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Ranitidine Induced Hepatotoxicity: A Review

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ABSTRACT

Background: Ranitidine (RAN) is one of the common drugs associated with idiosyncratic adverse drug reactions (IADRs) in humans. It was found to be associated with severe adverse drug reactions due to the presence of contaminants such as N-Nitrosodimethylamine (NDMA) which is claimed to be carcinogenic. As a consequence, on April 1, 2020, United States Food and Drug Administration (USFDA) had decided to call off all the RAN products from the market. The exact cause of RAN associated idiosyncratic hepatotoxicity is not clear yet.
Purpose: To summarize and analyze the reason behind the withdrawal of RAN products from the market and whether ranitidine will be available again in future or will FDA withdraw approvals of ranitidine National Drug Authority (NDA) and an abbreviated new drug application (ANDA)?
Methods: We performed a systematic PubMed/MEDLINE search of studies investigating the reason behind the withdrawal of RAN products and explored the possible mechanism associated with RAN induced hepatotoxicity.
Conclusion: RAN induced liver injury is difficult to diagnose and study because of its relative rarity and unpredictive occurrence. Recent studies suggest that most of the RAN associated idiosyncratic reactions may lead to hepatocyte damage, followed by a series of events, such as activation of specific T- and B-cells, release of proinflammatory mediators like TNFα, interleukins, various cytokines and chemokines. The exact cause of RAN associated idiosyncratic hepatotoxicity is not clear yet. More studies must be carried out on this to know about the exact reason behind RAN associated hepatotoxicity.

1. Introduction

Drug induced liver injury (DILI) is a primary safety concern during drug discovery and those drugs which are found to be associated with severe adverse drug reactions (ADRs) are mainly withdrawal from the market. There are few drugs which have been withdrawn due to its severe ADRs reported over the period of time in the post-marketing surveillance (PMS) [summarized in Table 1] and Ranitidine (RAN) is one of them and it is found to be associated with idiosyncratic hepatotoxic reactions (Teschke et al., 2018). RAN is widely used in the treatment of gastrointestinal diseases and is one of the most frequently prescribed drugs worldwide (Chalasani et al., 2010). An estimated 34.2 ± 10.7 cases of DILI per 1 million people per year were reported in the Spanish DILI Registry. It has been observed that, amongst all the DILI cases about 53% had to be hospitalized, 2% undergone liver transplant, 10% and 5% had a chronic liver disease and acute liver disease respectively (Andrade et al., 2005). DILI is a major reason behind the withdrawal of various pharmaceutical products. RAN induced liver injury may be an associated factor for its withdrawal from pharmaceutical market (Kaplowitz et al., 2005). Based on its clinical characteristics, RAN induced hepatotoxicity can be classified as cholestatic (mainly an increase in alkaline phosphatase, ALP), hepatocellular (primarily an increase in alanine aminotransferase, ALT) and mixed hepatotoxicity depending upon the type of observed liver injury.

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Table 1: List of drugs called off due to hepatotoxicity worldwide.

