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National Institute of Health Sciences

Risk assessment of the use of ranitidine products and nizatidine products in which carcinogenic substance N-nitrosodimethylamine was detected

Background

Following the announcements by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) that very low levels of N-nitrosodimethylamine (NDMA) have been detected in ranitidine hydrochloride products and the drug substance, the Ministry of Health, Labour and Welfare (MHLW) instructed marketing authorization holders (MAHs) of ranitidine and nizatidine, which has a similar chemical structure to ranitidine, to analyze NDMA in these drugs.

In response to the instruction, a voluntary recall of ranitidine was implemented by some of the MAHs as a precautionary measure, and as a result of their analysis, NDMA was detected in some of the drug substances and it was found that there was a potential for NDMA to be contained also in ranitidine products in levels above the acceptable limit.* Consequently, a voluntary recall was initiated for all ranitidine products by October 4. With regard to nizatidine, NDMA in levels above the acceptable limit was detected in some of the nizatidine products and a voluntary recall of the affected lots was initiated by the MAHs on October 23 and after.

The National Institute of Health Sciences recently has conducted an assessment of the health effects of the use of ranitidine and nizatidine products in light of their carcinogenic potency based on the results of the analysis of NDMA content in ranitidine and nizatidine products and other relevant data. The basic assessment methods referred to in the sections "NDMA formation," "NDMA toxicity summary," and "NDMA carcinogenic risk assessment" below are quoted with no modifications from the risk assessment for exposure to NDMA detected in valsartan products conducted in fiscal year 2018 because no new findings have been reported since its publication that would specifically affect the risk calculation methods for health effects from NDMA exposure.

* 0.32 ppm (calculated based on the acceptable daily intake limit for NDMA at 0.0959 µg/day)

NDMA formation

NDMA is the simplest dialkylnitrosamine. It is no longer used industrially or commercially but known to form as a by-product of various chemical reactions. Consequently, it could be released as a by-product and contaminant into the environment from various industries and municipal wastewater treatment plants. Because of its solubility and low partition coefficient, NDMA has the potential to leach into and persist in groundwater, but it is metabolized in the environment and does not bioaccumulate. Generally, NDMA has not been detected in surface water, except for limited localized contamination detected at industrial sites in the past. NDMA is also known to be endogenously produced in very low levels in the human stomach from simultaneously ingested fish and nitrate/nitrite in vegetables. A Dutch study noted a possible intake of NDMA by humans of approximately 0.4 to 4 ng/kg/day.

NDMA toxicity summary

NDMA is highly acutely toxic after oral administration or via inhalation. Liver disorder with increased mortality, congestion in the organs such as liver, lung, spleen, and myocardium, as well as gastrointestinal haemorrhage have been reported in repeated oral dose studies with high doses of NDMA for a month or so. Although data on non-neoplastic effects in laboratory animals associated with exposure to NDMA are inadequate, there has been clear, consistent evidence of carcinogenicity in a number of studies on carcinogenicity in which rodents were exposed to NDMA orally, via inhalation, or by intratracheal instillation.

In addition, NDMA increased the incidence of liver and Leydig cell tumors in rats when administered via drinking-water or diet. Hepatic, pulmonary, and renal carcinogenicity was observed in mice administered NDMA via drinking-water. In genotoxic studies conducted *in vitro* in bacterial and mammalian cells, there has been consistent evidence that NDMA is mutagenic and clastogenic. Similarly, clear evidence of mutagenicity in various organs has also been observed in *in vivo* studies. DNA adducts formed by the methyldiazonium ion generated during metabolism likely play a critical role in the mechanism of NDMA carcinogenicity. Qualitatively, this metabolism of this substance may be similar among species. Therefore, NDMA is likely to be carcinogenic to humans with relatively low levels of exposure. While a limited number of epidemiological studies have been reported to indicate an association between NDMA exposure and tumors in the digestive organs and the lungs, no studies have been reported in which the dose-response relationships can be assessed. NDMA has been classified by the International Agency for Research on Cancer (IARC, 1987) as a "probable human carcinogen (Group 2A)."

