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Review Article

Metformin and nitrosamine impurities

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ABSTRACT

Metformin is considered as gold standard anti-diabetic drug and is the preferred initial pharmacologic agent for most of the patients with type 2 diabetes mellitus. Metformin is cheap, widely available and safe, backed by pharmaco-epidemiological evidence of more than 60 years regular use in clinical practice. Due to its durable efficacy, once initiated, metformin will be continued as long as it is tolerated and not contraindicated. It has got additional benefits on cholesterol, liver, cardio vascular system and cancer. Recent evidence and recall of metformin extended release formulation due to detection of excess amount of cancer-causing nitrosamine impurities has created concern among health care providers and patients. Adherence to regulatory guidelines and use of approved technologies in manufacturing and quality control may help in solving the issue.

Keywords: Metformin, N-Nitrosodimethylamine, Nitrosamine, Impurities, Recall

INTRODUCTION

Metformin and nitrosamine impurities

Metformin was discovered in the year 1922.[1] Human trials on metformin were began in 1950s by the French physician Jean Sterne. It was introduced as a glucose lowering medication in France in 1957 and the United States in 1995.[2]Metformin is currently, the most widely used oral medication used to treat type 2 diabetes worldwide. It is on the WHO's List of Essential Medicines, and is considered as the safest and most effective medicine for diabetes management.[3]

N-Nitrosodimethylamine (NDMA) is an organic compound found at low levels in numerous processed items of human consumption, including cured and grilled meats (that contain sodium nitrite as a preservative), bacon, fish, dairy products, cheese, vegetables like lettuce and spinach,pepper, fruits, beer, whisky, tobacco smoke and even in some cleansers, toiletry, rubber and cosmetic products.[4]

NDMA arises by the combination of nitrous acid and dimethyl amine derived from the degradation of protein from the food in the lower gut. NDMA is a known common environmental contaminant and everyone is exposed to some level of NDMA through air, soil and water.

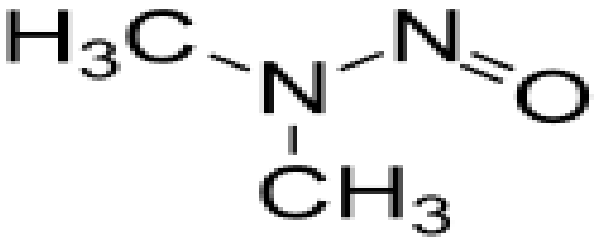

Figure 1: NDMA.

NDMA and cancer risk

NDMA, the chemical once used to manufacture pesticides, toys and rocket fuel is mainly a by-product of industrial processes and water disinfection (via chlorination).[5] NDMA is primarily used in laboratory research to induce tumours in experimental animals. Liver enzyme converts NDMA to methyldiazonium an agent, that then leads to O6-methylguanine, both of which alter a process at the cellular level called methylation that is a cancer turbocharger.[8]

The carcinogenic nature of nitrosamines in general, and NDMA specifically, has been well documented in the scientific literature since the 1960s.[9,10] This substance is reasonably anticipated to be a human carcinogen. At high doses, it is a potent hepatotoxin that can cause fibrosis of the liver in rats. The induction of liver tumours in rats after chronic exposure to low doses is well-documented.[11] Its toxic effects on humans are inferred from animal experiments, but not well-established experimentally. Animal studies have suggested that chronic ingestion and inhalation of NDMA may cause an increase in liver tumours and other types of tumours in stomach, oesophagus, small intestine, colon, rectum pancreas, bladder, kidney, prostate, testis, ovary, breast, lung, blood vessels, leukaemia, non-Hodgkin's lymphoma, multiple myeloma and still birth. Research does not indicate a specific increase in the risk of cancer among people exposed to NDMA. However, the World Health Organization (WHO) does warn that research is Supportive of the assumption that NDMA consumption is positively associated with either gastric or colorectal cancer. NDMA, is part of a group of chemicals known as nitrosamines and has been identified by the WHO and Centers for Disease Control and Prevention(CDC) and the International Agency for Research on Cancer (IARC) as a probable human carcinogen Group 2A compound (means it may cause cancer in humans).[12] Since there is sufficient evidence of carcinogenicity in animals overall evaluation, the US Environmental Protection Agency (EPA) has classified NDMA as a Group B2, probable human carcinogen.[13,14]

Metformin, NDMA and FDA recall

A Dutch study reported last year that exposure to NDMA-contaminated medicines was associated with a small increase in risk for overall cancer (HR, 1.09; 95% CI, 0.85-1.41).**[15]** The HR increased to 1.46 for colorectal cancer and 1.81 for uterine cancer, although confidence intervals were wide. FDA currently recognizes the danger of this compound and, as a result, has set strict daily acceptable intake limits on NDMA in pharmaceuticals of 96 nano grams.**[16]** There are currently no reports of NDMA causing cancer in humans, however, and the CDC maintains that exposure to NDMA does not mean that any effect on health will definitely occur. But, the cancer-causing impact of NDMA is believed to be cumulative.

