REVIEW ARTICLE

Folia Cardiologica 2019
vol. 14, no. 6, pages 564–571

ISSN 2353–7752

The antihypertensive drugs and contamination with carcinogenic nitrosamines

Leki przeciwnadciśnieniowe a skażenie rakotwórczymi nitrozoaminami

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Artykuł jest tłumaczeniem pracy: Tatarkiewicz J, Bujalska-Zadrożny M. Leki przeciwnadciśnieniowe a skażenie rakotwórczymi nitrozoaminami. Folia Cardiol. 2019; 14(6): 556–563. DOI: 10.5603/FC.a2019.0109. Należy cytować wersję pierwotną

Abstract

At the end of June 2018, small amounts of a highly carcinogenic N–nitrosamine, N–nitrosodimethylamine (NDMA), were found to contaminate some angiotensin receptor blockers (sartans) used for the treatment of arterial hypertension. By July 2019, four N-nitrosamine impurities were identified in sartans, including NDMA, N–nitrosodiethylamine, N–nitrosodiisopropylamine and N-nitroso-N-methyl-4-aminobutyric acid. Seven manufacturers of three contaminated active substances (valsartan, losartan and irbesartan) from China, India and Mexico were also identified. These compounds had infiltrated the active pharmaceutical ingredients probably as a consequence of ill-considered synthesis modifications. The number of people who have been prescribed contaminated valsartan alone has been estimated at around 20 million worldwide.

This paper discusses the therapeutic role of sartans in the context of the physiological significance of the renin–angiotensin–aldosterone system as well as the role of tetrazole moiety in the mechanism of sartan receptor activity. The synthesis of tetrazole moiety and its modifications have been characterized as possible causes of the appearance of nitrosamine impurities in sartans. The toxicological properties of nitrosamines are also briefly outlined. The fact that nitrosamines had been entering medicines for at least five years undetected and outside the knowledge of the authorities responsible for drug safety has exposed a gross malfunctioning of the system intended to guarantee the safety of medicinal products. As a result, the valsartan scandal has forced changes to some drug regulations, in particular the requirements for analytical procedures.

Key words: sartans, active pharmaceutical ingredient contamination, nitrosamines, chemistry of tetrazoles

Folia Cardiologica 2019; 14, 6: 564–571

Introduction

In July 2018, the public opinion worldwide has been alarmed by detection of small amounts of potentially highly carcinogenic N–nitrosamines in some angiotensin II receptor AT_1 blockers (sartans) used for the treatment of arterial hypertension. These contaminations had been entering medicines for at least five years undetected and outside the knowledge of the authorities responsible for drug safety, and the number of people who have been prescribed contaminated valsartan alone was estimated in January 2019 at around 20 million worldwide [1]. The

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underlying cause was an ill-considered modification of the synthesis of tetrazole ring, present in the structure of most sartans, which is formed during one of the last steps of sartan synthesis. As a result, many sartan lots were recalled from the market in multiple countries, and companies producing both pharmaceutical products and their active ingredients were subjected to inspections. These events have had ongoing consequences, and investigations have been undertaken to evaluate the true size of this problem and the number of exposed people, and to determine the underlying causes [2–5].

The present paper discusses likely chemical mechanisms of N–nitrosamine contamination, its toxicological and analytical aspects, and also provides the necessary background pharmacological and physiological information.

Detected N–nitrosamines, contaminated active pharmaceutical ingredients and their manufacturers

In June 2018, the Food and Drug Administration (FDA) received information that an U.S. company, Prinston Pharmaceuticals Inc., dba Solco Healthcare LLC., stopped manufacturing its valsartan products, as trace amounts of N–nitrosodimethylamine (NDMA) were detected in an active ingredient purchased from one of its manufacturers in China, Zhejiang Huahai Pharmaceutical Co., Ltd. (ZHP). On July 17, 2018, the company voluntarily recalled all its valsartan products from the market [6, 7]. During the same month, also the European Union (EU) authorities were informed that ZHP detected the presence of previously unnoted technological contamination with NDMA in an active pharmaceutical ingredient (API), valsartan manufactured in a factory in Chuannan, China [8]. Detection of NMDA in valsartan initiated the so-called valsartan scandal and resulted in inspections performed in many countries that included not only a growing number of valsartan product lots (with their subsequent recall in large amounts, including of fixed-dose combinations, in several dozen countries [3]) but also other sartan products and API suppliers, as the regulatory authorities believed it was necessary to inspect closely all substances utilised during the drug synthesis. As a result, other nitrosamines in addition to NDMA, including N–nitrosodiethylamine (NDEA), N–nitrosodiisopropylamine (NDIPA) and N–nitroso-N-methyl-4-aminobutyric acid (NMBA) were soon detected in several other sartans. The extent of the recall increased, and the number of manufacturers of contaminated API grew to seven in three different countries. Details on location and sources of API contamination are shown in Table 1.

