Canterbury District Health Board
Te Poari Hauora ō Waitaha

Clinical Pharmacology Bulletin

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NDMA, Nitrosamine Impurities in Medicines

Due to concerns about cancer risks from contamination with NDMA, ranitidine tablets and injection have been unavailable in New Zealand since September 2019, following a global recall by the manufacturers. This bulletin aims to provide information for health professionals about NDMA impurities in medicines and the possible health risks for their patients.

What is NDMA?

N-nitrosodimethylamine (NDMA) is a member of the N-nitrosamine family of organic chemicals that form from both natural and industrial processes. Human exposure can occur from consuming certain foods and beverages (e.g. smoked meats, chargrilled foods, beer, whisky), drinking water (e.g. when waste water is recycled by being treated with chloramines), or inhaling tobacco smoke. NDMA is classified by the WHO International Agency for Research on Cancer as a group 2A carcinogen: no data are available in humans but there is sufficient evidence of carcinogenicity in animals.

When was NDMA detected in medicines?

In 2018, NDMA was found incidentally in some batches of valsartan active pharmaceutical ingredient (API) from China, during routine screening of raw materials for solvent contamination. Increasingly, the synthesis of APIs has been globally outsourced to reduce production costs of generic medicines. Consequent investigation of the valsartan API supply chain lead to the global recall of several brands of angiotensin receptor blockers (ARBs) because of unacceptable levels of N-nitrosamine impurities. None of the approved ARBs in New Zealand were found to be affected and were not recalled. In 2019, the U.S. Food and Drug Administration (FDA) were alerted to NDMA impurities in ranitidine tablets by an analytical pharmacy. Consequent investigation led to a global recall of ranitidine products contaminated with NDMA, but also voluntary withdrawals. This precipitated a global shortage of ranitidine as well as alternatives such as omeprazole and famotidine.

How does NDMA contamination occur?

How APIs become contaminated with N-nitrosamines is still being investigated. Impurities could be caused by incomplete chemical reactions or contamination with solvents or reagents during synthesis of the API. The contamination of valsartan and losartan tablets appears to have been from a change in reagent used by the API manufacturers. How the nitrosamine impurities are occurring in some ranitidine products is still being determined.

What are the risks?

The recalled valsartan tablets contained 8 to 20 micrograms of NDMA per tablet. The European Medicine Agency (EMA) review concluded that if 100,000 patients took the highest dose of contaminated valsartan tablets every day for 6 years, there could be 22 extra cases of cancer due to NDMA over the lifetimes of those 100,000 patients. They noted that these rates are very low compared to the lifetime risk of being diagnosed with cancer in the European Union which is 1 in 2. The recalled ranitidine tablets contained 0.01 to 0.86 micrograms of NDMA per tablet.

Do other medicines contain NDMA?

In October 2019 the EMA advised all companies supplying medicines to the European Union to do a risk assessment for nitrosamines and test any suspect products. Medsafe will be requesting similar action however, they note this is a precautionary measure to manage a very small risk for patients.

The presence of nitrosamine impurities in medicines raises questions about the regulation and quality control of generic medicines. However, the impact of the amounts of nitrosamine impurities found on a patient's absolute lifetime cancer risk is very low. This needs to be balanced with the risks to the patient of not receiving a medicine because of anxiety around perceived cancer risks or drug shortages following voluntary withdrawals by industry.