S. No.	Drug name	Withdrawn	Country	Remarks	Reference
1.	Xenazoic acid	1965	France	Hepatotoxicity	Fung et al., 2001
2.	Phenoxypropazine	1966	UK	Hepatotoxicity, drug interaction	Fung et al., 2001
3.	Ibufenac	1968	UK	Hepatotoxcity	Fung et al., 2001
4.	Fenclozic acid	1970	UK, US	Hepatotoxicty	Fung et al., 2001
5.	Diacetoxydiphenolisatin	1971	Australia	Hepatotoxicity	Fung et al., 2001
6.	Triacetyldiphenolisatin	1971	Australia	Hepatotoxicity	Fung et al., 2001
7.	Nialamide	1974	UK, US	Hepatotoxicity, drug interaction	Fung et al., 2001
8.	Mebanazine	1975	UK	Hepatotoxicity, drug interaction	Fung et al., 2001
9.	Ticrynafen (Tienilic acid)	1980	Germany, UK, US, France	Liver toxicity and death.	Fung et al., 2001
10.	Benoxaprofen	1982	Germany, Spain, US, UK	Liver and kidney failure; gastrointestinal bleeding; ulcers.	Qureshi et al., 2011; Fung et al., 2001
11.	Clomacron	1982	UK	Hepatotoxicty	Fung et al., 2001
12.	Zimelidine	1983	Worldwide	Hepatotoxicty	Fung et al., 2001; Fagius et al., 1985
13.	Isaxonine phosphate	1984	France	Hepatotoxcity	Fung et al., 2001
14.	Clometacin	1987	France	Hepatotoxicty	Fung et al., 2001
15.	Cyclofenil	1987	France	Hepatotoxicity	Fung et al., 2001
16.	Exifone	1989	France	Hepatotoxicty	Fung et al., 2001
17.	Pirprofen	1990	France, Spain, Germany	Liver toxicity	Fung et al., 2001
18.	Dilevalol	1990	UK	Hepatotoxicty	Fung et al., 2001
19.	Fipexide	1991	France	Hepatotoxicty	Fung et al., 2001
20.	Bendazac	1993	Spain	Hepatotoxicity	Fung et al., 2001
21.	Alpidem (Ananxyl)	1995	Worldwide	Not approved in US, withdrawan in France in 1994 and the rest of the market in 1995 because of rare but serious hepatotoxicity.	Fung et al., 2001; Berson et al., 2001
22.	Chlormezanone (Trancopal)	1996	European Union, US, South Africa, Japan	Hepatotoxicity & Steven-Johnson Syndrome	Fung et al., 2001
23.	Tolrestat (Alredase)	1996	Argentina, Canada, Italy, others	Severe form of hepatotoxicity	Fung et al., 2001
24.	Pemoline (Cylert)	1997	Canada, UK	Withdrawn from US in 2005. Hepatotoxicity	Drug Bank website
25.	Ebrotidine	1998	Spain	Hepatotoxicty	Fung et al., 2001
26.	Tolcapone (Tasmar)	1998	European Union, Australia, Canada	Hepatotoxicty	Fung et al., 2001
27.	Troglitazone (Rezulin)	2000	Germany, US	Hepatotoxicity	Qureshi et al., 2011
28.	Kava Kava	2002	Germany	Hepatotoxicity	Schubert-Zsilavecz, 2011

29.	Alatrofloxacin	2006	Worldwide	Serious liver injury leading to liver transplant or death.	Qureshi et al., 2011
30.	Ximelagatran (Exanta)	2006	Germany	Hepatotoxicity	Schubert-Zsilavecz, 2011
31.	Lumiracoxib (Prexige)	2007-2008	Worldwide	Liver damage	Qureshi et al., 2011
32.	Sitaxentan	2010	Germany	Hepatotoxicity	Schubert-Zsilavecz, 2011
33.	Flupirtine	2018	European Union	Liver toxicity	European Medicines Agency, 2018
34.	Ranitidine	2020	US	Hepatotoxicity, idiosyncratic hepatotoxic reactions	Shaik et al., 2020
35.	Oxyphenisatin (Phenisatin)		Australia, France, Germany, UK, US	Hepatotoxicity	Fung et al., 2001

Scientific data showed that there are numerous drugs, such as Ranitidine, Cimetidine and Famotidine, which are responsible for induction of hepatotoxicity. Hepatic cellular dysfunction initiates various immunological reactions such as innate and adaptive immune responses. Stress and/or damage to the hepatocytes may trigger the activation of Kupffer cells (KC), natural killer cells (NK) and natural killer T (NKT) cells which enhance the release of various pro-inflammatory mediators and chemokines in the liver (Blazka et al., 1995; Blazka et al., 1996; Ishida et al., 2002). Although, RAN induced liver injury subsides after the termination of drug treatment, still it is a major diagnostic and therapeutic concern for doctors. Majority of RAN associated liver injury cases are not recognized during clinical trials, later on they are reported in post marketing surveillance. There is a lack of preclinical and clinical studies on ranitidine, but there are some case studies [summarized in Table 2] which evidenced that ranitidine therapy raises the risk of liver disorders (Alfirevic et al., 2012). The present review focuses on the possible mechanism behind the etiology of RAN induced liver toxicity and reason behind the withdrawal of RAN from the market.

Table 2: Case study reports on ranitidine therapy.

