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DRUG RECALL: AN OVERVIEW

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ABSTRACT

Drug prescribing is the most vital element of the medical field. The safety of drug products approved by the US Food and Drug Administration is conducted in a small number of people before it comes to the market. All the adverse effects and toxicities cannot be elicited in the limited number of volunteers used in the phased trial so some problems can remain unknown and can only be discovered when a product is used in large number of people or after prolonged use. A drug recall process is an approach of the drug regulatory bodies to withdraw the drugs that can cause potential harm or deficit in its safety or efficacy. The process can be time consuming leaving the dangerous prescription drugs on the current market and also in the hands of consumers. Other than the regulatory bodies the responsibilities to monitor a drug and to avoid its use after its recall also lays in the hand of the pharmaceutical companies, the healthcare professionals and last but not the least the consumers. This review is an attempt to create awareness about drugs that are no longer used due to lack of safety and can aid in being cautious regarding the drugs of same genus in the future.

Keywords: drug recall, recall classification, withdrawal reasons, Indian scenario.

INTRODUCTION

Drugs have become an essential part of medical setup. At present there are abundant numbers of drugs available in the market for prescribing by the doctors[1]. Number of these drugs are known to cause hazardous effects in humans, but are still used. Some are been withdrawn voluntarily by some manufacturers and/or regulatory authorities due to their deficiency in the quality, safety or efficacy.

A recall is term used when a product is removed from the market because it has either defective quality or is potentially harmful due to deficiencies in the safety or efficacy of the goods[2]. A company might discover a problem with its product and recalls may be conducted on a firm's own initiative or a company recalls its product after US Food and Drug Administration (FDA) request, or by FDA order under statutory authority. The establishment of the safety of drug products approved by the FDA is conducted in small group of people before it comes to the market, so some problems can remain unknown and can only be discovered when a product is used in large number of people or only show up after prolonged use[2, 3]. When the harmful effects show up the FDA works along with manufacturers to bring out a recall. Sometimes this procedure can take a lengthy while, leaving the dangerous prescription drugs on the market and in the hands of consumers.

In typical cases, prescription based drug recalls are voluntarily controlled by the drug manufacturers. When companies recognize their products are defective or dangerous, then they issue recalls on their own. If the FDA gets involved, it can demand a recall, which companies usually follow. This is the reckless way to eliminate a harmful drug from the market. Under the Federal Food, Drug and Cosmetic Act, the FDA has the power to take the manufacturer to court and force it to comply. Once the FDA appeals a prescription drug recall, companies are accountable for prescription drug recalls and making sure the recalls are successful. Mostly, the companies are also necessary to communicate with the FDA when the prescription drug recall is underway and to make the progress reports. Once the recall is accomplished, the FDA oversees the demolition of the dangerous prescription drug. The FDA then instigates an investigation to see why the prescription drug recall was necessary and to find out what made the prescription drug risky.

Recall Classifications[4, 5]:

The recalls are categorized into three classes, according to the level of hazard involved:

- Class I recall: A situation in which there is a reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death. Examples: Food with undeclared allergens; a label mix-up on a lifesaving drug; or a defective artificial heart valve. The level or depth of recall is at consumer level, a widespread public notification urging return or disposal of affected product, retrieval of product from retail shelf and retrieval of products from distributor’s warehouses.

- Class II recall: A situation in which use of or exposure to a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote. Example: A drug that is under-strength but that is not used to treat life-threatening situations. The level or depth of recall is at retail level, retrieval of product from retail shelves and from distributor's warehouses.

- Class III recall: A situation in which use of or exposure to a violative product is not likely to cause adverse health consequences but that violates FDA labeling or manufacturing laws. Examples include: A minor container defect and lack of English labeling in a retail food. The level or depth of recall is at wholesale level, retrieval of product from distributor's warehouses.

Drug recalls and manufacturers' actions regarding the recalls have been frequent news with items in the past several years which approached 1,800 in 2009. These recalled brands have been among the most trusted consumer products for decades. An eminent company has received praise for their remarkable response to the crisis by issuing an immediate recall of a product called Tylenol, the most popular consumer branded product in the United States[6]. It has also been found that in US nearly 20 million people have at least one time taken a drug which was recalled their lifetime between September 1997 to September 1998Reporting by the consumers, health professionals, and FDA-regulated companies allows evaluating how serious a drug problem is and may request for additional information on which stand an action can be taken.

Drugs which was Withdrawn from the Market due to their Severe Adverse Drug Events Since 2005:

1. Hydromorphone hydrochloride extended-release capsule

Trade name: Palladone, Dilaudid, Dilaudid Oros, Dilaudid-hp, DiMo, Dimorphone, Hymorphan, Idromorfone, Laudacon, Laudicon, Novolaudon, and Paramorphan.