The therapeutic importance of sartans calls for a summary of the physiological and pharmacological background of their action.

Physiological role of the renin–angiotensin–aldosterone system and the effect of sartans on this system

The renin–angiotensin–aldosterone system (RAAS), a hormonal and enzymatic system activated by a renal hormone renin, is one of the most important body systems regulating vascular smooth muscle tone and water and electrolyte balance (and thus also blood pressure). Increased RAAS activity leads to increased vascular smooth muscle tone, reduced urinary sodium and water excretion, and increased urinary potassium excretion, all leading to an increase in blood pressure [9, 10].

The key pressor RAAS component is an octapeptide angiotensin II (Ang II) which increases blood pressure mostly by activating specific angiotensin II type 1 receptor (AT_1R). Understanding of the role of Ang II in the regulation of the cardiovascular system (CVS) led to a search for synthetic compounds with a high affinity for AT_1R, characterized by a significant structural resemblance to Ang II but lacking its agonist effect. As the initial attempts to develop peptide structure-based drugs failed, researchers focused on compounds containing several connected rings, the structure of which in body fluids bore sufficient resemblance to the stereochemical structure of aminoacids forming Ang II. This has led to the development of losartan (on the market since 1994), followed by other non-peptide AT_1R antagonists, also known as sartans, that entered the clinical practice. Currently, more than ten sartans are available, including azilsartan, eprosartan, irbesartan, candesartan, losartan, olmesartan, telmisartan and valsartan that have been marketed in Poland/EU. They are indicated for several clinical conditions — all are used to lower blood pressure in arterial hypertension (AH), and some have been licensed to treat heart failure (HF) or left ventricular systolic dysfunction, concomitant renal disease in patients with AH and diabetes type 2, and prevention of stroke in adult patients with AH. Valsartan, which is the major sartan discussed in the present paper, is used in Poland for the treatment of essential AH, some cases of symptomatic HF in adults, and asymptomatic left ventricular systolic dysfunction after recent myocardial infarction. Currently, a significant trend can be observed to extend indications for sartans beyond CVS treatment [11].

Structural components of sartans and their receptor binding

To provide desired angiotensin receptor antagonist effects at the molecular level, *i.e.*, binding to AT_1R and blocking this receptor, the structure of most sartans used in the clinical practice includes several main functional moieties, of which most important are three: a biphenyl-methyl moiety forming

Table 1. List of contaminated sartans including manufacturers of drugs with contaminated active pharmaceutical ingredient (API) and the timing of impurity reporting

Sartan	Impurity	Manufacturer of contaminated API (name and country)	Reporting agency	Date* of impurity reporting and reference***
Valsartan	NDMA	ZHP, China	US FDA	June 2018 [6, 7]
			EMA following ZHP	June 2018 [8]
		ZTP, China	EMA, EDQM**	10.08.2018 [a]–28.08.2018 [b]
		ZChP, China	EDQM**	28.08.2018 [b]
		Hetero Labs, India	EDQM**	28.08.2018 [b]
			US FDA	20.12.2018 [c]
Valsartan	NDEA	ZHP, China	EMA, US FDA	13.09.2018 [d, e]
		Mylan, India	EMA, EDQM**	19.11.2018 [f, g]
			US FDA	21.11.2018 [h]
		Aurobindo, India	EDQM**	Before 24.12.2018 [i]
			US FDA	2.01.2019 [j]
Valsartan	NDIPA	*Signa S.A.*, Mexico	TGA, EDQM**	18.12.2018 TGA [i, k]
Irbesartan	NDEA	*Aurobindo*, India	EDQM**	Before 8.10.2018 [l]
			EMA, US FDA	15.10.2018 [m]–30.10.2018 [n]
		ZHP, China	EDQM**, FDA	18.01.2019 [o, p]
Losartan potassium	NDEA	ZHP, China	US FDA	9.11.2018 [r]
			EDQM**	18.01.2019 [o]
		Hetero Labs, India	EDQM**,	Before 17.10.2018 [l]
			EMA,	Before 21.09.2018 [s]
			US FDA	25.02.2019 [t]
Losartan potassium	NMBA	*Hetero Labs*, India	EDQM**, FDA	4.02.2019 [u]–28.02.2019 [w]

