1991
6.	Nialamide	Antihypertensive	Severe and fatal cheese reactions	1991
7.	Practolol	Anti-hypertensive	Severe oculo-mucocutaenous syndrome	1991
8.	Tetracycline liquid oral preparations	Antibiotic	Brown discolouration of teeth, depre16ssion of bone growth	1991
9.	Dexfenfluramine	Antiobesity	Pulmonary hypertension, valvular defects	1999
10	Fenfluramine	Antiobesity	Pulmonary hypertension, valvular defects	1999
11.	Astemizole	Antiallergic	Torsades de pointes	2002
12.	Phenformin	Antidiabetic	Cardiovascular mortality, lactic acidosis	2003
13.	Terfenadine	Antiallergic	Torsades de pointes	2003
14.	Rofecoxib	NSAID	Myocardial infarction	2004
15.	Valdecoxib	NSAID	Fatal cutaenous reactions	2005

(Table/Fig 2)Drugs Which Are Discarded Internationally But Available In India[16]

S. no.	Generic name	Property	Reason for withdrawal
1.	Analgin*	NSAID	Bone marrow depression
2.	Cisapride	Prokinetic	Irregular heart beats, heart rhythm disorder, sudden death.
3.	Furazolidone*	Anti-diarrhoeal	Carcinogenicity
4.	Nimesulide	NSAID	Liver failure/toxicity, Myocardial Infarction, Reye's syndrome
5.	Nitrofurazone*	Antibiotic (topical)	Carcinogenicity
6.	Oxyphenbutazone	NSAID	Bone marrow depression, blood dycrasias, Stevens-Johnson syndrome
7.	Phenolphthalein	Laxative	Carcinogenicity
8.	Phenylpropanolamine	Nasal decongestant	Stroke (pregnant women)
9.	Piperazine	Anthelmintic	Nerve damage
10.	Quiniodochlor	Anti-diarrhoeal	Ocular toxicity
11.	Phenformin	Antidiabetic	Fatal acidosis

*Banned even for animal use in U.S.A

(Table/Fig 3) Drugs Which Should Be Banned / Severely Restricted

S. no.	Generic name	Use	Reason for banning the drug
1.	Hydroxyquinolines-Diiodohydroxyquin, Iodochlorohydroxyquin, Quinido-chlor, Broxyqu-inoline	Anti amoebic	SMON (subacute myelo-optic neuropathy)
2.	Paroxetine	Anti depressant	Suicidal tendencies in pediatric patients
3.	Bromocriptine	Prevention of lactation	Rebound phenomenon, only 10% women seem to benefit
4.	Buprenorphine	Opioid analgesic	Significant abuse potential
5.	Mifepristone	Abortifacient	Bleeding, pain, peritonitis, septicemia, death.

Drugs surrounded by controversies – to use or not to use?

1. Rosiglitazone (Thiazolidinedione Antidiabetic)

In May 2007, the New England Journal of Medicine (NEJM) published an analysis linking rosiglitazone to increased risk of heart attacks. The meta-analysis reviewed 42 studies and found patients taking rosiglitazone to be at a 43% higher risk of heart attacks and a 64% elevated rate of cardiovascular death[17]. However analysis of the 42 studies showed that 40 of them were small and all these put together did not yield statistically significant difference for Myocardial Infarction (MI) between groups. Of the 42 studies included 30 were unpublished and none of them were designed to address MI as either primary or secondary endpoint[18]. Thus the presently available data are not conclusive and henceforth United States Food And Drug Administration (US FDA) has not withdrawn the drug but asked for strict review and some changes have been made on the prescription label[19]. Undoubtedly, data, if confirmed would be of significant concern since patients with diabetes are already at an increased risk of heart disease.

2. Gatifloxacin (Fluoroquinolone Antibiotic)

According to a March 2006 article in NEJM about 2 Canadian studies, one of every 100 patients who take gatifloxacin were hospitalized for either hypoglycaemia or hyperglycaemia[20]. On May 1, 2006, the consumer advocacy group Public Citizen asked FDA to ban this drug[21]. On April 27, 2006 Bristol-Myers Squibb Co. announced that it would stop selling their brand of gatifloxacin (Tequin)[22].

