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From Acid Reflux to Health Hazard: The Growing Cancer Threat Associated with Ranitidine

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ABSTRACT-
Ranitidine is a medication used for heart burn, stomach ulcer, gastroesophageal reflux disorder and other conditions that cause an accumulation of stomach acid. The side/adverse effects of ranitidine use include CNS disturbance such as dizziness and vomiting, nausea. Other reported side effects include cholestatic hepatitis, hematologic disorders such as leucopenia, and granulocytopenia, respiratory effects, and musculoskeletal complications.
It is an H2 histamine blocker drug. Recently some studies have found that ranitidine may containthe presence of potentially carcinogenic compounds such as N-Nitrosodimethylamine. The purpose of this study was to assess the relationship between ranitidine consumption and gastrointestinal cancer. Proton pump inhibitor (PPI) ana H2 antagonist-related events that were reported to the FDA Adverse Events Reporting System were chosen. To compare the percentage of all reported adverse events that were for gastrointestinal system malignancies among ranitidine adverse event reports to adverse event reports for other H2 antagonists, proportionate reporting ratios (PRRs) and related 95% confidence intervals were calculated.Compared to PPIs and other H2 antagonists, ranitidine had a higher percentage of adverse events for any gastrointestinal system malignancy relative to all other events (PRR 3.66, 95% Ci 3.19-4.20). Cancers of the pharynx (PRR 9.24), esophagus (PRR 3.56), stomach (PRR 1.48), colorectal (PRR 16.31), liver (PRR 2.64), and pancreas(PRR 2.18) all had elevated and substantial PRRs. Although not statistically significant, the PRRs for gallbladder (PRR 4.62) and anal (PRR 4.62) cancer were likewise higher. This discovery is raising concerns about drug related diseases long-term consumption of ranitidine may increase the risk of cancerseveral health authorities have launched an investigation and recommended its removal from the market. To make consumer aware in the context and it is necessary to guide towards safe option.

Keywords-Ranitidine, Gastrointestinal cancer, N-Nitrosodimethylamine (NDMA)

I. INTRODUCTION OF RANITIDINE:

Ranitidine(Zantac) is an H2 antagonist and available in various forms including tablet, injection and effervescent tablet preparations. A type of medication which used to treat and prevent heart burn, stomach ulcers, gastroesophageal reflux disorder. It is also used to treat conditions in which stomach produces too much acid such as Zolingerelision syndrome.

Ranitidine is a competitive and reversible inhibitor of the action of histamine, released by enterochromaffin-like (ECL) cells, at the histamine H2-receptors on parietal cells in the stomach, thereby inhibiting the normal and meal-stimulated secretion of stomach acid.It was approved for use in the United States in 1988 it had becomes the world's bestselling drug. Ranitidine was first approved for over-the-counter use in 2004 and until recently was sold as Zantac as well as private label and generic products.

On September 13,2019, the US Food and Drug Administration (USFDA) revealed that early tests detected unsafe amounts of NDMA in ranitidine. On October 9, 2019, the Korea Food and Drug Administration (KFDA) announced that all ranitidine products in the Korean market contained prohibited amounts of N-nitrosodimethylamine (NDMA) Thus, regulatory agencies in South Korea, Singapore, Germany, Indonesia, Hong Kong, Ireland, France, and Canada suggested that all ranitidine products be recalled. Furthermore, clinical research conducted during the 1990s have shown that ranitidine usera had greater blood levels of NDMA than nonusers

NDMA has been identified as a possible human carcinogen and has been shown to be a strong carcinogen in experimental animal. NDMA is a byproduct of several industrial operations and can be discharged into the air, soil, and water as a result, even though it is not currently manufactured in the US for commercial use. Additionally, NDMA

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can develop spontaneously, usually through the ingestion of certain foods. By consuming tainted water and/or foods that contain nitrosamines (like cured meat) or alkylamines (like tea), humans are often exposed to NDMA through their diet. Exposure can also happen in the workplace and when using cosmetics that contain NDMA.