*First reporting of a given impurity by a drug agency in general or the first reporting of an impurity in API from a given manufacturer. Due to differences in dates reported in references, dates shown in the table should be considered approximate; **in cases monitored by the European Directorate for the Quality of Medicines & HealthCare (EDQM), this agency immediately suspended manufacturers' certificates of suitability (CEP) that confirm compliance with the European Pharmacopoeia requirements; by this mechanism, 11 CEP were suspended by mid-May 2019; ***due to their large volume, references to materials published by the United States Food and Drug Administration (US FDA), European Medicines Agency (EMA), EDQM and other agencies that appear only in Table 1 and not in the main text are available in a supplementary file available on-line. These references are marked with alphabet letters in square brackets, in the order of their appearance in the table; *Aurobindo* — Aurobindo Pharma Limited (India); *Hetero Labs* — Hetero Labs Limited (India); *Mylan* — Mylan Laboratories Ltd. (India); NDEA — N–nitrosodiethylamine; NDIPA — N–nitrosodiisopropylamine; NDMA — N–nitrosodimethylamine; NMBA — N–nitroso-N-methyl-4-aminobutyric acid; *Signa S.A.* — Signa S.A. de C.V. (Toluca, Mexico, member of Apotex Pharmachem Group); TGA — The Therapeutic Goods Administration (Australia); ZChP — Zhejiang Changming Pharmaceutical Co., Ltd. (China); ZHP — Zhejiang Huahai Pharmaceutical Co., Ltd. (China); ZTP — Zhejiang Tianyu Pharmaceutical Co., Ltd. (China)

the basic axis of sartan structure (of eight sartans listed above, only eprosartan is lacking this moiety), imidazole ring (absent only in valsartan), and aromatic 1H-tetrazole or 2H-tetrazole moiety at the 5-position [12]. The three above moieties bind to various domains of AT_1R [13]. The tetrazole moiety seems of key importance as its presence is particularly important for the sartan antagonist effect on AT1R [13]. The tetrazole moiety is present in five (irbesartan, candesartan, losartan, olmesartan, valsartan) of eight sartans that have been widely marketed [12].

Structure of tetrazole moiety and its location in the sartan structure

The above mentioned functional moieties responsible for the action of sartans at the molecular level are shown in Figure 1, depicting the structure of valsartan, and in Figure 2, depicting the structure of the first developed drug of this class, losartan. In the valsartan molecule, N-acyl valine has been substituted for the imidazole ring.

Synthesis of the tetrazole moiety

Sartans can be synthesized by various pathways [14–16], and the selected method affects the possibility of formation of dangerous by-products. To understand the process of sartan N–nitrosamine contamination, it is necessary to review synthesis of the tetrazole ring, as N–nitrosamines may be generated during that step. Tetrazole ring synthesis in sartan molecules is based on a general principle whereby nitrils (organic hydrogen cyanide [HCN] derivatives, R-CN) may react, using various methods, with some organic or

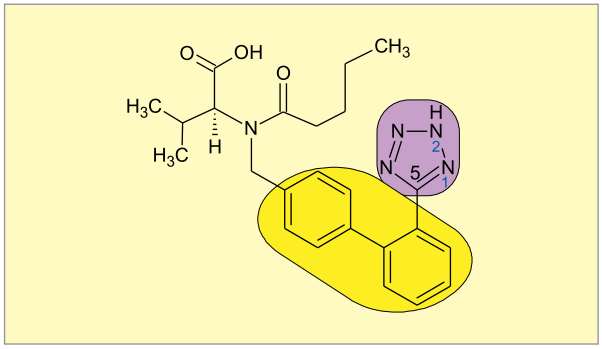

Figure 1. Structural formula of valsartan or N-(1-oxopentyl)-N-[[2'-(2H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-L-valine (International Union of Pure and Applied Chemistry [IUPAC] name: (S)-3-methyl-2-(N-{[2'-(2H-1,2,3,4-tetrazol-5-yl)biphenyl-4-yl]methyl}pentanamido) butanoic acid). Functional moieties providing the angiotensin II receptor antagonist effect at the molecular level were marked in colours: the biphenyl-methyl moiety with yellow; the 2H-tetrazole moiety at the 5-position with purple. Only selected atoms relevant for the text discussion are numbered