NDMA may increase the risk of cancer if people are exposed to it above the acceptable level and over a long period of time, but a person taking a drug that contains NDMA at-or-below the acceptable daily intake limit every day for 70 years is not expected to have an increased risk of cancer. But, whether shorter-term exposure at levels above the acceptable intake limit would lead to an increase in the risk of cancer is unknown. In 2018, and then again in late 2019, various brands of Angiotensin Receptor Blocker valsartan were recalled because of contamination with *N*-nitrosodimethylamine.[17] In 2019, H2- receptor antagonist ranitidine was recalled across the world due to contamination with NDMA.[18,19]

In December 2019, the FDA announced that, it had become aware of NDMA in some metformin products in other countries.[20]The agency immediately began testing to determine whether the metformin in the U.S. supply was at risk, as part of the ongoing investigation into nitrosamine impurities across medication types. By February 2020, the agency had identified very low levels of NDMA in some samples, but at that time, no FDA-tested sample of metformin exceeded the acceptable intake limit for NDMA. The FDA has maintained that it would continue with ongoing testing of metformin and other medications, and if any levels of NDMA or other impurities were identified, swift action would be taken.[21]

Recently, the FDA has become aware of reports of higher levels of NDMA in certain Extended Release (ER) formulations of metformin via a citizen petition filed by a private online pharmacy.[22-24] FDA laboratories tested the same metformin lots that the private laboratory found to contain NDMA above the acceptable intake limit (which was confirmed by another FDA registered/inspected, cGMP/GLP compliant analytical laboratory). The agency confirmed unacceptable NDMA levels in some, but not all, of those lots. The agency also found that the levels of NDMA, when present, were generally lower than reported by the private laboratory. Given FDA scientists' deep experience in quantifying these impurities in drugs, the agency said, is confident in the reliability of the FDA's testing method and results and will continue to take action based on the latest scientific information. The results have also been consistent with the findings of other regulatory agencies' laboratories around the world.

The agency has contacted five firms to recommend they voluntarily recall (class-2) their products.[25] There are additional manufacturers of the metformin ER formulation that supply a significant portion of the U.S. market, and their products are not being recalled. The FDA is continuing to work closely with manufacturers to ensure appropriate testing. Assessments are underway to determine whether metformin ER recalls will result in shortages and the agency will work closely with manufacturers to prevent or reduce any impact of shortages especially during the current COVID pandemic.

The agency has also asked all manufacturers of metformin containing ER products to evaluate the risk of excessive NDMA in their product and to test each batch before it is released into the U.S. market. If tests show NDMA above the acceptable intake limit, the manufacturer should inform the agency and should not release the batch to the U.S. market. Many companies have notified its distributors and customers affected by this recall via overnight mailing, notification letter and press release and has arranged for return/replacement of recalled product lot.

42% of the batches analysed by the private laboratory contained NDMA exceeding the FDA's daily acceptable intake limit with the highest detected amount over 16 times the permissible limit. It alleges that, 4 out of 10 Americans currently taking metformin are being exposed daily to unacceptable levels of NDMA. It's unclear why the private lab results differ from the FDA findings. The FDA may have acquired the drug samples through voluntary submission, which can introduce significant sampling bias. The private lab claims that, it largely followed the FDA's protocol for testing for NDMA in metformin, with the exception of using crowd sourced samples of the drug metformin and changes it said were made to make the method more precise.[26] Or, it's also possible that the FDA got samples that weren't representative of the general drug supply. Interestingly, the agency could detect NDMA in lots that the private laboratory did not.