NDMA carcinogenic risk assessment

NDMA is considered to exhibit carcinogenicity based on its mutagenicity. Therefore, a quantitative estimate of the carcinogenic unit risk from low level exposure as "non-threshold" is common practice. Low dose extrapolation should be used based on the results of animal studies because quantitative epidemiological studies with NDMA exposure to humans are not available. As the carcinogenicity study for quantitative assessment, a large drinking-water study with 60 male and female rats in 15 dose groups each (240 rats in the control group) has been adopted by different international assessment agencies in order to analyze detailed dose-response relationships.

On the other hand, several methods are available to assess the toxicity by low dose extrapolation of animal studies' data. The Assessment and Control of DNA Reactive (Mutagenic) Impurities In Pharmaceuticals To Limit Potential Carcinogenic Risk (M7 guideline) recently agreed upon in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) recommends the following methods to calculate acceptable intakes based on compound-specific risk assessments:
The method to calculate from rodent carcinogenicity data such as TD_{50} values (doses giving a 50% tumor incidence), and the method to use linear extrapolation from Benchmark Dose Lower Confidence Limit 10% ($BMDL_{10}$, an estimate of the lowest dose which is 95% certain to cause no more than a 10% cancer incidence in rodents).

Among the above-mentioned methods for low dose extrapolation that were used in the fiscal year 2018 assessment, only the one with TD_{50} value was used in this assessment to calculate the risk in order to assess the risk on the utmost safer side. In addition, the principle of Haber's rule (concentration (C) × time (T) = constant (k)), which is also applied in the ICH M7 guideline, was applied to the calculation of the risk associated with exposures in the short-term period compared to the lifetime exposure. Thus, the risk was calculated by multiplying the risk with the lifetime exposure by the ratio of years of exposure to the lifetime exposure assuming a lifetime is 70 years. Of note, based on the idea that the carcinogenic risk of NDMA due to its mutagenicity is proportional to the duration of exposure, it was assumed in the following risk estimation calculations that carcinogenic risk is proportional to the dose and the duration of exposure to carcinogen even when the exposure is remarkably shorter than the lifetime.

Lifetime (70 years) average exposure corresponding to 1 in 100 000 risk when using TD_{50} value

TD_{50} value for NDMA according to the Carcinogenic Potency Database (CPDB) is 0.0959 mg/kg/day (95.9 µg/kg/day).

Assuming a body weight of 50 kg, the lifetime average exposure is:

95.9 ÷ 50 000 × 50 = 0.0959 µg/day.

1. Effects of ranitidine products use

1-1. Effects of receiving ranitidine oral products

The drug utilization survey (DUS) on the use of ranitidine oral products revealed that the duration of ranitidine use varied greatly. Moreover, it turned out that the number of cases receiving the drug in longer durations than 3 years, which is the coverage period of DUS, has been limited since the drug was launched in the Japanese market more than 30 years ago. Therefore, with reference to the academic society's guidelines we calculated the carcinogenic risk for two standard periods of use, namely, the short-term use and the long-term use.

The NDMA contents in the drug products used for the calculation were decided as follows:

- The highest NDMA content (28.7 ppm) of all lots from all MAHs was used for the short-term use because a short-term use dose not assume use of multiple product lots.
- Long-term use assumes use of multiple product lots. Therefore, the average NDMA content for lots for each of the individual drug products from relevant MAHs (0.24-5.91 ppm) was determined, and the highest average value (5.91 ppm) was used. For lots presenting values below the detection limit, the detection limit value was used in place of such values and an average was calculated.

(1) Assuming short-term use

Evidence-based Clinical Practice Guidelines for Peptic Ulcer 2015 (2_{nd} Edition) (compiled by the Japanese Society of Gastroenterology)[1] (hereinafter referred to as the “Guidelines”) stated regarding the administration of H_2 receptor antagonists in non-sterile treatment (initial treatment) for stomach ulcer or duodenal ulcer that high ulcer-healing rates are achieved with usual dosages (dosages covered by health insurance) for all drug products administered for 8 weeks for stomach ulcer and 6 weeks for duodenal ulcer.

300 mg/day was selected as the daily dose of ranitidine oral products based on the

[1] Although the Evidence-based Clinical Practice Guidelines for Peptic Ulcer 2020 (3_{rd} Edition) was published on July 15, 2020, the 2_{nd} Edition, which was used before the recall of ranitidine products, is used here.

dosage and administration of the package insert, suggestions in the Guidelines, and the results of DUS. 8 weeks was selected as the treatment duration of ranitidine products based on suggestions in the Guidelines and the results of DUS.