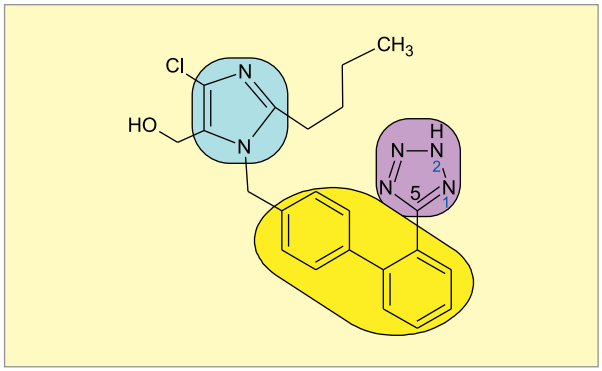

Figure 2. Structural formula of losartan or (2-butyl-4-chloro-1-{[2'-(2H-tetrazol-5-yl)biphenyl-4-yl]methyl}-1H-imidazol-5-yl)methanol (IUPAC name). Functional moieties providing the angiotensin II receptor antagonist effect at the molecular level were marked in colours: the biphenyl-methyl moiety with yellow; the imidazole ring with blue; the 2H-tetrazole moiety at the 5-position with purple. Only selected atoms relevant for the text discussion are numbered

inorganic azides (hydrogen azide [HN_3] derivatives), leading to the formation of tetrazole derivatives.

One of the most commonly used methods to synthesize the tetrazole ring in sartan molecules (including that of valsartan) is a reaction that uses an organic azide, azido(n-tributyl)stannane or tri(n-butyl)tin azide, commonly known as tributyltin azide [17]. This reaction involves adding tributyltin azide (Figure 3B) to a nitril compound (Figure 3A) that is an intermediate molecule in the valsartan synthesis pathway, which yields a stannyl tetrazole compound (Figure 3C) [18].

Following the above reaction, the only next step needed is hydrolysis of the resultant stannyl tetrazole compound (Figure 3C), yielding the actual API — valsartan.

Possible causes of sartan contamination with N–nitrosamines

In addition to the above method of sartan synthesis, other methods to synthesize the tetrazole ring exist, including those based on the reactions of nitrils with organic or inorganic azides described above [19, 20]. These multiple pathways leading to the same end-product create an opportunity to introduce many technologically simple modifications of the sartan synthesis process, including that of valsartan, even within the same patent-protected solution (*see, e.g.,* patents number CN104045602A [20] and WO2012001484A2 [21]). In fact, some changes in reagents or solvents are often allowed in patent specifications. However, if all potential side reactions are not foreseen, such modifications may lead to errors in synthesis, which was likely the cause of sartan contamination with N–nitrosamines.

A wide search of patent specifications performed by German authors Buschmann and Holzgrabe [18] after detection of nitrosamines in valsartan has indicated with a high likelihood that the Chinese manufacturer, ZHP, had modified the process of synthesis previously using tributyltin azide which led to formation of N–nitrosamines. In this modification (Figure 4), tributyltin azide (Figure 3B) used for the nitril reaction was replaced with much cheaper sodium azide (NaN_3). This could have been concluded, among others, based on the fact that in 2014, ZHP published the patent number CN104045602A (translated title: "Improved method to synthesize the tetrazole moiety of valsartan"), in which it patented an improved synthesis method without the use of an organic tin compound [20, 22]; this also indicates an economic background of this change. For simplification, the schematic representation of this reaction in Figure 4 shows hydrogen azide (HN_3) which is created in an acidic environment from sodium azide added to the reagent mixture. Following this reaction, similarly to the process described above, the resultant tetrazole derivative is hydrolyzed (Figure 4C) to create the actual API — valsartan.

Sodium azide used for this synthesis modification is a salt, and thus it poorly dissolves in organic solvents that are usually used for the synthesis of the tetrazole moiety, such as dimethylformamide (DMF) [19]. Probably also for that reason, sodium azide was added to the reagent mixture in some excess, which in turn necessitated later removal of unreacted sodium azide by adding sodium nitrite ($NaNO_2$), as could be concluded from one of the patents [20, 22] which also recommends adding sodium nitrite in an excess due to toxicity of sodium azide. Sodium nitrite

