wjpmr, 2023, 9(7), 84-88

SJIF Impact Factor: 5.922

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Review Article

ISSN 2455-3301

WJPMR

A STUDY ON BANNED FIXED DOSE COMBINATIONS IN INDIA

Dhiraj Kumar*, Kashish Bhardwaj, Ankit Sharma, Sazid, Shivani and Saurabh

Dreamz College of Pharmacy, Sundernagar (H.P).

***Corresponding Author: Dhiraj Kumar**

Dreamz College of Pharmacy, Sundernagar (H.P).

Article Received on 09/05/2023 **Article Revised on 29/05/2023** **Article Accepted on 19/06/2023**

ABSTRACT

In the current scenario India is a large center of banned drugs. There are large number of banned drugs present in Indian market which is banned in foreign countries. The market of banned drug is increasing day by day in the developing countries due to lack of prescriber awareness, low enforcement, laxity of drug control authorities and corruption. The main purpose of making all medicine is treatment and prevention from diseases. As we know that every drug has some side effect but banned drugs have more side effects as compared to other drugs. The most common banned drug in world-wide is present in the market of India and other developing countries. For example: nimesulide, furazolidone, phenyl-propanolamine etc. due to their side effects major organs or systems of the body are harmed and sometimes it causes death of patient. The use of fixed dose combination is trending now a days but a large number of fixed dose combinations is banned in India due to their side effects and no effects on the patient. In this study our main focus will be on the case study of some fixed dose combination of drugs which are banned by Indian government including their reason of banning, uses and all other information.

KEYWORDS: Banned drugs, fixed dose combination, regulatory bodies.

INTRODUCTION

Banned drugs are drugs that now no longer allowed to intake because they could artificially enhance their overall performance and shows various negative outcomes extra than healing outcomes. Whose manufacturing or use is prohibited or strictly controlled through prescription. “Drug Controller general of India” is the maximum authority in India to extend the approval of any drug or to prohibit a drug. Some of the harmful drugs have been globally discarded but are available in India.[1]

An adverse drug reaction (ADR) can be defined as ‘an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product; adverse effects usually predict hazard from future administration and warrant prevention, or specific treatment, or alteration of the dosage regimen, or withdrawal of the product’. Since 2012, the definition has included reactions occurring as a result of error, misuse or abuse, and to suspected reactions to medicines that are unlicensed or being used off-label in addition to the authorized use of a medicinal product in normal doses. While this change potentially alters the reporting and surveillance carried out by manufactures and medicines regulators, in clinical practice it should not affect our approach to managing ADRs.[2]

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. [3] In India the highest authority is Drug controller General of India (DCGI) which extends the approval of any drug or banned drug.

Any drug is banned due to there.

- Unexpected problem creating reactions
- Producing excess toxicity
- Availability of other safer option.
- Harmful interactions inside the body.

Reasons for Availability of Banned Drugs In India

1. Pharmaceutical companies' commercial interests.
2. A lack of responsibility and openness.
3. Our regulatory bodies seek authority over implementation.
4. As a result of India's high level of need, those medications are available for affordable prices.
5. Many non-public specialists and physicians are unaware of the pullout.
6. Non-Compliance with the use of the patient without anyone else's input proposing the medications for major illnesses and scathes.

7. Parts of hypersensitive and anaphylactic reactions are happening occasionally in India as a result of self-medication. By using open mindfulness programmes and paying attention to one's own behaviors and reactions, this can be prevented.
8. This communication gap between the DCGI and national drug regulators is one of the factors causing the loose accessibility of pulled lower back medications within the market.[4]

Flow chart of process of banning.

Executive committee examines harmful effects of the drug

↓

The results are reported to the drugs technical advisory board

↓

The government issues the ban order

↓

DCGI notifies all state drug authorities

↓

Authorities are instructed to carry out inspection

Why India Still Selling Banned Drugs

Some banned drugs are still present in India because gap between Drug Controller General India and State Drug Controllers as well as non aware physicians and patients, poverty, self medication, relexation in inspection by regulatory bodies, non availability of required drugs, high cost, and communication barriers. The sarcasm is that there are very less people having appropriate knowledge about the banned drugs and they don't take it serious so that it causes lots of harm to them. The issue is severe and we should not late to send the awareness and warning message to the innocent people and law breakers. The many drugs are present over the counter that's why the general population is ignoring the serious side effects of these drugs. India has major problem with use, availability and distribution of banned drugs.[5]

If the adverse effects are more than the benefit, or if the drug is not effective to cure the disease, the country should ban the drug or the drug manufacturer may withdraw the drug by their own. Some drugs may produce adverse effects only when they are combined with particular drugs. In most of the cases, only the fixed dose combination is banned.[6]

A number of single drugs as well as fixed dose combinations have been banned for manufacturing, marketing and distribution in India. Some case studies of fixed dose combination drugs banned in India are mentioned below.