Discovery of Potential Cancer Risk of Ranitidine

Ranitidine, a popular medication used to treat conditions like gastroesophageal reflux disease (GERD) and stomach ulcers, came under scrutiny in 2019 due to concerns about its potential to cause cancer. The controversy stemmed from the discovery of N-nitrosodimethylamine (NDMA), a probable carcinogen, in some ranitidine products. This revelation led to widespread recalls, investigations, and a reassessment of the drug's safety profile.

The issue first came to light in September 2019, when the U.S. Food and Drug Administration (FDA) announced that it had detected low levels of NDMA in certain ranitidine products. NDMA is a substance that is recognized as a carcinogen, meaning it has the potential to cause cancer. NDMA is not typically present in ranitidine, but the contamination was linked to the chemical's instability and the potential for it to form under certain conditions, such as when the drug is stored improperly or exposed to high temperatures .

The discovery of NDMA contamination raised significant concerns, as NDMA is known to cause cancer in laboratory animals, and long-term human exposure has been linked to liver, stomach, and other cancers. The FDA's initial tests indicated that the levels of NDMA in some ranitidine products were low, but the agency took this seriously enough to begin an investigation and issue a public warning. In response, major drug manufacturers and pharmacies voluntarily recalled their ranitidine products, pulling them from the shelves to prevent further exposure to consumers.

The source of NDMA contamination in ranitidine was traced to the manufacturing process, particularly the degradation of the active ingredient in the drug. Ranitidine is part of a class of drugs known as H2 blockers, which reduce stomach acid production. NDMA can form as a byproduct when ranitidine is exposed to heat, light, or certain chemical reactions over time (U.S. FDA, 2020). This finding led to the belief that extended use of ranitidine, especially products that had been improperly stored, could pose a potential long-term cancer risk to users.

As more tests were conducted globally, regulatory bodies such as the European Medicines Agency (EMA) and the World Health Organization (WHO) began examining the potential carcinogenic risk of NDMA exposure through ranitidine. A study published in 2020 by the European Medicines Agency confirmed the presence of NDMA in some ranitidine formulations but concluded that the levels were too low to present an immediate significant risk to public health. However, they stressed the importance of consumers discontinuing use and finding alternatives .

In addition to the FDA's investigation, a class action lawsuit was filed against manufacturers of ranitidine, claiming that consumers who used the drug were unknowingly exposed to harmful research into the safety of ranitidine and similar medications, leading to heightened scrutiny on pharmaceutical manufacturing standards.

Contraindications:

- Hyper sensitivity
- Gastric cancer
- Infections
- Hepatic diseases
- Tobacco smoking
- Bradycardia

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How does ranitidine act on the body?