3. Telithromycin (Ketolide Antibiotic)

On March 21 2006, the Annals of Internal Medicine reported three cases of liver problems associated with telithromycin[23]. The drug has been associated with liver damage, liver failure and hepatitis. In mid-May 2006 FDA recommended that a black box warning should to be added to the telithromycin label, stating that "severe, life threatening, and in some cases fatal" liver toxicity has been reported in patients put on this drug[24]. In February 2007, FDA has recommended this drug only for Community Acquired Pneumonia (CAP)[25].

4. Alendronate (Bisphosphonate)

Recent studies have shown a possible link between using alendronate and developing osteonecrosis of the jaw (ONJ)[26]. ONJ can be very painful and may lead to infection, breakdown of the jaw bone, oral ulceration and osteomyelitis. FDA has advised the manufacturers to include a warning in the drug label to highlight this serious side effect[27].

5. Pergolide And Carbergoline (Antiparkinson's Dopaminergic Agonists)

On March 2007 FDA announced that pergolide would be withdrawn from the market on account of two separate studies published in January 2007 in NEJM which concluded that patients put on pergolide and carbergoline are four to seven times more likely to suffer from heart valves' damage

than patients on alternative drug therapy[28].

6. Tegaserod (Serotonin agonist for Irritable Bowel Syndrome)

FDA has asked Novartis to suspend the sales of tegasarod (Zelnorm) following analysis of trial data showing adverse side effects such as heart attack and stroke[29]. Recently in March 2007, Novartis agreed to voluntarily suspend the sales of their brand Zelnorm.

7. Rosuvastatin (Hypolipidemic)

During clinical trials patients taking 80 mg dose of rosuvastatin began to show signs of muscle weakness, rhabdomyolysis and kidney damage, and this dose was discontinued. A new analysis of post marketing safety still suggests that this statin is more likely to cause Adverse Drug Reactions (ADRs) than the other statins[30].
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8.Rimonabant (Antiobesity drug)

This drug sold in 18 countries and promoted for marketing in USA by Sanofi-Aventis, is likely to cause adverse psychiatric reactions including suicidal thoughts and actions, neurological problems and seizures[31]. US FDA approval is still under consideration.

9. Sparfloxacin (Fluoroquinolone)

Reports suggest higher incidence of QT prolongation (2.1 %) as compared to 0.6 % for cefaclor and suggestions are increasing to label this drug as bannable.

10. Propofol (General Anaesthetic)

FDA has issued alerts about several patients experiencing chills, fever and body aches after receiving propofol[32]. FDA is currently investigating the various reasons for these acute febrile reactions.

Similarly, few other drugs like ezetimibe and simvastatin for their harmful effects on liver and nesiritide for its kidney failure reports[33] are under strong controversies presently and surely require lot of vigilance.

Drugs Once Withdrawn But Re-Introduced

These are drugs which were banned initially due to their adverse effects but have been reintroduced into the market subsequently either for a totally different indication or for similar indication to be used with strict restriction[34],[35].

(Table/Fig 4)

S.no	Generic name	Property	Reasons of withdrawal	Year of withdrawal	New indication	Year of re-introduction
1.	Thalidomide*	Hypnotic	Phocomelia	1962	Erythema nodosum leprosum	1998
2.	Tranylcypromine †	MAO inhibitor, antidepressant	Serious adverse effects like stroke, hypertension	1964	Parnate specific depression, atypical depression, phobias	1964
3.	Aminoglutethimide*	Anti-convulsant	Endocrine disorders	1966	Hormone dependant neoplasms	---
4.	Megestrol*	Progestogen, oral contraceptive	Thrombosis in beagle dogs	1970	Hormone dependent neoplasms	---
5.	Clozapine†	Anti-psychotic	Agranulo-cytosis	1975	Treatment resistant schizophrenia, treatment intolerant schizophrenia	1990
6.	Alphraprodine†	Narcotic analgesic	Apnea, CNS depression	1980	Analgesic in pediatric dentistry	1981
7.	Methoxamine‡	Hypertensive	Decreased sales	1980	To avoid hypotension after initiation of spinal anesthesia	1982
8.	Mecamylamine‡	Anti-hypertensive	Decreased sales	1983	Treatment resistant hypertension, autonomic hyperreflexia	1983
9	Methotrimeprazine‡	Analgesic	Decreased sales	1983	Pain disorder	1984
10.	Felbamate†	Anti-convulsant	Aplastic anemia	1994	Lenox Gastaut syndrome, second line for partial and generalised tonic clonic seizures	1995