So far, Poland and Singapore have completed their NDMA testing on metformin. In Poland, a small amount of NDMA was found after the investigation, but no products exceeded the standard. In Singapore, NDMA was detected in more than three versions out of the 46 metformin-containing preparations, which were sold for a short time resulting in low patient risk and a recall was initiated for those products by Singapore's Health Sciences Authority (HSA). There are metformin recalls by Health Canada also.[27,28] European Medicines Agency (EMA) stated there are no data indicating that EU metformin medicines are affected. But, EMA is assessing the impact of recent tests which found NDMA in some EU batches of metformin.[29-32] MoHAP Saudi Arabia and Therapeutic Goods Administration (TGA) Australia are also observing the incident. In Korea, MFDS halted production and sale of 31 metformin products after NDMA detection.

ANALYTICAL METHODS

Routine, traditional methods for estimation of impurities by HPLC or residual solvents by Gas Chromatography (GC) are not sufficient to estimate impurities like NDMA.[33,34] FDA published a method titled "Liquid Chromatography-High Resolution Mass Spectrometry (LC-HRMS) Method for the Determination of NDMA in metformin Drug Substance and Drug Product" (FY20-058-DPA-S). Based on the testing principle of this method, the private laboratory used LC-HRMS instrumentation but with modified methodology that achieved a lower limit of detection (LOD), a lower limit of quantitation (LOQ), and a wider reportable range than shown by FDA, and used isotopically labelled NDMA to measure recovery in the background of each unique medication matrix.

The Private Lab's method generates increased chromatographic resolution and sharper peaks, thus resulting in higher signal to noise ratio at same concentration than FDA method. Three tablets from each batch were tested individually and the amount of NDMA detected was reported as mean followed by the standard deviation of the results from the three tablets. Several batches contained over 10 times the daily acceptable intake limit and there was significant variability from batch to batch, even within a single company; underscoring the importance of batch-level chemical analysis and the necessity of overall increased quality surveillance of medications. Without use of an internal standard, the FDA method has the potential to underestimate the NDMA concentration due to matrix effects.

According to the FDA, the discrepancy was due to the presence of a substance that interfered with the private labs testing results. In summary, the agency found the private laboratory method to be inappropriate for quantifying NDMA in metformin drug products due to presumptive overestimation of NDMA caused by the presence of dimethylformamide (DMF), a solvent commonly used in pharmaceutical manufacturing that interfered with the testing results.

FDA has posted its testing method on the public website for use by industry, third party laboratories and other international regulatory partners. Manufacturers may use their own testing method or use the FDA's posted method, but any testing method should be validated by the user if the resulting data are used to support a required quality assessment of the active pharmaceutical ingredient or drug product, or if the results are used in a regulatory submission.

SOURCE OF NDMA IN METFORMIN

There are multiple reasons for the presence of NDMA in drugs. Dimethyl amine (DMA), which is a precursor of NDMA, is used in the synthesis of Metformin. Thus, there is always a possibility of NDMA showing up in lots of Metformin. The FDA has previously found that the source of NDMA can be related to change in drug's manufacturing process (like in case of valsartan) or its chemical structure, during its testing process (like in ranitidine) or even the conditions in which they are stored or packaged. As food and drugs are processed in the body, nitrosamines, including NDMA, can be formed. The presence of NDMA in metformin products may be primarily due to contamination during manufacturing (as

only some batches/brands exceeded the acceptable standard of NDMA) as opposed to a fundamental instability of the drug molecule, which is the case with ranitidine. But, possible role of the drug itself cannot be ruled out entirely now. There may be more than one entry point by which NDMA is introduced. NDMA in some ranitidine products was found to increase over time and, when stored at higher than room temperatures. NDMA may be formed due to contact with oxidants in the process of synthesis of metformin like valsartan. As valsartan was found to have a problem in the manufacturing process, the metformin manufacturing process should also be checked first.

IMPACT OF RECALL

Metformin is the 3rd-most-prescribed drug in India. Independent chemical testing and certification before being sold to a patient or pharmacy without increasing the cost may improve the quality of supply of the product in long term. To date, FDA or pharma companies has not received any reports of adverse events that have been confirmed to be directly related to this recall.

Regulatory interventions and voluntary establishment of scoring or rating system are suggested as short term measures to improve the drug quality. While most people won't get cancer from the contaminants in these pills, it's an unacceptable demonstrable risk, and avoidable. Regulatory agencies need to hire more qualified investigators and needs to conduct more inspections of the facilities producing drug ingredients. The Indian drug regulator, Central Drug Standard Control Organisation (CDSCO), is also monitoring the US FDA updates closely but, haven't noticed any concerns with the products marketed in India.