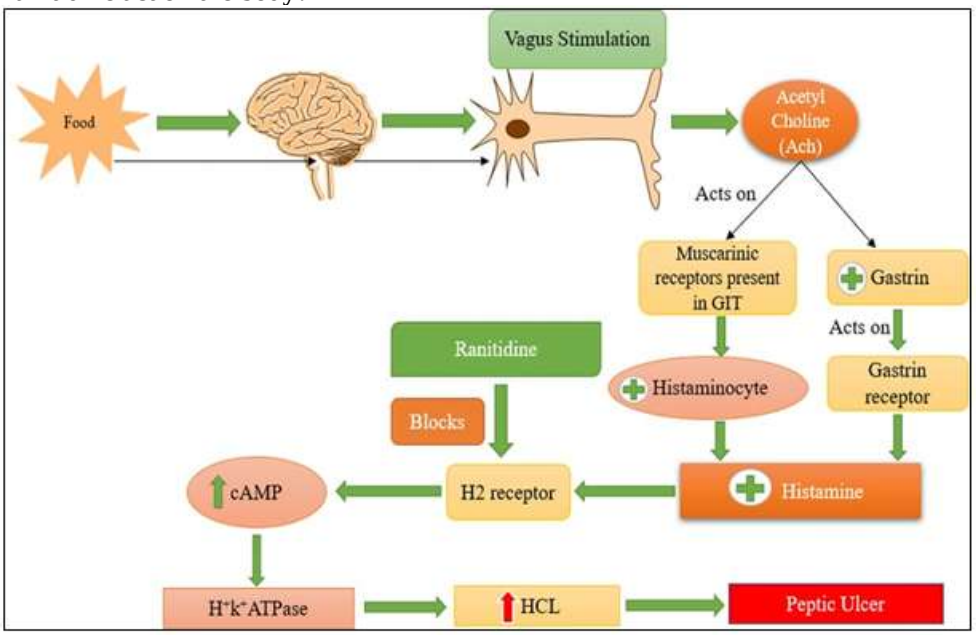

Fig: Mechanism of action of ranitidine

After a meal, the hormone gastrin, produced by cells in the lining of the stomach, stimulates the release of histamine, which then binds to histamine H2 receptors, leading to secretion of gastric acid. Ranitidine reduces the secretion of gastric acid in the stomach by blocking the effect of histamine on H2 receptors located on the parietal cells lining the stomach wall. this process leads to the inhibition of histamine binding to this receptor, causing the reduction of gastric acid secretion. The relief of gastric-acid related symptoms can occur as soon as 60 minutes after administration of a single dose, and the effects can last from 4-10 hours, providing fast and effective symptomatic relief.

Side Effects:

- Abdominal pain
- Hypotension, Arrythmia
- Insomia, Depression
- Nausea, Dizziness
- Jaundice, Pneumonia
- Blurred, Headache

Regulatory Actions and Recalls:

U.S. Food and Drug Administration (FDA) Actions

The U.S. Food and Drug Administration (FDA) played a central role in the regulatory response to the discovery of NDMA contamination in ranitidine. In September 2019, the FDA acknowledged the findings of NDMA in ranitidine products after independent lab testing revealed the presence of the carcinogen in both prescription and over-the-counter formulations. The FDA stated that while the levels of NDMA were considered low, they exceeded the acceptable daily intake limit established by regulatory bodies, triggering concern over the long-term effects of NDMA exposure.

In response to the findings, the FDA initiated a series of actions:

1. Investigation and Testing: The FDA tested multiple ranitidine products from various manufacturers to assess the extent of NDMA contamination. The results confirmed the presence of NDMA in varying amounts, with some formulations containing significantly higher levels than others. The FDA also began working with pharmaceutical companies to identify the causes of NDMA formation in ranitidine.
2. Recalls: In April 2020, the FDA recommended that all ranitidine products be removed from the market due to concerns about NDMA contamination. The agency encouraged consumers to stop using the medication and consult healthcare providers for alternatives. While some manufacturers had already

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voluntarily withdrawn their products, the FDA's recall recommendation officially removed ranitidine from the U.S. market

3. Public Warnings: The FDA issued public warnings about the potential risks of ranitidine use, urging consumers to discontinue use of the drug until further investigations were conducted. The agency also recommended patients who had been using ranitidine consult their healthcare providers to discuss alternative treatment options for acid-related conditions like GERD and peptic ulcers.

European Medicines Agency (EMA) Actions

In Europe, the European Medicines Agency (EMA) followed suit after the FDA's announcement, conducting a thorough review of ranitidine safety. The EMA issued a statement in early 2020 confirming the presence of NDMA in certain ranitidine products. The agency found that while the NDMA levels were variable, they were still concerning for public health.

Following its review, the EMA concluded that the benefits of ranitidine no longer outweighed the risks, particularly with the risk of cancer associated with NDMA exposure. The agency recommended that ranitidine be withdrawn from the European market, and manufacturers were asked to discontinue the sale of the drug. The EMA's decision was based on the available evidence that long-term exposure to even low levels of NDMA could increase the risk of cancers such as bladder, liver, and stomach cancers.

The withdrawal of ranitidine from the European market mirrored the actions taken by the FDA, reinforcing the global concern about the carcinogenic potential of NDMA in this widely used medication.

Manufacturer Actions and Class-Action Lawsuits

As the FDA and EMA issued their warnings and recalls, ranitidine manufacturers, including major pharmaceutical companies like Sandoz, Sanofi, and Apotex, voluntarily withdrew their products from the market. These companies took immediate action to prevent further exposure of consumers to potentially harmful levels of NDMA in ranitidine.

In addition to regulatory actions, several class-action lawsuits were filed against the manufacturers of ranitidine. The lawsuits alleged that consumers who had taken the drug for extended periods were exposed to harmful levels of NDMA without their knowledge. These legal actions further fueled public awareness of the issue, highlighting the potential long-term health consequences of NDMA contamination. The litigation brought additional pressure on both manufacturers and regulatory bodies to take decisive action to protect public health.