Strength: 12, 16, 24 and 32 mg capsule.

Therapeutic classification: Narcotic analgesic

Pharmacological classification: Opioid agonist.

Mechanism of action: Hydromorphone interacts predominantly with the opioid mu-receptors. These mu-binding sites are discretely distributed in the human brain, with high densities in the posterior amygdala, hypothalamus, thalamus, nucleus caudatus, putamen, and certain cortical areas. They are also found on the terminal axons of primary afferents within laminae

I and II (substantia gelatinosa) of the spinal cord and in the spinal nucleus of the trigeminal nerve. In clinical settings, Hydromorphone exerts its principal pharmacological effect on the central nervous system and gastrointestinal tract. Hydromorphone also binds with kappa-receptors which are thought to mediate spinal analgesia, miosis and sedation. Hydromorphone appears to increase the patient's tolerance for pain and to decrease discomfort, although the presence of the pain itself may still be recognized.

Indication: For the relief of moderate to severe pain such as that due to surgery, cancer, trauma/injury, or burns.

Dose: Total daily dose of 12 mg

Reason from withdrawal from the market: The FDA to remove the drug from the market because of a potentially fatal interaction with alcohol that leads to accidental overdose.

Indian Scenario: The extended release tablet is approved in the year 2010.

2. Pemoline:

Trade name: Cylert, Endolin, Ronyl, Sistra.

Strength: 18.75, 37.5 and 75 mg tablet.

Therapeutic classification: Central nervous system (CNS) stimulant.

Pharmacological classification: It is an indirect-acting sympathomimetic with alpha- and beta-adrenergic agonist.

Mechanism of action: Pemoline is a CNS stimulant. A minimal sympathomimetic action that stimulates the brain, probably by affecting neurotransmitters, the chemicals in the brain that nerves use to communicate with each other.

Indication: For treatment of Attention Deficit Hyperactivity Disorder (ADHD)

Dose: Effective dose generally 25-75 mg/day

Reason from withdrawal from the market: Was approved by FDA in 1975. In 2005, FDA withdrew approval for pemoline as a result of serious potential liver complications including death.

Indian Scenario: Not yet banned.

3. Pergolide mesylate:

Trade name: Permax

Strength: 0.05 mg, 0.25 mg and 1 mg tablet

Therapeutic classification: Antiparkinsonism drug.

Pharmacological classification: Ergoline-based dopamine receptor agonist.

Mechanism of action: Pergolide stimulates centrally-located dopaminergic receptors resulting in a number of pharmacologic effects. Five dopamine receptor types from two dopaminergic subfamilies have been identified. The dopaminergic D1 receptor subfamily consists of D_1 and D_5 subreceptors and are associated with dyskinesias. The dopaminergic D2 receptor subfamily consists of D_2, D_3 and D_4 subreceptors and has been associated with improvement of symptoms of movement disorders. Thus, agonist activity specific for D2 subfamily receptors, primarily D_2 and D_3 receptor subtypes, are the primary targets of dopaminergic antiparkinsonian agents.

Indication: Indicated as adjunctive treatment to levodopa/carbidopa in the management of the signs and symptoms of Parkinson's disease.
Dose: Initial dose: 0.05 mg orally once a day for the first 2 days.
Maintenance dose: Gradually increase in increments of 0.1 to 0.15 mg every third day over the next 12 days. Then increase by 0.25 mg every third day until an optimal dosage is achieved. The daily dose is usually divided into 3 to 4 doses/day. The average dosage is 3 mg/day.
Reason for withdrawal from the market: Increased rates of cardiac valvular dysfunction (cardiac valvulopathy) withdrawn from the U.S. market on 2007.
Indian Scenario: Not yet banned.

4. Tegaserod maleate:

Trade name: Zelmac, Zelnorm
Strength: 2 and 6 mg tablet
Therapeutic classification: Motility stimulant.
Pharmacological classification: 5-hydroxytryptamine 4 (5 HT4) receptor partial agonist. Both the enteric nervous system, which acts to integrate and process information in the gut, and 5-hydroxytryptamine (5-HT, serotonin) are thought to represent key elements in the etiology of both irritable bowel syndrome and idiopathic constipation.

Mechanism of action: Tegaserod is a 5-HT_4 receptor partial agonist that binds with high affinity at human 5-HT_4 receptors, whereas it has no appreciable affinity for 5-HT_3 or dopamine receptors. It has moderate affinity for 5-HT_1 receptors. Tegaserod, by acting as an agonist at neuronal 5-HT_4 receptors, triggers the release of further neurotransmitters such as calcitonin gene-related peptide from sensory neurons. The activation of 5-HT_4 receptors in

the gastrointestinal tract stimulates the peristaltic reflex and intestinal secretion, as well as inhibits visceral sensitivity.