S. No.	Case study	Ranitidine therapy	Observation	Pathological outcomes	Latency	Recovery	Reference
1.	63-year-old woman with duodenal ulcer	150 mg twice daily	Elevated serum aminotransferase levels (ALT, AST,GGT)	anicteric hepatitis	2 weeks	10 days	(Barr et al., 1981)
2.	66 year old	150 mg daily	mild focal necrosis, with moderate portal inflammation and mild cholestasis (ALT and ALK P)	granulomatous hepatitis	4 week	1 week	(Offit et al.,1984)
3.	77 year old peptic ulcer disease.	150 mg twice daily	Elevated ALT ad alkaline phosphatase (ALK P)	liver biopsy showing focal necrosis	3 days	2weeks	(Souza et al., 1984)
4.	58 year old man with duodenal ulcer	150 mg daily	mild elevations in serum alanine aminotransferase (ALT) and alkaline phosphatase.	cholestatic hepatitis and jaundice	2 weeks	4 weeks	(Devuyst et al., 1993)
5.	29 year old man with symptoms of gastroesophageal reflux.	150 mg twice daily	marked elevations in serum bilirubin, mild elevation in serum aminotransferase and ALK P.	Bland cholestasis	2 weeks	2-3 month	(Ramrakhiani et al., 1998)
6.	73 year old	150 mg twice daily	hyperbilirubinemia (15.6 mg/dL) with conjugated bilirubin, a 2.5-fold elevation of alkaline phosphatase and moderate increase in aspartate aminotransferase and alanine aminotransferase.	diffuse canalicular cholestasis	3 weeks	50 days	(Liberopoulos et al., 2002)

2. History of Ranitidine Associated Toxicity

Ranitidine was first introduced by john Bradshaw in the UK as AH19065 in 1977 at the Ware research laboratories of Allen and Hanburys, division of a larger Glaxo organization (Lednicer, 1993). Further it was developed by Sir James Black at Smith, Kline and French in response to the first H2-receptor, antagonist, launched as *Tagamet* on November 1976 in United Kingdom. Furthermore, Glaxo developed the model with modification to the structure to nitrogen containing substituent, i.e. substituting the cimetidine imidazole ring with a furan ring and creating ranitidine. The tolerance level of RAN (i.e. fewer adverse reactions) was said to be much better and more powerful than cimetidine. RAN has about 10% interaction with cytochrome P 450 which indicates fewer side effects, but there are no major interactions with cytochrome P450 and other H2 blockers, such as nizatidine and famotidine (Newhouse, 1986). Ranitidine was the newly introduced and a United States Food and Drug Administration (US-FDA) approved H2 receptor antagonist for short-term oral use in duodenal ulcer therapy and untrammelled use of the Zollinger-Ellison syndrome in hypersecretory states (Med Lett, 1982). Few reports of clinical hepatotoxicity have been reported in Europe, Australia and Canada while undergoing oral preparation therapy and symptomatic liver disease have occurred in the United States during treatment with oral ranitidine (Barr, 1981; Cleator, 1983). A study showed that patients had symptomatic liver disease between 3 and 5 weeks after the ranitidine treatment, concerned symptoms like headache, "flu-like symptoms" (shaking chills and fever) and dark urine had also been observed for one day (Black et al., 1984).

Recently, on April 1, 2020, the presence of contaminants was recognized as N-Nitrosodimethylamine (NDMA), the US-FDA immediately demanded the manufacturers for withdrawal of all the over-the-counter (OTC) and prescription RAN products. However in some of the samples, the US-FDA failed to detect inappropriate NDMA levels, they found that the contamination of some ranitidine products increased over the course of the time, when stored at higher room temperatures. As a consequence, ranitidine products are banned for use in the US (Lim et al., 2020). NDMA (a cancer causative agent) is a possible human carcinogen, and low NDMA levels are normally consumed in diets. These levels, do not contribute to rise in cancer risk. The US-FDA conducted comprehensive testing on ranitidine and found a very low level of NDMA and suggested to avoid the use of Ranitidine products. In September 2019, the US-FDA concluded its analysis and informed the people about possible hazards and proposed alternative OTC and prescription therapies (Francis et al., 2005).

3. Molecular Mechanism Involved in Ranitidine Associated Hepatotoxicity

It is believed that RAN induced hepatotoxicity involves two pathways i.e. Immune mediated (Immunoallergic reactions) and direct cellular dysfunction. Though, the exact mechanism behind ranitidine induced hepatotoxicity still remains unclear (Bleibel et al., 2007), a schematic diagram concerned with the possible mechanism of RAN induced hepatotoxicty has been hypothesized in Figure 1.