Role of Other Regulatory Authorities

Other regulatory agencies across the world also took steps to address the potential risks posed by ranitidine:

1. Health Canada: In Canada, the Health Canada agency initiated a review of ranitidine products following the FDA's announcement. In 2020, Health Canada confirmed the presence of NDMA in ranitidine products and recommended that consumers stop using the drug and consult healthcare providers for alternatives
2. Therapeutic Goods Administration products. As a result, Australia followed the lead of the FDA and EMA in recalling ranitidine products from the market .
3. Other Countries: Countries like Japan and South Korea took similar actions, recalling ranitidine products from the market and urging healthcare providers to stop prescribing the drug due to concerns about NDMA contamination.

Public Health Implications and Ongoing Research

The regulatory actions surrounding ranitidine reflect broader concerns about pharmaceutical safety and the need for rigorous testing and monitoring of drugs throughout their lifecycle. The FDA's investigation of NDMA in ranitidine has led to increased scrutiny of other commonly used drugs, particularly those that may also be vulnerable to chemical degradation and contamination. This has highlighted the importance of manufacturing practices that prevent the formation of potentially harmful byproducts like NDMA.

While the recall of ranitidine products has been widely supported by public health authorities, the long-term implications for those who used the drug over an extended period remain uncertain. As of now, no definitive epidemiological evidence links ranitidine directly to cancer, but concerns about NDMA exposure have led to ongoing studies. Public health researchers are studying the cumulative effects of NDMA exposure from pharmaceutical products and the impact of regulatory actions on consumer safety.

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Dosage:

- The dose should not exceed 300mg/day
- Onset of action: 55-65 minutes (150mg),55-115 minutes (75 mg dose)
- Duration of action: 15hrs
- Dosage form: Tablets(oral and effervescent), Syrup, Injectable solution
- Company name: GlaxoSmithKline(GSK)

Epidemiological and Clinical Evidence:

1.**Background and NDMA Contamination in Ranitidine**

Ranitidine's safety came under scrutiny in 2019 when it was discovered that some ranitidine products contained NDMA, a chemical compound classified as a probable carcinogen by the International Agency for Research on Cancer (IARC). NDMA is a potent mutagen that has been linked to liver, kidney, and gastrointestinal cancers in animal studies. The contamination was thought to result from the drug's instability under certain storage conditions, leading to the production of NDMA in some formulations.

2. Epidemiological Studies on Ranitidine and Cancer Risk

Epidemiological research on the association between ranitidine and cancer risk has focused on several key areas, including cohort studies, case-control studies, and population-based analyses. Some studies have indicated a potential increased risk of certain cancers, while others have not found strong evidence to support a direct link.

- Cohort Studies: Some cohort studies have explored whether long-term use of ranitidine is associated with cancer. These studies suggest that while the risk may be marginally increased, the evidence is inconclusive. A large-scale study conducted by the National Cancer Institute found no significant difference in cancer rates among those using ranitidine compared to other medications, suggesting that any potential risk is likely very low.
- Case-Control Studies: Case-control studies examining ranitidine use in patients with gastrointestinal and liver cancers have produced mixed results. Some studies have suggested a small increased risk of gastrointestinal cancers, while others have shown no such correlation. These inconsistencies are likely due to differences in methodology, sample size, and confounding factors such as lifestyle behaviors (e.g., smoking and alcohol consumption).
- Population-Based Analyses: Population-level data have been analyzed to assess the broader impact of ranitidine use on cancer incidence. One such study, based on data from Denmark's national cancer registry, found no significant correlation between ranitidine and an increased risk of cancer. However, this study was limited by the inability to control for other medications or health conditions that could influence cancer risk.

3. Mechanism of Action – NDMA as a Carcinogen

The potential carcinogenicity of ranitidine has been primarily linked to NDMA. When ranitidine is metabolized in the body, it can form NDMA, which has been shown to cause genetic mutations and DNA damage. Animal studies have confirmed that exposure to NDMA can increase the risk of liver, kidney, and gastrointestinal cancers. However, the levels of NDMA found in ranitidine are much lower than those used in experimental carcinogenic studies, making it uncertain whether such exposure would lead to cancer in humans.