The risk with ranitidine oral products administered at 300 mg daily for 8 weeks is estimated as follows as the risk associated with exposure to NDMA at 8.61 µg/day for 0.153 year (56 days/365 days):

$(8.61 \div 0.0959)/(70 \text{ years} \div 0.153 \text{ year})\ 10^{-5} = 0.196 \times 10^{-5} \approx 1.9 \times 10^{-6}$.

The estimated risk corresponds to an excess risk of approximately 1 in 500 000 persons subjected to the exposure developing cancer during the person's lifetime (70 years) due to the exposure.

(2) Assuming long-term use

H_2 receptor antagonist is recommended in the Guidelines as one of the alternatives in non-sterile treatment (maintenance therapy) for stomach ulcer or duodenal ulcer, and treatment durations up to 1 year and up to 2 years were noted as effective for stomach ulcer and duodenal ulcer, respectively.

300 mg/day was selected as the daily dose of ranitidine oral products based on the dosage and administration of the package insert and the results of DUS.

2 years was selected as the treatment duration of ranitidine oral products based on the suggestions in the Guidelines and the results of DUS as the duration for duodenal ulcer, which is associated with a longer treatment duration than stomach ulcer.

The risk with ranitidine oral products administrated at 300 mg daily for 2 years is estimated as follows as the risk associated with exposure to NDMA at 1.773 µg/day for 2 years:

$(1.773 \div 0.0959)/(70 \text{ years} \div 2 \text{ years}) \times 10^{-5} = 0.528 \times 10^{-5} \approx 5.3 \times 10^{-6}$.

The estimated risk corresponds to an excess risk of approximately 1 in 200 000 persons subjected to the exposure developing cancer during the person's lifetime (70 years) due to the exposure.

1-2 Effects of receiving ranitidine injections

200 mg/day and 7 days were selected as the daily dose and treatment duration of ranitidine injections, respectively, based on the dosage and administration of the package insert and the results of DUS. For the NDMA contents of the drug products used in the calculation, the highest value (1.14 ppm) from the results of analysis of all the drug products was used because administration of a single lot is assumed in the use

of injections.

The risk with ranitidine injections administered at 200 mg daily for 7 days is estimated as follows as the risk associated with exposure to NDMA at 0.228 µg/day for 0.019 year (7 days/365 days):

$(0.228 \div 0.0959)/(70 \text{ years} \div 0.019 \text{ year}) \times 10^{-5} = 0.00065 \times 10^{-5} \approx 6.5 \times 10^{-9}$.

The estimated risk corresponds to an excess risk of approximately 1 in 150 million persons subjected to the exposure developing cancer during the person's lifetime (70 years) due to the exposure. The animal study that calculated TD_{50} was a study in which NDMA was orally administered to animals, potentially requiring correction in assessing the risk associated with exposure by injections. It was considered and decided that no correction for differences of administration route was necessary because of the known rapid absorption of NDMA from the digestive tract.

2. Effects of receiving nizatidine products

Similarly to ranitidine oral products, risk for cancer was calculated with nizatidine oral products in standard durations of use.

The NDMA contents in the drug products used for the calculation were decided as follows:

- The highest NDMA content (0.59 ppm) of all lots from all MAHs was used for the short-term use because a short-term use dose not assume use of multiple product lots.
- Long-term use assumes use of multiple product lots; therefore, among average NDMA content values for lots calculated for each of the individual drug products recalled by the MAHs (0.17, 0.20 ppm), the value (0.20 ppm) that indicated the highest risk was used. For lots presenting values below the detection limit, the detection limit value was used in place of such values and the average was calculated. Nizatidine products are only available in the oral dosage form and no injections are available.

(1) Assuming short-term use

300 mg/day was selected as the daily dose of nizatidine oral products based on the dosage and administration of the package insert and the results of DUS. 8 weeks was selected as the treatment duration of nizatidine oral products based on the suggestions in the Guidelines and the results of DUS.