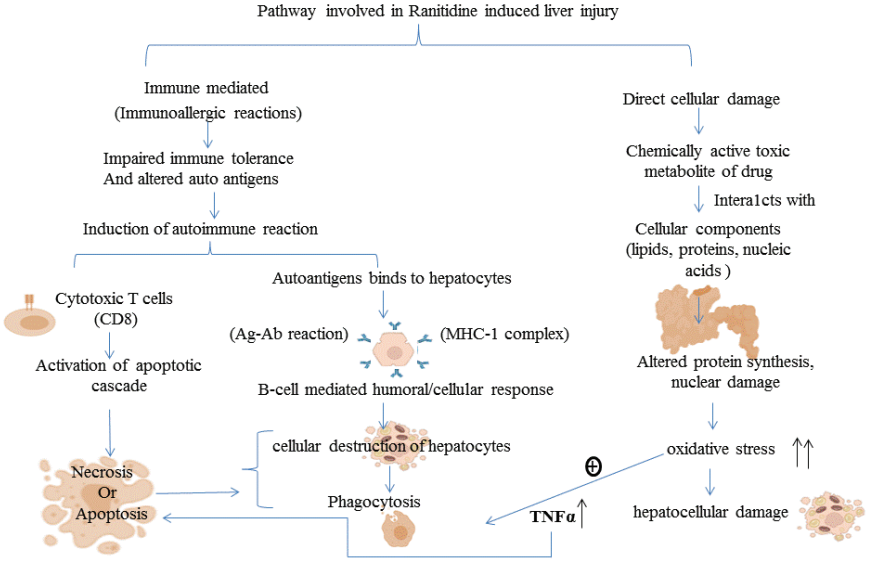

Figure 1: Illustration of pathways involved in ranitidine induced liver injury/ hepatotoxicity.

3.1. Immune-Mediated Liver Injury (Immunoallergic reactions)

The liver contains abundant sinusoidal macrophages i.e. Kupffer cells, which are responsible for the removal of foreign antigens, cellular debris and waste via hepatic portal system. It promotes the activation of cytotoxic T cells and induces apoptotic death of activated T cells and suppresses the immune response against these foreign antigens thereby increase immune tolerance (Maddrey et al., 2005). In case of ranitidine associated liver injury this process gets disrupted and results in impaired immune tolerance and generate altered autoantigens (Bleibel et al., 2007). These autoantigens binds to the surface of B-cells and forms MHC type I with hepatocytes via antigen-antibody reaction which subsequently causes induction of autoimmune reactions or antibody dependent immune response or B-cell mediated humoral response which is responsible for cellular destruction of hepatocytes via phagocytosis (Bleibel et al., 2007). In addition, these cellular immune responses triggers the release of pro-inflammatory mediators and various cytokines such as Tumour Necrosis Factor α (TNFα), nitrogen oxide (NO), FasL, and various interferons particularly IFN-γ (Kaplowitz et al., 2004).

3.2. Direct Cellular Damage

In majority of cases, RAN induced liver injury is triggered by chemically active toxic metabolite of drug which binds to cellular components such as lipids, proteins, nucleic acids and other cellular organelles leading to direct cellular dysfunction such as altered protein synthesis, nuclear damage and lipid peroxidation, which subsequently increases mitochondrial oxidative stress and promotes hepatocellular damage (Holt et al., 2006). Additionally, this direct cellular damage also increases the sensitivity of cells to the TNF receptor (Particularly TNFα) which triggers apoptotic cascade activation and induces apoptosis and promotes phagocytosis by the activation of cytotoxic T-cells (CD8) and leads to necrotic or apoptotic damage of hepatocytes. There is lot of phenotypic genetic variation amongst people; some people are vulnerable to RAN associated idiosyncratic reactions, whereas some are resistant. The microsomal P450 is responsible for the metabolism of RAN. Patients who lack cytochrome P450 enzyme are more prone to idiosyncratic reactions, because in the absence of cytochrome P450, metabolism of ranitidine is affected which leads to formation of its toxic metabolites and various intermediates which are responsible for hepatocellular damage (Kaplowitz et al., 2004).

4. Case Study Reports on Ranitidine Therapy

Ranitidine has been used for years in the treatment of gastrointestinal diseases and considered as the most prescribed drugs in the world. As DILIs are generally idiosyncratic, infrequent and unpredictable therefore difficult to induce in animal models therefore, either no or very fewer preclinical models have been developed for idiosyncratic DILI which makes it difficult to understand its exact pathogenesis (Chalasani et al., 2010). A few case studies have been tabulated in Table 2.