NDMA is also formed in the body during the breakdown of other chemicals, including some food preservatives and environmental pollutants. This background exposure makes it difficult to isolate the cancer risk directly attributable to ranitidine. Additionally, the drug's instability in the human digestive system may influence the amount of NDMA that is absorbed into the bloodstream.

4. **Clinical Research and Long-Term Use**

Clinical studies investigating the long-term use of ranitidine have primarily focused on its effectiveness and safety in treating acid-related disorders. Although most of these studies have not specifically addressed cancer risk, concerns over NDMA contamination have prompted additional research into its long-term effects.

- Pharmacokinetics of NDMA: Clinical pharmacology studies have assessed the levels of NDMA in patients using ranitidine, finding detectable amounts of NDMA in the blood and urine. However, these levels have typically been low, and the clinical significance of these findings remains uncertain.
- Cancer Surveillance: Clinical surveillance studies have been initiated in some countries to track the long-term health outcomes of patients who have used ranitidine extensively. These studies aim to determine if cumulative

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exposure to NDMA could increase cancer incidence over time.

5. Regulatory Actions and Recommendations

The U.S. Food and Drug Administration (FDA) and other regulatory bodies around the world have closely monitored the safety of ranitidine following the discovery of NDMA contamination. In 2019, the FDA advised manufacturers to recall ranitidine products if they contained unacceptable levels of NDMA. The FDA has since recommended that patients using ranitidine switch to alternative medications, such as proton pump inhibitors (PPIs) or other H2 blockers, due to the potential cancer risk.

Despite the recalls, many healthcare providers and patients remain concerned about the long-term health implications of past ranitidine use. Several organizations, including the American Cancer Society, have called for further research into the link between ranitidine and cancer, particularly in light of the NDMA contamination.

Potential Cancer Risks and Organ-Specific findings of Ranitidine-Induced Cancer:

NDMA, a potent carcinogen, has raised significant concerns about the risks associated with long-term exposure and its potential link to various cancers. This review examines how NDMA is formed during the degradation of ranitidine, its carcinogenic effects, and the organ-specific cancer risks associated with its exposure.

NDMA and Ranitidine:

NDMA is produced as a byproduct when ranitidine breaks down in the body or during its manufacturing process. In 2019, the U.S. Food and Drug Administration (FDA) detected high levels of NDMA in ranitidine products, leading to widespread recalls. NDMA is classified as a Group 2A carcinogen by the International Agency for Research on Cancer (IARC), based on its ability to induce cancer in animal studies. While the exact mechanisms by which NDMA causes cancer in humans are still being investigated, it is known to cause DNA mutations that can lead to malignant transformations in various tissues.

Liver Cancer:

The liver is one of the primary organs affected by NDMA exposure. Animal studies have shown that NDMA can lead to liver cancer through the formation of reactive metabolites that damage liver cells. Chronic exposure to NDMA can result in liver fibrosis and cirrhosis, which are precursors to hepatocellular carcinoma (HCC). Although epidemiological studies have not definitively linked ranitidine use to liver cancer in humans, the possibility of NDMA-induced liver toxicity raises concerns .

Kidney Cancer:

NDMA has also been implicated in kidney cancer. Animal studies suggest that NDMA exposure can lead to renal cell carcinoma, particularly in the proximal tubules of the kidneys. The kidneys filter NDMA, which can cause cellular damage and increase the risk of malignant transformation. Although human studies confirming this connection are lacking, prolonged exposure to NDMA through ranitidine use could potentially contribute to the development of kidney cancer .

Lung Cancer:

The potential link between NDMA exposure and lung cancer is another areaof concern. While NDMA is primarily ingested, studies have demonstrated that it can cause lung tumors in animal models, especially if inhaled. The potential risk of lung damage from NDMA due to oral ranitidine use in humans is not fully understood, but the risk could be heightened with prolonged or high-dose exposure. This concern remains mostly supported by animal data, but there are ongoing concerns about long-term pharmacological exposure.