Relying on pharmaceutical companies' data integrity and data reporting on self-reporting of analytical results is not sufficient to protect the pharmaceutical supply from potentially dangerous contamination. There are roughly three drug recalls in the U.S. every day, which can be attributed, at least in part, to the fact that the chemical quality of medications is primarily checked by manufacturers, which self-report the results.

Furthermore, even when recalls are voluntarily performed by industry, the lengthy period of time over which such recalls occur is of significant concern to healthcare professionals, including those who have witnessed the over year-long recall process of the sartan medication recalls. It appears that the situation with metformin may be similar and a proactive drive for broad, robust, independent testing and verification of the chemical content of batches of pharmaceuticals in an objective manner direct from the pharmaceutical supply chain that delivers medications to the public should be combined with decisive action on the part of regulators to quickly request recalls and take other actions (like labelling revisions) as appropriate.[35]

The quality of drugs manufactured in India will come into greater scrutiny. This will potentially bring in a slew of new regulations, which will make it even more costly for Indian generic pharma companies to comply with rigorous monitoring, testing and reporting regulations, ultimately squeezing profit margins.[36] These changes, and increased testing have added to the cost of production and analysis, the timeline of the manufacturer, and also required the purchase of new equipment. Most companies in India use the LCMS to check for NDMA since LCHRMS testing devices are not easily available. New techniques will help to analyse the final API and formulated product for presence of all listed nitrosamine compounds in a single method and restore stakeholder confidence (regulatory agencies, providers and patients) in the industry. The control strategy for NDMA involves various process parameters like temperature, humidity and extra purification, additional time cycles and such, during API manufacturing and similar stringent controls during formulation manufacturing. Most manufacturers have procured LCMS systems to detect NDMA, to ensure that each batch is tested for NDMA before releasing the batch to the market so that the quality of the final product reaching patient is assured, so that recalls should not overly burden the healthcare system.

FDA does not have scientific evidence to determine how long NDMA has been present in metformin products and are investigating the root cause of its presence. Improved technology enables the detection of even trace amounts of impurities in drug products and may be the reason why more products have been found to have low levels of NDMA. Today, better testing methods exist, and the FDA better understands the specific manufacturing steps that may increase the risk of nitrosamine formation. These findings underscore the importance of batch-level chemical analysis and the necessity of effective quality surveillance of medications, and underscore the importance of chemically validating all batches of medications for safety and quality.

EMA has given companies six months (on or before June 19, 2020) for the risk evaluation and three years (on or before December 20, 2022) for remediation, if any. FDA suspects the origin of the problem to be the reuse of solvent and/or change in materials used during the manufacturing process of the drug and/or change in synthesis route to a cheaper and higher-yielding route, but a more toxic one. Intensifying competition and thinning profit margins in generics prompt manufacturers to introduce these changes.

ADVICE TO HEALTHCARE PROVIDERS AND PATIENTS

Metformin is the preferred first-line treatment for Type 2 diabetes based on safety, efficacy, and low cost. Unlike Ranitidine or Sartan, there is no class substitute for metformin. The benefits of metformin are very likely to outweigh the risks (the probable risk of cancer would be

0.21to1 in 100,000 patients) for most people taking it. Metformin in an extended-release formulation is often used for convenience, as it requires only a once-daily dose instead of two doses per day, and because some patients tolerate this formulation better. It could be dangerous for patients with type 2 diabetes to stop taking their metformin without first talking to their health care professional. FDA advises patients to continue taking metformin ER tablets until they can consult with their healthcare professional who can prescribe a replacement or a different treatment option and recommends that healthcare professionals continue to prescribe metformin where clinically appropriate. Extended-release metformin figures would represent only around a quarter of overall metformin prescriptions. FDA testing has not found NMDA in metformin immediate release (IR) products, which is the most commonly prescribed formulation of the product.[37] In terms of medication efficacy, they're both equally effective. There are no alternative medications that treat this condition in the same way. The presence NDMA, probable carcinogen in a medication that is taken daily by adults and adolescents for a chronic condition like diabetes, makes this finding particularly troubling. No doctor would prescribe, no patient would consume, and no insurance company would pay for, a drug that contained NDMA, a probable human carcinogen. Even though, there are many other alternatives and other medication classes, but many of them have side effects, are more expensive and some of the newest ones may not be covered by insurance. So, keep the public informed on actions taken to protect patients and reassure them about the quality of their medicines.

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