5. Steps Taken by Government and Any Regulations

US-FDA, European Medicines Agency (EMA), and Central Drugs Standard Control Organisation (CDSCO) have spotted the stringent content of nitrosamine in various products of RAN (Shaik et al., 2020). India's drug regulatory authority has ordered to withdraw samples of RAN, after the US regulator declared the presence of a cancer-causing impurity in some products (Woodcock, 2019). The Drug Controller General of India (DCGI) has asked the state drug regulators to withdraw all the samples of RAN from the major manufacturers and send those to Central Drug Laboratory (CDL) in Kolkata in order to test the impurity i.e. N-Nitrosodimethylamine (NDMA). Meanwhile, the appellate laboratory in Kolkata may not have the equipment to conduct the *Liquid Chromatography-High Resolution Mass Spectrometry* (LC-HRMS) test which has been recommended by the US-FDA for testing NDMA in ranitidine products. Venues have now been explored to get these tests done by private analytical laboratories. The US-FDA has released an update on NDMA testing for ranitidine, which warns manufacturers that they should not perform the aforementioned test in high-temperature because they produce high impurities for the presence of NDMA (Teena Thacker, 2019). In India, GSK agreed to withdraw all dosage forms of ranitidine hydrochloride from the market due to the pending outcome of ongoing tests and investigations as a precautionary action in correspondence with regulatory authorities (The Hindu, 2019).

Conclusion

RAN induced liver injury is difficult to diagnose and study because of its relative rarity and unpredictive occurrence (Watkins et al., 2005). Recent studies suggest that most of the RAN associated idiosyncratic reactions may lead to hepatocyte damage, followed by a series of events, such as activation of specific T- and B-cells, release of proinflammatory mediators like TNFα, interleukins, various cytokines and chemokines. However RAN induced hepatotoxicity is self-limiting in majority of cases, if early diagnosis is not made, then it may develop into severe hepatic failure (Rashid et al., 2004). In a preclinical study, it was observed that ranitidine

(30 mg/kg) did not produce liver injury in healthy animals; it was hepatotoxic in only those rats which are having mild inflammatory response induced by LPS (Luyendyk et al., 2003). The liver injury caused by RAN is usually rapidly reversible with cessation of the treatment. Gastroenterologists must be aware of the consequences before prescribing RAN to the patients who are already suffering from any liver diseases. The exact cause of RAN associated idiosyncratic hepatotoxicity is not clear yet. However, some studies suggest that the H2 receptor antagonists may be a potential cause for idiosyncratic hepatotoxic reactions; therefore it is not prescribed now-a-days. Due to the lack of preclinical and clinical studies on RAN associated liver injury, it is difficult to conclude the exact pathogenesis and the possible ADRs. However, Nitrosamines are genotoxic impurities, and due to their carcinogenicity, they pose an alarming threat to all creatures of earth. To alleviate this global issue, regulatory agencies such as CDSCO, US-FDA, and EMA have given their continuous effort for quantitative determination of amine impurities present in food stuffs, and in various intermediates in organic synthesis (Shaik et al., 2020). More studies must be carried out on this to know about the reason behind its hepatotoxicity.

Future Prospective

It is a topic of debate among various academicians and scientists "whether ranitidine will be available again in future or will FDA withdraw approvals of ranitidine National Drug Authority (NDA) and An abbreviated new drug application (ANDA)?" However USFDA detected NDMA as a carcinogenic impurity still they failed to detect the optimum level or concentration at which it may harm the liver and other vital organs. There can be a possibility that RAN will come again in the market if the level of NDMA is found negligible or harmless concerned regarding patients health. There is a need to carry out more experimental studies in order to detect the optimum level of NDMA which is ultimately causing RAN associated hepatotoxicity.

Competing interests

The authors declare that they have no competing interests.

Availability of Data and Materials

Data and material regarding the material reported as self-citation by the authors in this Mini-review is available upon request.

Consent for Publication

All are aware of its submission to the Journal and its publication.

Ethics Approval and Consent to Participate

There are no mandatory ethics documents associated with this mini review report.

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Abbreviations

ADR: Adverse drug reactions; ALK P: Alkaline phosphatase; ALP: Alanine phosphatase; ALT: Alanine aminotransferase; ANDA: An abbreviated new drug application; AST: Aspartate aminotransferase; CDCSO: Central Drugs Standard Control Organisation; CDL: Central Drug Laboratory; DCGI: Drug Controller General of India; DILI: Drug induced liver injury; EMA: European Medicines Agency; GGT: Gamma-glutamyl transpeptidase; H2: Type-2 histamine; IADRs: idiosyncratic adverse drug reactions; IFN: Interferon; LC-HRMS: Liquid Chromatography-High Resolution Mass Spectrometry; LPS: Lipopolysaccharides; NDA: National Drug Agency; NDMA: N-Nitrosodimethylamine; NK: Natural killer cells; NKT: Natural killer T cells; NO: Nitrogen oxide; OTC: Over-the-counter; PMS: Post-marketing surveillance; RAN: Ranitidine; TNF: Tumour necrosis factor; US-FDA: United States Food and drug administration.

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