Stomach Cancer:

Ranitidine works by reducing stomach acid, which has raised concerns about a potential increase in gastric cancer risk with prolonged use. However, the relationship between ranitidine and stomach cancer is still unclear. While NDMA exposure might contribute to gastric carcinogenesis, there is insufficient evidence to directly link ranitidine use to an increased risk of stomach cancer in humans.

Pancreatic cancer and other organ cancer:

There is some emerging evidence suggesting that NDMA exposure could raise the risk of pancreatic cancer. Animal studies have shown that long-term exposure to NDMA can cause pancreatic ductal adenocarcinoma. However, further research is needed to determine the clinical relevance of these findings concerning ranitidine use. Other organs, such as the bladder, esophagus, and intestines, may also be affected by NDMA

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exposure, but evidence connecting ranitidine to cancer in these areas remains limited.

Alternative Medications and Future Directions:
Alternative Medications to Ranitidine:
Proton Pump Inhibitors(PPIs):

PPIs such as omeprazole, esomeprazole, and lansoprazole are commonly used to replace ranitidine for acid suppression. These drugs work by blocking the proton pump in the stomach, thereby reducing acid production. PPIs are effective in treating conditions like GERD, peptic ulcers, and Zollinger-Ellison syndrome. However, concerns about long-term PPI use include potential risks such as kidney disease, fractures, and gastrointestinal infections.

Antacids:

Over-the-counter antacids, including calcium carbonate and magnesium hydroxide, provide quick relief from heartburn and indigestion by neutralizing stomach acid rather than reducing its production. While these medications are safe for short-term use, they may not be as effective for chronic conditions such as GERD. Prolonged use can lead to complications, including kidney stones and electrolyte imbalances .

H2-Receptor Antagonists (H2RAs):

Other H2-receptor antagonists, such as famotidine and cimetidine, are alternatives to ranitidine. Famotidine, in particular, has not been linked to the NDMA contamination issues seen with ranitidine and remains commonly used to treat conditions like acid reflux and peptic ulcers. Although famotidine may be a safer option than ranitidine, further long-term safety studies are needed.

Lifestyle Modifications:

In addition to medications, lifestyle changes can significantly help manage GERD and acid reflux. Modifications such as dietary changes, weight loss, and avoiding trigger foods like spicy foods, alcohol, and caffeine can improve symptoms. Other non-pharmacological interventions, such as elevating the head of the bed, eating smaller meals, and quitting smoking, can also reduce the need for medication and help manage acid reflux.

Future Studies Needed:
NDMA and Cancer Risk:

Given concerns about NDMA contamination, future research should focus on understanding the mechanisms by which NDMA causes cancer in human tissues. Studies should aim to determine whether long-term exposure to NDMA from ranitidine is a significant cancer risk factor, and whether the carcinogenic effects are dose-dependent. Additionally, research into the metabolism of ranitidine and its conversion to NDMA would be crucial in assessing its cancer risk

Epidemiological Studies on Ranitidine and Cancer:

Large-scale, population-based studies are necessary to explore whether there is a direct link between ranitidine use and cancer. These studies should investigate the potential association between ranitidine and cancers such as liver, kidney, and gastric cancers, to better understand the extent of any risks. Comparative studies between ranitidine, other H2RAs, and PPIs would also help clarify the relative safety of these alternatives .

Safety of Alternatives:

As ranitidine is removed from the market, it's critical to conduct long-term safety evaluations of alternative medications like famotidine, PPIs, and antacids. These studies should examine potential risks, particularly concerning kidney function, bone density, and the possibility of infections.

Pharmacovigilance and Post-Market Surveillance:

Ongoing pharmacovigilance is essential to monitor the long-term safety of alternative medications after they hit the market. Regular surveillance will enable early identification of any unforeseen risks and facilitate the development of safer therapeutic approaches for managing acid-related disorders.

II. CONCLUSIONS:

There is no strong evidence that ranitidine raises the risk of upper gastrointestinal cancer, according to our extensive prospective analysis that included high quality prescription and cancer incidence data with two active comparator groups. Nonetheless, further studies with longer follow-up periods are required to confirm these findings. However, strict global rules must be kept on the production of medical agents to keep public health problems around the world from happening, especially with widely used drugs.

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