Indication: Provides relief from the symptoms of irritable bowel syndrome including chronic idiopathic constipation.

Dose: Irritable bowel syndrome: 6 mg twice daily for 4–6 weeks.

Consider additional 4- to 6-week course of therapy in patients who respond.

Chronic Idiopathic Constipation: <65 years of age: 6 mg twice daily.

Reason from withdrawal from the market: The FDA alleged a relationship between prescriptions of the drug and increased risks of heart attack or stroke and was withdrawn in the year 2007.

Indian scenario: Not available in Indian market.

5. Aprotinin

Trade Name: Tisseel, Trasylol, Tacho sil, Artiss, Iniprol, Trazinin

Strength: 2, 4 and 10 ml injection.

Therapeutic classification: Antifibrinolytic

Pharmacological Classification: Pancreatic trypsin inhibitor

Mechanism of Action: Inhibits several serine proteases, specifically trypsin, chymotrypsin and plasmin at a concentration of about 125,000 IU/ml, and kallikrein at 300,000 IU/ml. Its action on kallikrein leads to the inhibition of the formation of factor XIIa. As a result, both the intrinsic pathway of coagulation and fibrinolysis are inhibited. Its action on plasmin independently slows fibrinolysis.

Indication: For prophylactic use to reduce perioperative blood loss and the need for blood transfusion in patients undergoing cardiopulmonary bypass in the course of coronary artery bypass graft surgery who are at an increased risk for blood loss and blood transfusion.

Dose: Loading dose 200 ml (280 mg); Constant infusion dose 50 ml per hour (70 mg)

Reason from withdrawal from the market: The drug was temporarily withdrawn worldwide in 2008 after studies suggested that its use increased the risk of complications or death; after this was confirmed by follow-up studies.

Indian scenario: Available in the form of injection in the Indian market.

6. Efalizumab

Trade name: Raptiva

Strength: 125 mg powder for injection.

Therapeutic classification: Immunosuppressive agents

Pharmacological classification: Recombinant humanized monoclonal antibody

Mechanism of action: Binds to CD11a, the α subunit of leukocyte function antigen-1 (LFA-1), which is expressed on all leukocytes, and decreases cell surface expression of CD11a. Efalizumab inhibits the binding of LFA-1 to intercellular adhesion molecule-1 (ICAM-1), thereby inhibiting the adhesion of leukocytes to other cell types. Interaction between LFA-1 and ICAM-1 contributes to the initiation and maintenance of multiple processes, including activation of T lymphocytes, adhesion of T lymphocytes to endothelial cells, and migration of T lymphocytes to sites of inflammation including psoriatic skin. Lymphocyte activation and trafficking to skin play a role in the pathophysiology of chronic plaque psoriasis. In psoriatic skin, ICAM-1 cell surface expression is up regulated on endothelium and keratinocytes. CD11a is also expressed on the surface of B lymphocytes, monocytes, neutrophils, natural killer cells, and other leukocytes. Therefore, the potential exists for efalizumab to affect the activation, adhesion, migration, and numbers of cells other than T lymphocytes.

Indication: Treatment of adult patients (18 years or older) with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Dose: 0.7mg/kg subcutaneously conditioning dose followed by weekly dose of 1 mg/kg.

Reason from withdrawal from the market: Genentech and FDA notified healthcare professionals of the voluntary, phased withdrawal due to a potential risk to patients of developing progressive multifocal leukoencephalopathy (PML) and fatal brain infections in 2009.

7. Sibutramine

Trade name: Reductil, Meridia, Medaria, Butramin

Strength: 5, 10 and 15 mg capsule.

Therapeutic classification: Central Nervous System Stimulant.

Pharmacological classification: Norepinephrine, Serotonin and Dopamine reuptake inhibitor.

Mechanism of action: Sibutramine is a neurotransmitter reuptake inhibitor that reduces the reuptake of serotonin, norepinephrine, and dopamine, thereby increasing the levels of these substances in synaptic clefts and helping enhance satiety; the serotonergic action, in particular, is thought to influence appetite.

Indication: As an adjunct to a reduced calorie diet for the management of obesity, including weight loss and maintenance of weight loss. Recommended for patients with an initial body

mass index greater than 30 kg/m^2 or greater than 27 kg/m^2 in the presence of other risk factors, eg, hypertension, diabetes, dyslipidemia.
Dose: 10 mg once daily.