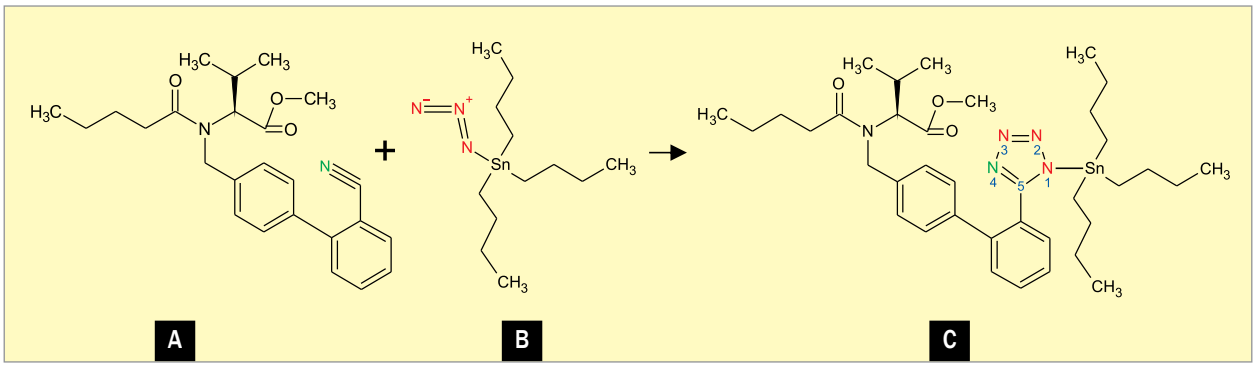

Figure 3. Synthesis of the tetrazole ring at the 5-position during the conventional valsartan synthesis process. Nitrogen atoms forming the tetrazole ring are marked with colours: **A.** Nitril compound; **B.** Tributyltin azide; **C.** Stannyl tetrazole compound

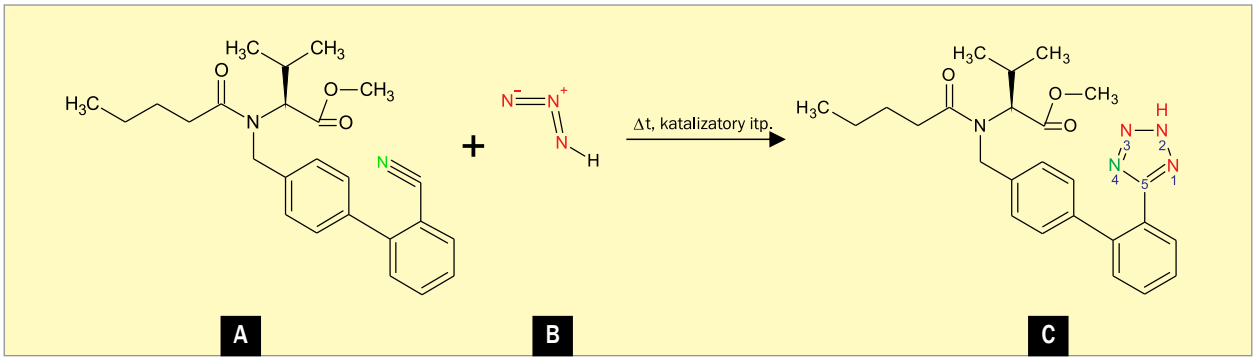

Figure 4. A simplified scheme of a tetrazole derivative synthesis from a respective nitrile and hydrogen azide released from sodium azide during an alternative valsartan synthesis process. Nitrogen atoms forming the tetrazole ring are marked with colours: **A.** Nitril compound; **B.** Hydrogen azide. **C.** Resultant compound (valsartan methyl esther) with tetrazole moiety at the 5-position

is a water-soluble salt, known for years as a reagent which may generate N–nitrosamines, particularly in the presence of secondary amines [23].

Further investigations seem to suggest that the other necessary factor that contributed to valsartan contamination with N-nitrosamines was the use of DMF as a solvent, releasing a secondary amine (mostly dimethylamine [DMA]), present either as an impurity and/or as a breakdown product due to specific reaction conditions.

Thus, two compounds that quite easily react with each other with formation of N–nitrosamines were simultaneously present in the reagent mixture. Sodium nitrite left after neutralization of azide may enter secondary/undesirable reactions, including N–nitrosylation of organic amines which leads to the formation of N–nitrosamines [24, 25]. In this way, NDMA is formed by a reaction of sodium nitrite with DMA [18], NDEA by a reaction of nitrites with triethylamine (TEA) which is used in some sartan synthesis processes, and NDIPA found in valsartan manufactured by Signa S.A. de C.V. is formed by a reaction of nitrites with diisopropylamine (DIPA), also used in some sartan synthesis processes [8, 26]. Finally, NMBA detected in losartan potassium manufactured by Hetero Labs is generated by the reaction between nitrities and a cyclic tertiary amine used as a solvent, N-methyl-2-pyrrolidone (NMP) [8].