1. **Ranitidine + Drotaverine**
2. **Cefixime + Ornidazole**
3. **Paracetamol + Alprazolan**
4. **Ondansetron + Omeprazole**
5. **Levocetirizine + Montelukast**

Case study 1

RANITIDINE+DROTAVERINE

Available brands

Ranispas DV by Mainkind Pharma Ltd.
Averine R by Plenteous Pharmaceutical Ltd.
Dose : 40mg/150mg tablet.

RANITIDINE

Ranitidine is a histamine H2-receptor antagonist, Furan derivative, Anti-secretory G.I agent, Anti ulcer.

Mechanism of Action of Ranitidine

Ranitidine is a H2 (Histamine) receptor antagonist. Histamine is the most potent stimulus of acid secretion and acts as the common mediator. It induces adenylate cyclase which converts ATP to cyclic AMP. This cyclic AMP acts on proton pump and exchange extracellular potassium ion for intracellular hydrogen ion across the parietal cell membrane. Ranitidine reversibly competes with Histamine for binding to H2 receptors on the parietal cells and predominantly inhibits and result in the acid secretion and concentration.

Side Effects of Ranitidine

Headache, Dizziness, Constipation, Vertigo, Confusion, Rash, Blurred vision, malaise, hypersensitivity reaction, Thrombocytopenia, Leukopenia.[7]

DROTAVERINE

Drotaverine hydrochloride, chemically 1-[(3,4-Diethoxyphenyl) methylene]-6,7- diethoxy1, 2,3,4-tetrahydroisoquinoline hydrochloride, it is an derivative of isoquinoline and it works as an antispasmodic agent.

Mechanism of Action of Drotaverine

Drotaverine having spasmolytic and vasodilating property. It shows its action by inhibiting phosphodiesterase enzyme IV. This will decrease the level of cyclic AMP and decrease the concentration of calcium ions (Ca2+) results dilation of unstipped muscles and blood vessels strongly and reduce the smooth muscles spasm and pain mainly labor pain.[8]

REASON OF BAN

Ranitidine is indicated in peptic ulcer, a condition not caused by smooth muscle spasm. Hence it is irrational to use drotaverine in a FDC with H2 blocker.[9]

Case study-02

DOXYCYLINE + TINIDAZOLE

Available Brands

Tido by Eskag pharma ltd.
Dobact by tidal healthcare Pvt. Ltd.
Ceedoxy TZ by Baxter India Pvt. Ltd.
DOSE: Doxycycline 100mg + Tinidazole 600mg tablets.

DOXYCYCLINE

Doxycyline is a class of medications called tetracycline antibiotics it works to treat infections by preventing the growth and spread of bacteria. It displays excellent

activity against gram positive and gram negative aerobic and anaerobic bacteria.[10]

MOA of Doxycycline

Doxycycline having bacteriostatic action. allosterically binding to the 30S prokaryotic ribosomal unit during protein synthesis. Doxycycline helps in preventing the association of the charged aminoacyl-tRNA (aa-tRNA) with the ribosomal A site to stall the elongation phase, yielding an unproductive cycle of protein.

Side effect of Doxycycline

Mild diarrhoea, Photosensitivity, Nausea, Vomiting, Skin rash/itching, Headaches, Tooth discoloration Bloody diarrhoea are the common side effect but in exceptional cases it show some severe adverse effects like; Leukopenia, Migraines, Haemolytic anaemia, Throat irritation or trouble swallowing Chest pain, Exacerbation of systemic lupus erythematosus, Shortness of breath, Irregular or fast heart rate, Dysuria, hypertension, Esophagitis/oesophageal ulcerations if taken without water.[10]

TINIDAZOLE

Tinidazole is the structural analogue of metronidazole, which is an anti protozoalagent this drug is used for the treatment of trichomoniasis, giardiasis, amebiasis, amebic liver abscess[11]. Tinidazole have property against protozoa and anaerobic bacteria.[12]