The risk with nizatidine oral products administered at 300 mg daily for 8 weeks is

estimated as follows as the risk associated with exposure to NDMA at 0.177 µg/day for 0.153 year (56 days/365 days):

$(0.177 \div 0.095)/(70 \text{ years} \div 0.153 \text{ year}) \times 10^{-5} = 0.00403 \times 10^{-5} \approx 4.0 \times 10^{-8}$.

The estimated risk corresponds to an excess risk of approximately 1 in 25 million persons subjected to the exposure developing cancer during the person's lifetime (70 years) due to the exposure.

(2) Assuming long-term use

300 mg/day was selected as the daily dose of nizatidine oral products based on the dosage and administration of the package insert and the results of DUS. 2 years was selected as the treatment duration of nizatidine oral products based on the dosage and administration of the package insert, suggestions in the Guidelines, and the results of DUS.

The risk with nizatidine oral products administered at 300 mg daily for 2 years is estimated as follows as the risk associated with exposure to NDMA at 0.0615 µg/day for 10 years:

$(0.0615 \div 0.0959)/(70 \text{ years} \div 2 \text{ years}) \times 10^{-5} = 0.0179 \times 10^{-5} \approx 1.8 \times 10^{-7}$.

The estimated risk corresponds to an excess risk of approximately 1 in 5.6 million persons subjected to the exposure developing cancer during the person's lifetime (70 years) due to the exposure.

Discussions on the risk assessment

The calculations in the risk assessment for the cases of the exposure mentioned above are based on the assumption that Haber's rules are also valid in the short-term, in the order of weeks, compared to the lifetime exposure. However, understanding of the quantitative relationship between the risk for mutagenicity as a consequence of short-time exposure and the risk for carcinogenicity as a consequence of lifetime exposure is limited. ICH M7, for example, provides acceptable levels of exposure of impurities for administration for as short as 1 month and the values are simply 80-fold the acceptable levels for the lifetime exposure. In other words, the values are not calculated in a simple proportion to 70 years, or 840 months, of exposure. As for the correction of the risk in the cases of short-term exposure based on the lifetime exposure in the assessment of carcinogenic risk by overseas risk assessment agencies such as the U.S. EPA, examples of correction of the risk in exposures in the order of months or weeks have been scarce compared with the correction of the risk with exposures in the order of years. Consequently, it is considered reasonable to limit the

scope of Harber's rules to the correction of the risks with exposures for 1 year or longer when correcting the risk based on the lifetime exposure. Based on this limitation, for the estimation of the risk with exposures shorter than 1 year among the aforementioned cases of exposure, calculating the risk for 1 year on the assumption that the daily exposure value used in the estimation continues for 1 year, and concluding that the estimated risk would be less than the thus calculated risk for 1 year exposure should be the limit for quantitative risk estimation.

For example, the estimated risk with the short-term use of ranitidine will be less than $(8.61 \div 0.0959)/(70 \text{ years}) \times 10^{-5} \approx 1.3 \times 10^{-5}$.

The estimated risk with the use of ranitidine injections will be less than $(0.228 \div 0.0959)/(70 \text{ years}) \times 10^{-5} \approx 3.4 \times 10^{-7}$.

Therefore, the risk will be estimated as less than the risk of approximately 1 in 80 000 to 3 million persons subjected to the exposure developing cancer during the person's lifetime (70 years) due to the exposure.

The estimated risk with short-term use of nizatidine will be less than $(0.177 \div 0.0959)/(70 \text{ years}) \times 10^{-5} \approx 2.6 \times 10^{-7}$.

Thus, the risk will be estimated as less than the risk of approximately 1 in 3.8 million persons subjected to the exposure developing cancer during the person's lifetime (70 years) due to the exposure.

In conclusion, the risk for cancer with ranitidine is considered as follows:

- To be less than the risk of approximately 1 in 80 000 persons developing cancer if short-term use of ranitidine is assumed, and,
- to be approximately 1 in 200 000 persons developing cancer if long-term use is assumed.

Similarly, the risk for cancer with nizatidine is considered as follows:

- To be less than the risk of approximately 1 in 3.8 million persons developing cancer if short-term use of nizatidine is assumed, and,
- to be approximately 1 in 5.6 million persons developing cancer if long-term use is assumed.

References

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