Reason from withdrawal from the market: Sibutramine was approved November 1997 for weight loss and maintenance of weight loss in obese people, as well as in certain overweight people with other risks for heart disease. FDA requested market withdrawal on 2010 due to increase in the risk of serious heart events, including non-fatal heart attack, non-fatal stroke, the need to be resuscitated once the heart stopped, and death, in a group of patients given due sibutramine compared with another given placebo.
Indian scenario: Was banned in 2010.

8. Gemtuzumab ozogamicin

Trade name: Mylotarg
Strength: 5 mg lyophilized powder for injection.
Therapeutic classification: Antineoplastic agent
Pharmacological classification: Immunoglobulin antibody.
Mechanism of action: Chemotherapy agent composed of a recombinant humanized immunoglobulin G_4 kappa antibody conjugated with a cytotoxic antitumor antibiotic, calicheamicin, isolated from fermentation of a bacterium. The antibody portion of gemtuzumab ozogamicin binds specifically to the CD33 antigen, which is expressed on the surface of leukemic blasts in patients with acute myeloid leukemia (AML). This ultimately results in DNA double-strand breaks and cell death.

Indication: CD33-positive acute myeloid leukemia in first relapse in patients at least 60 yr of age who are not candidates for other antineoplastics.
Reason from withdrawal from the market: Can result in severe hypersensitivity reactions (including anaphylaxis), and other infusion-related reactions which may include severe pulmonary events. Infrequently, hypersensitivity reactions and pulmonary events have been fatal.

Hepatotoxicity, including severe hepatic veno-occlusive disease (VOD), has been reported in association with the use of gemtuzumab as a single agent, as part of a combination chemotherapy regimen, and in patients without a history of liver disease or hematopoietic stem cell transplant (HSCT). Death from liver failure and from VOD has been reported in

patients who received gemtuzumab. In June 2010, Pfizer withdrew gemtuzumab from the market at the request of the US FDA.

Indian scenario: Not available in India.

9. Rosiglitazone

Trade name: Avandia, Rosiglizole

Strength: Tablet 2, 4, and 8 mg.

Therapeutic classification: Antidiabetic agent

Pharmacological classification: Peroxisome proliferator activated receptor- gamma agonist.

Mechanism of action: Acts as an agonist at peroxisome proliferator activated receptors (PPAR) in target tissues for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPAR-gamma receptors regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization.

Indication: Used in type II diabetes mellitus. Works as an insulin sensitizer, by binding to the PPAR receptors in fat cells and making the cells more responsive to insulin.

Dose: 4 mg either as single dose or in two divided dose.

Reason for withdrawal from the market: Withdrawn from the European medicines agency and face severe restriction in US by FDA on 2010 after its approval in 1999 due to it's increased risk of cardiovascular events; increased risk of congestive heart failure (CHF), myocardial infarction (MI), and mortality when compared with other combination oral hypoglycemic agent treatments.

Indian Scenario: Rosiglitazone was banned in Indian market in the year 2010.

10. Benfluorex

Trade name: Mediator

Strength: 150 mg tablet

Therapeutic classification: Dyslipidaemic agent and adjuvant antidiabetic.

Pharmacological classification: Reverse serotonin transporter.

Mechanism of action: A lipid regulating drug decreases the intestinal absorption of triglycerides, the lipid synthesis and facilitates cellular penetration and utilization of glucose.

Indication: Adjuvant therapy of overweight diabetics, in combination with an appropriate diet.

Dose: 50 mg three times per day

Reason for withdrawal from the market: European medicine agency has recommended for withdrawal in the year 2009 due to their risk of heart valve disease are greater their benefits.
Indian Scenario: Available in India.

DISCUSSION

Drug recalls are considered as an ever increasing problem. More new drugs are synthesized and marketed with better efficacy and improved safety. Drug authorities should be prompt enough to withdraw the sale of drugs which are harmful, useless or of little benefit to mankind. There should be a serious attempt to implement the pharmacovigilance program for the interest of common man. Regulatory frameworks should take strict measures to probe the healthcare professionals, the pharmaceutical companies in voluntary recall of already banned drugs or drugs with documented adverse effect profile. Steps should be taken to pick up adverse effects of drugs at the earliest such that the harmful drug will not stay back for a long to affect the consumers. Awareness programs should be conducted in the hospitals as well as for private medical practitioners to make them aware of the current status of drugs in market and the physicians should begin reporting adverse drug reactions to the nearest pharmacovigilance centre to generate database. Another object of interest is in the time variation of the drug recall seen between the western world and the Indian settings. The regulatory authorities that have recalled a drug product can initiate steps to give immediate such that the drug is not used in other countries if the drugs are available in their market. The review on the above mentioned discussions can create awareness about drugs that are no longer used due to lack of safety and can aid in being cautiously monitoring the drugs of same genus in the future.

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