Mechanism of action of Tinidazole

Tinidazole is a prodrug that is converted to cytotoxic forms in vivo.This drug work against the both aerobic and anaerobic microorganisms cell membrane due to their low molecular weight. tinidazole is reduced to its nitro group to toxic radicals by a ferridoxin-mediated transport system when it diffuses into the cells of susceptible organisms. these toxic intermediates cause DNA damage after binding with DNA which ultimately leads to cell death.[13]

REASON OF BAN

Doxycycline is comes under tetracycline and tinidazole is nitroimidazoles. This is the combination of two antibiotics drugs. It may cause antibiotic resistance. And risk for adverse reactions. Some time combination therapy of antibiotics can cause antagonistic or synergistic effect thus making the FDC irrational.[14]

Case study-03

PARACETAMOL + ALPRAZOLAM

This combination is used in insomnia treatment.

Available brands

Zema P by Genesis Biotech. Inc
Alpa by Alpic Biotech Ltd.
Dose : Paracetamol 500 mg Alprazolam 0.25mg.

PARACETAMOL

Other name of paracetamol is acetaminophen and it is one of the most popular and most commonly used analgesic and antipyretic drug.

This drug is having the comlex **mechanism of action** which includes the effects of both the peripheral (COX inhibition), and "redox" mechanism and central antinociception processes.[15] the nonsteroidal anti-inflammatory drugs (NSAIDs) produced there action at COX pathway. The inhibition of prostaglandins (PGE2, PGI2, PGF2α) by NSAIDs and produced resultant effect. They also influence thromboxane (TXA2). TXA2 is a vasoconstrictor, potent hypertensive agent, and facilitator of platelet aggregation.[16]

SIDE EFFECTS OF PCM

Hepatotoxicity is the common problem in the use of paracetamol which occurs after an overdose.[17]

ALPRAZOLAM

Alprazolam is a derivative of benzodiazepine which is currently used in the treatment of generalized anxiety, panic attacks with or without agoraphobia, and depression.

Mechanism of action of Alprazolam

Alprazolam mainly binds to the BZD receptor which acts on Limbic system and ascending reticular formation in the CNS. This will produce hyperpolarisation by facilitating the GABA mediated chloride channel opening. increase production of the inhibitory neurotransmitter GABA and increase in chloride ions which can result decreases firing rate of neuron and normal functions of the body turn alters.[18]

Adverse effects of alprazolam

Drowsiness, Tiredness, Dizziness, Sleep problems, Memory problems, Poor balance or coordination, Slurred speech, Trouble concentrating.

Reason of ban: Alprazolam and paracetamole having different mechanism of action may exert synergistic effect . Benzodiazapine which acts on brain and central nervous system for producing a calming effect but they are having risk for abuse and addiction which can lead to overdose and also may causes death.[19]

Case study 04

Ondansetron + Omeprazole

Available brands

Sentro by Secure Healthcare India Pvt Ltd.
Ondelux P by kivonyx Healthcare
Pantago O by Aingo Pharma Pvt Ltd.
Dose: Ondansetron 4mg + Omeprazole 40 mg.

Ondansetron: Ondansetron is commonly used in treatment of nausea and vomiting. It is used when chemotherapy induced and radiation-induced nausea and vomiting are there, it is also used in the prevention of

postoperative, off lebel and pregnancy caused nausea and vomiting.

Mechanism of action of ondansetron

Ondansetron is a selective 5-HT3 serotonin-receptor antagonist used for its antiemetic properties. Ondansetron acts both centrally and peripherally to prevent and treat nausea and vomiting. Central effects are mediated by the antagonism of 5HT-3 serotonin receptors in the area postrema. The area postrema, located on the fourth ventricle floor, contains the "chemoreceptor trigger zone." This zone senses neurotransmitters like serotonin, toxins, and other signals and plays a role in mediating the sensation of nausea and subsequent vomiting. Ondansetron also has effects peripherally by acting on the vagus nerve. It works on the 5-HT3 receptors that can be found at the vagus nerve terminals. The vagus nerve can sense nausea and vomiting triggers within the GI tract, such as stomach irritants. It forms synapses within the nucleus tractus solitarius of the brainstem, another region important in vomiting. The peripheral actions of ondansetron are thought to be the predominant mechanism for its antiemetic effects.[20]

Side Effects (occurring in more than 10% of adults) include headaches, fatigue, dry mouth, malaise, constipation, drowsiness and sedation.[21]

