Nitrosamines in ARBs – Major impact on generic drug quality and What is the culprit?

Recently, Thai FDA announced a voluntary recall of Angiotensin Receptor II Blockers (ARBs) for the treatments of high blood pressure and heart failure, namely losartan due to the contamination in active pharmaceutical ingredient (API) with carcinogenic nitroso compounds e.g. N-Nitrosodiethylamine (NDEA) and N-Nitroso-N-Methyl-4-aminobutyric acid (NMBA)[1]. As a result, this phenomenon raised awareness and lots of concerns from patients administered losartan. Whether they are exposed to those carcinogens and what they should do are very common questions brought up from patients and their relatives.

The nitrosamine phenomenon in ARBs is not a new story. In 2018, Thai FDA alerted healthcare professionals and patients on a voluntary recall in several drug products containing valsartan due to N-Nitrosodimethylamine (NDMA) contamination [2]. NDMA, NDEA, and NMBA are all categorized in the group of nitrosamines. More importantly, the questions are also raised from healthcare professionals and patients whether the risks still exist in different brands containing the recalled API and other ARBs drugs i.e. candesartan, irbesartan, olmesartan, etc. This article can help any interested readers answer all doubts in aspects of the pathway of nitrosamine formation, the risk factors in the ARBs manufacturing process, the health impact of nitrosamines, and recommendation for patients.

Nitrosamines and health impacts

Nitrosamines refer to an organic compound containing nitroso functional group and amino derivative shown in Figure 1. There are more than 300 compounds in nitrosamine group [3, 4] i.e. N-Nitrosodimethylamine (NDMA), N-Nitroso-N-Methyl-4-aminobutyric Acid (NMBA), N-nitrosopyrrolidine (NPYR), etc. International Agency for Research on Cancer (IARC) and the United States Environmental Protection Agency (US EPA) classified nitrosamine as a carcinogenic agent [5, 6]. A number of studies [7, 8, 9, 10] supported that nitrosamine can potentially induce several kinds of cancers in any organs e.g. liver, kidney, esophagus, and respiratory tract.

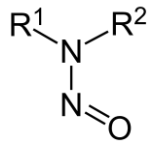

Figure 1 Nitrosamine chemical structure

Source of nitrosamine and formation pathway

A trace amount of nitrosamine can generally be found in the air, water, and food. However, a high concentration of nitrosamine is presented in processed meat (e.g., bacon, sausages, ham), grilled or fermented food (e.g., beer, cheese). Regarding cured meat, sodium nitrate is an additive ingredient used as a preservative to keep natural meat have fresh appearance, desirable odor, and appetizing taste. Nitrate is reduced to nitrite by nitrate reductase enzyme, which may be produced from a number of bacteria presented in meat. Nitrite can cause nitrosation on amines from natural meat under acidic condition during processing, cooking, and storage to form nitrosamine[4]. The higher amount of sodium nitrate is added, the higher risk for nitrosamine contamination is produced. High amount of nitrosamine can also be found in rubber, tanning, or steel industry [12] and can be cross-contaminated in drinking water and food. In some research studies, there are data demonstrating that daily intake of nitrosamine on average from food is 1 µg per person per day [11].

Nitrosamine forming factors in ARBs antihypertensive drug class

There are 3 critical factors involved in the nitrosamine formation process– sodium nitrite acting as a nitrosating agent, amine acting as substrate, and acidic condition as the most preferable environment for the reaction. Chemically, nitrosamine formation is apparently found in the API raw material manufacturing process. Route of API synthesis having 3 factors as previously mentioned has a high risk of API nitrosamine contamination in no doubt. In other words, only ARBs finished products which used APIs obtained from the high-risk manufacturing process consisting of three factors (sodium nitrite, amine derivative, and acidic condition) has possibly nitrosamine contaminated in a drug product. A lack in one

of those three factors is not possible for nitrosamine formation during API synthesis.

Three probable carcinogens had already been identified in the ARBs APIs. The impurities were formed during API synthesis in two manufacturers located in China and India[1, 2]. Both manufacturing processes contained 3 critical factors. As a result, Thai FDA announced voluntary recalls products containing valsartan and losartan from generic manufacturers that used defect APIs in the certain lot numbers.

European Medical Agency (EMA) disclosed that NDMA can be generated during the formation of the tetrazole ring by reaction of dimethylamine, which may be present as impurity or degradant in the reaction solvent of dimethylformamide (DMF) and sodium nitrite under acidic conditions (where nitrous acid is formed) (green box in Figure 2). [14] Similarly, NDEA and NMBA can be generated from other sources of amines in the tetrazole ring synthetic step. The proposed amine for NDEA formation is diethylamine, which may be present as impurity or degradant in the triethylamine reagent often used in ARBs synthesis e.g. losartan and irbesartan (red box in Figure 2). N-methyl 4-aminobutyric acid contaminated in N-methyl-2-pyrrolidone can probably cause the NMBA formation in the same scenario (blue box in Figure 2). Figure 2 also illustrates NMBA, NDEA, and NDMA formation pathways in the tetrazole ring forming process of the ARBs synthesis. In this step, Sodium azide (NaN3) is added in order to create the tetrazole functional group, which is an importance pharmacophore in ARBs drug class. As a consequence, sodium nitrite (NaNO2) is essentially added to quench the unreacted sodium azide. Accidentally, it also becomes a critical factor in the nitrosamine generation. To avoid using sodium nitrite in the reaction can, therefore, prevent nitrosamines formation. Alternatively, unreacted sodium azide must be taken care of by other clean-up processes e.g. acid-base extraction or future recrystallization. On the other way, the change of reaction solvents or reagent by not having the use of dimethylformamide (DMF) or triethylamine can avoid NDMA and NDEA formation due to the lack of the corresponding source of amine.