* - drugs which have been reintroduced with a different indication
† - drugs which have been reintroduced to be used with strict restriction and close monitoring of patient.
‡ - drugs withdrawn from the market by the drug manufacturing companies due to decreased sales and reintroduced due to requests made by physicians.

Here Are A Few Examples Of Drugs Of Doubtful Efficacy But Routinely And Commonly Prescribed[36] .

1. Digestive Enzymes

Digestive enzymes are prescribed to promote digestion in patients who lack one or more of the specific substances that are required for digestion. Although a large number of products are marketed, only the preparations of pancreatic enzymes are considered efficacious.

The pancreatic enzymes are destroyed by the acid and peptic activity in the stomach; hence enteric coated capsules are used. However, the enteric coating sometimes may prevent the delivery of enzymes in the duodenum. In addition, at recommended doses, the enteric coated preparations have a lipase activity that is less than half the lipase activity of conventional preparations.

2. Cerebral vasodilators

The vasodilatation induced by cerebral vasodilators is thought to be of questionable value. Some researchers advise cautious use of these drugs in patients with severe coronary artery disease or cerebral vascular disease since the disease areas may be compromised because of the vasodilatory action of these drugs elsewhere.

Examples-nimodipine, pentoxiphylline, isoxsuprine, cyclandelate, xanthinol nicotinate, nylidrin, piracetam, ginkgo biloba, codergocrine, piribedil, L-Glutamic acid and pyritinol.

3. Clofibrate In Cardiology

The lithogenecity of bile is increased by all fibric acid derivatives. Clofibrate use was associated with increased myocardial infarction and increased mortality in addition to increased risk of gallstone formation in the Coronary Drug Project and the WHO trial.

4.AppetiteStimulants(Cyproheptadine And Buclizine) In Children

These should not be used in infants and children because overdosage has serious adverse effects on the central nervous system and may even cause death.

Concluding Remarks

Banned and Bannable drugs are an ever increasing problem. More and more drugs are being synthesized and marketed with better efficacy and improved safety. Availability of better alternatives raise doubts about earlier drugs of doubtful efficacy or harmful safety profile and need to be replaced. Drug authorities should be prompt enough to withdraw the sale of drugs which are harmful, useless or of little benefit to mankind.

There is a clear need for pharmacovigilance studies in our country as it is still in infancy[37]. With the unhindered availability of bannable drugs over the counter in India[38] it's time that the Drug Controller General of India (DCGI) should seriously attempt to implement the pharmacovigilance program for the interest of common man. It should take strict measures towards pharmaceutical companies which seem to be uninterested in voluntary recall of already banned drugs or drugs with documented adverse effect profile. This will ensure marketing of safe medicines and aid better patient care. Measures should be taken to pick up adverse effects of drugs at the earliest. It's the need of hour that suggestions given by Biswas et al in her article[8] should be followed, where she fantastically describes and discusses the various strategies and proposals to build, maintain and implement a robust pharmacovigilance system for various stakeholders and eventually trying to make it happen in India.

Drugs banned elsewhere need to be seriously looked at and banned from use or in certain cases restricted to be used only for severe illness, in absence of other available drugs for the same indication. Awareness programs should be conducted in Government hospitals as well as for private

medical practitioners to make them aware of the current status of drugs in market. Medical students should be taught about drugs banned from use and drugs surrounded by various controversies, so that they can refrain from using the same for patient care. Physicians should begin reporting ADRs to the nearest pharmacovigilance centre to help generate ADR database[39]. As suggested by Parmar et al[40] the current status of marketed drugs, particularly hazardous ones, should be clearly mentioned in interest of public as citation of such information will help to increase the awareness about hazardous drugs and will serve the purpose of pharmacovigilance in a true sense.

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