Omeprazole

Omeprazole is comes under classification of proton pump inhibitor (PPI), which is commonly used to treatment of different gastrointestinal (GI) disorders it is also use to treat uncomplicated heartburn, peptic ulcer disease, gastrointestinal reflux disease, Zollinger-Ellison syndrome, multiple endocrine adenomas, systemic mastocytosis, erosive esophagitis, gastric ulcers, and helicobacter pylori infection.[22]

Mechanism of Action of omeprazole

Omeprazole is a proton pump inhibitor. It is a substituted form of benzimidazole that belongs to the antisecretory class of compounds. It decrese the acid production by inhibits the H+ / K+ ATP pump present on parietal cells. In turnThe inhibitory effects of omeprazole occur rapidly within 1 hour of administration, with the maximum effect occurring in 2 hours.[23]

Side effects Proton pump inhibitors increase the risk of fractures, possibly cause Clostridium difficile-associated diarrhea, and may cause hypomagnesemia and dementia in the elderly, and possibly increase the risk of pneumonia in the elderly.[24]

Reason of ban: H2 blockers and proton pump inhibitors are effective in peptic ulcer and it is irrational to combine these drugs with an antiemetic as peptic ulcer is not always associated with vomiting.[25]

CASE STUDY 05

LEVOCETAZINE + MONTELUKAST

Availlbale brands

Montek LC by Sunpharmacetical industries
Monticpe by Mankind pharma Ltd
Odimont Lc by Zydus cadila

Dose: Montelukast 10mg and levocetirizine 5mg.

Levocetirizine

levocetrizine is an antagonist of H1 receptor selectively, potentaly. used in the symptomatic treatment of chronic idiopathic urticaria (CIU) and allergic rhinitiss it has quick onset action and long duration of antihistaminic effect, fast absorption and best bioavailability. It is the H_1 receptor antagonists available for oral administration.[26]

Side effects-drowsiness, fatigue, weakness, tired feeling, stuffy nose, sinus pain, sore throat, cough, vomiting, diarrhoea, constipation, dry mouth, orweight gain is the common side effect detected.

Montelukast

Montelukast is a selective antagonist of the leukotriene D_4 (LTD4) receptor. In asthma patients , montelukast produced the bronchoconstriction and it also works in decrease the fast and late airway response to allergen (dust mite extract) relative to placebo.[27]

Mechanism of action It acts by blocking the action of substances in the body that cause the symptoms of asthma and allergic rhinitis.

Side Effects of montelukast

Upper respiratory infection, Fever, Headache, Sore throat, Cough, Stomach pain, Diarrhea, Ear infection, Flu, Runny nose, Sinus infection.

Reason of ban

Irrationally this fixed dose combination FDC is used in the treatment of asthma. Levocetirizine is a antihistaminic agent which having no role in asthma. Montelukast is recommended only as an alternative to inhaled steroids in mild persistent asthma. Levocetirizine, a long acting beta-2 agonist is indicated in moderate to severe persistent asthma. Thus, there is no indication for Levocetirizine, and montelukast together in asthma.[28]

CONCLUSION

Large number of banned drugs present in Indian market which is banned in foreign countries as well as India. Thus our country need to adopt and enforce strict regulations for the production and use of fixed dose combinations. Companies need to realize that the short-term economic gains are counter-productive in the long run. Also, multinational companies should be expected to employ the highest scientific standards in all countries where they operate. Prescribers need to remember their core ethical guideline, and realize that use of fixed dose

combinations cause more harm than good. There are very common case study of fixed dose combination mention in our review work and mention their reason of banning, uses and all other information.