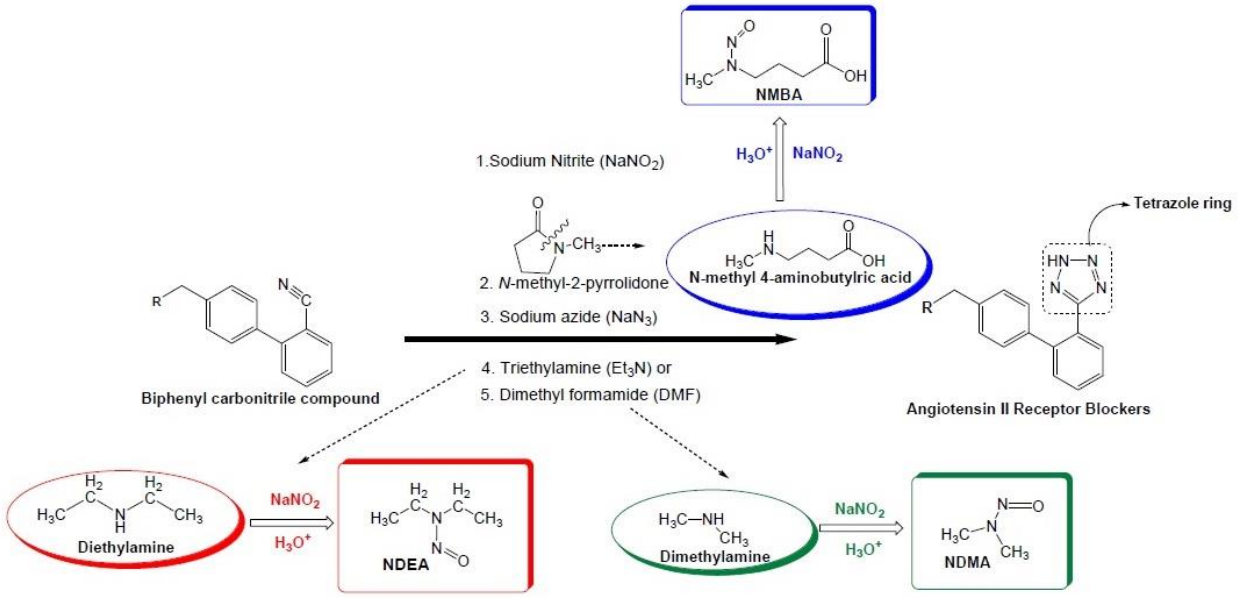

Figure 2 NMBA, NDEA, and NDMA formation pathway in the tetrazole ring building for ARBs drug class.

Recommendation for healthcare professionals and patients

To avoid nitrosamine exposure, processed or grilled meat should be refrained in a typical habit of consumption. The intake of vitamin C-enriched fruits and vegetables i.e. orange, guava, etc. may inhibit the formation of nitrosamine and antioxidation properties of vitamin C can also reduce the free radicals generated from nitrosamine [13]. Nevertheless, high dose administration of Vitamin C is not recommended because it may lead to harmful toxicity e.g. nausea, vomiting, and gastritis.

In case of drug recall situation, patients who are on anti-hypertensive medicine must check the product trade name, manufacturer details, and the product batch or lot number whether they match with those recall announced by Thai FDA. If so, the patients should take the medicine to exchange for different lot numbers or different brands at the hospitals or pharmacy stores where the medicine has been prescribed. If patients are unable to exchange the medicine

immediately, they should not abruptly withdraw medicine because of the increased life-threatening risk.

Furthermore, the studies showed that NDMA, NDEA, and NMBA caused cancer risk in animals in long-term exposure. Short-term exposure to NDMA, NDEA, and NMBA did not increase cancer risk. More importantly, no studies have shown the effect on human yet. Despite the fact that the FDA specifies certain lot numbers and manufacturers in each recall, the proper response to, and recognition of, FDA reports may be uneven. Patients might receive the recall information via social media, internet, friend or others. It may lead to misunderstanding in details or assume that all hypertensive drugs, all trade names are contaminated with a carcinogen resulting in the discontinued treatment. Therefore, it is the responsibility of healthcare professionals e.g. clinicians, pharmacists and even technicians from manufacturers to educate and give an explanation to the patients and drug consumers. Stop taking medicines without clear inspection or drug switching without adequate data from a physician may cause treatment failure and uncontrolled hypertension. All in all, consumers should closely follow the news and the notification from the trustworthy media or Thai FDA website in order to gain updated news.

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