REFERENCES

1. Shaji, Jessy, and Shital Lodha. "Regulatory status of banned drugs in India." *Indian Journal of Pharmaceutical Education and Research*, 2010; 44.1: 86-94.
2. Coleman JJ, Pontefract SK. Adverse drug reactions. Clinical Medicine, 2016 Oct 1; 16(5): 481-5.
3. Mudiganty SS, Dang A, Rataboli P. Crippled Pharmacovigilance: A Qualm of Medical Profession!!. Journal of Clinical and Diagnostic Research, 2008 Oct 1; 2(5): 1110-8.
4. Vitthal KS, Shinde S, Bhausaheb WV. REVIEW ON BANNED DRUGS IN INDIA.
5. Kengar MD, Jagtap GB, Gavade AS, Nitalikar MM. A Study on Banned Drugs in India: A Review. Asian Journal of Research in Pharmaceutical Sciences, 2018 Nov 3; 8(4): 258-60.
6. Dr. Simi Paknikar. "Banned Drugs | Drugs Banned in India | List of Banned Drugs".Medindia.Mar.31.2023. <https://www.medindia.net/patients/patientinfo/drugs-banned-in-india.htm>.
7. Morgan KA, Ahlawat R. Ranitidine. [Updated 2022 Dec 11]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK532989/
8. Pankaj K, Shrivastava BS, Anju G. Absorbances Ratio Method (Isoabsorptive Point) for Determination of Drotaverine Hydrochloride and Ranitidine Hydrochloride from Pharmaceutical Dosage Forms. Asian Journal of Pharmaceutical Analysis, 2014; 4(3): 113-5.
9. Verster, Joris C., and Edmund R. Volkerts. "Clinical pharmacology, clinical efficacy, and behavioral toxicity of alprazolam: a review of the literature." CNS drug reviews, 2004; 10.1: 45-76.
10. Patel RS, Parmar M. Doxycycline Hyclate. [Updated 2023 Jan 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK555888/
11. Fung HB, Doan TL. Tinidazole: a nitroimidazole antiprotozoal agent. Clinical therapeutics, 2005 Dec 1; 27(12): 1859-84.
12. Carl Erik Nord, Microbiological properties of tinidazole: spectrum, activity and ecological considerations, *Journal of Antimicrobial Chemotherapy*, Volume 10, Issue suppl_A, 1982; 35–42, https://doi.org/10.1093/jac/10.suppl_A.35
13. Mohamed A. Abd El Aziz, ForuzanSharifipour, Parvin Abedi, ShayestehJahanfar, Helen Marie Judge. (2019) Secnidazole for treatment of bacterial vaginosis: a systematic review. *BMC Women's Health*, 19: 1.
14. https://www.reactgroup.org/news-and-views/news-and-opinions/year-2018/why-are-fixed-dose-combinations-of-antibiotics-generally-not-a-good-idea/.
15. Jóźwiak-Bebenista, Marta, and Jerzy Z. Nowak. "Paracetamol: mechanism of action, applications and safety concern." *Acta poloniae pharmaceutica* 71.1 (2014): 11-23Soll, Andrew H., et al. "Nonsteroidal anti-inflammatory drugs and peptic ulcer disease." *Annals of internal medicine*, 1991; 114.4: 307-319.
16. Anderson, Brian J. "Paracetamol (Acetaminophen): mechanisms of action." Pediatric Anesthesia, 2008; 18.10: 915-921.
17. Graham, Garry G., and Kieran F. Scott. "Mechanism of action of paracetamol." *American journal of therapeutics*, 2005; 12.1: 46-55.
18. https://www.medicineindia.org/pharmacology-for-generic/819/alprazolam-paracetamol
19. https://www.ehealthme.com/drug-interaction/alprazolam/paracetamol/
20. Griddine, Alexandria, and Jeffrey S. Bush. "Ondansetron." *StatPearls [Internet]*. StatPearls Publishing, 2022.
21. https://www.webmd.com/drugs/2/drug-16910-8296/ondansetron-oral/ondansetron-disintegrating-tablet-oral/details
22. Rethinavel, Harini Sri, et al. "Omeprazole treatment manifests anxiolytic effects in a cysteamine hydrochloride induced mouse model of gastrointestinal disorder." *Heliyon*, 2022; 8.6: e09787.
23. Shah, Neal, and William Gossman. "Omeprazole." 2019.
24. Nodirovna, Azimbegova Sitora. "WHAT IS THE MECHANISM OF ACTION OF A PROTON PUMP INHIBITOR?."
25. Soll, Andrew H., et al. "Medical treatment of peptic ulcer disease: practice guidelines." *Jama*, 1996; 275.8: 622-629.
26. Hair PI, Scott LJ. Levocetirizine: a review of its use in the management of allergic rhinitis and skin allergies. Drugs, 2006 May; 66: 973-96.
27. Markham A, Faulds D. Montelukast. Drugs, 1998 Aug; 56: 251-6.
28. Nigam, Mayank Prakash, Vinson LG Fernandes, and Padmanabh V. Rataboli. "Fixed dose combinations-to prescribe or not to prescribe: a dilemma of medical profession.", 2014.