In summary, a modification introduced by some API manufacturers, whereby sodium azide was substituted for tributyltin azide — along with an unfortunate choice of solvents/reagents — has likely been the major factor responsible for formation of toxic N–nitrosamines.

Toxicity of nitrosamines

N–nitrosamines show mutagenic, teratogenic/embryotoxic, and genotoxic properties. In addition, they exert a very potent carcinogenic effect, and may damage the liver [23]. Since Barnes and Magee had discovered carcinogenic properties of NDMA (leading to the development of hepatic tumours) in 1956, more than 300 nitrosamines were tested and about 90% of them (approximately 300 compounds) were found to be carcinogenic in many animal species [27, 28]. N–nitrosamines are commonly present in the

human environment, for example in cold cuts and smoked meats, tobacco smoke, purified drinking water, rubber, and some plastics [27, 29].

N–nitrosamines are pre-carcinogens metabolized in the body to actual carcinogens, in particular carbenium cations, which show potent alkylating properties towards purine and pyrimidine bases present in proteins and nucleic acids (DNA, RNA) [24, 27]. This explains the mutagenic and carcinogenic effects of most N-nitrosamines and their toxicity already at very low levels, even as low as 1 μg/L [24].

However, when comparing the lowest concentrations required for the carcinogenic effect of NDMA in animal experiments with average exposure in humans, it has been found that the average daily exposure (from foods and water) in Western countries is many times lower that the no observed effect level (NOEL) in animals, although the number of animals in the cited experiments has been admittedly limited [27].

It has been estimated that in Western Europe, the average individual daily consumption of volatile nitrosamines is 0.2–0.3 μg [27]. In summer 2018, some valsartan samples were found to contain 3.4 to 120 ppm NDMA (average 66.5 ppm) [27]. It has been calculated that with nitrosamine contamination at the level of 120 ppm (= 120 μg/g), a daily sartan dose of 160 mg would contain as much as 19 μg of NDMA in one tablet. Compared with the daily dose consumed with food, taking just one tablet containing contaminated valsartan would thus mean that N–nitrosamine consumption is increased many times compared to the usual intake [27]. Taking into account that N–nitrosamines are toxic already in the ppm range doses, it has been clear that many processes of sartan synthesis must undergo or is already undergoing strict verification.

Analytical aspects

Many methods are available to detect even very low levels of N–nitrosamines. In addition, many new actions have been taken after these compounds were detected in sartans. Official Medicines Control Laboratories (OMCL) collaborating within the General European OMCL Network (GEON) have rapidly developed various methods for detecting trace amounts of NDMA and NDEA in valsartan and other sartans. Participants in this project included the Irish Public Analyst's Laboratory in Galway (PALG), French OMCL in the Montpellier Agence National de Sécurité de Medicament et de Produits de Sante (ANSM), and the German Chemischen und Veterinäruntersuchungsamt (CVUA) in Karlsruhe; a short summary of the introduced methods has been provided in the paper by Buschmann and Holzgrabe [26]. In the future, comprehensive monitoring of the drug synthesis process using analytical methods, taking into account all known and potential (including theoretical) impurities at the each step of API manufacturing, will be crucially important [26].

Summary and conclusions

An ill-considered modification of the valsartan synthesis process by some API manufacturers has led to the so-called "valsartan scandal" related to the detection of trace amounts of carcinogenic N–nitrosamines both in the drug products and APIs. On one hand, this situation drew attention to the manufacturing processes of these drugs and withdrawal of contaminated products, but on the other hand, it also provoked fear of sartans in general, also those synthesized using methods not associated with the formation of toxic N–nitrosamines. Sartans remaining on the market are tightly monitored by drug safety agencies, and the resulting detailed toxicological analyses of potential (both identified and theoretically possible) impurities have allowed establishing updated requirements for the drug product composition. An example of such new regulations resulting from the valsartan scandal are new monographs of tetrazole ring-containing sartans published on July 1, 2019 (effective Jan 1, 2020), included in the European Pharmacopoeia, 10th edition [30, 31] and specifying, among others, acceptable levels of N–nitrosamines in the transition period. After this period (*i.e.*, since April 2021) sartans will not be allowed to contain detectable amounts of NDMA and NDEA, equivalent to less than 0.03 ppm (μg/g) [32]. It has also been noted that the manufacturing processes of other drugs which might also lead to the formation of N–nitrosamines need to be similarly investigated.

Conflict of interests

The authors declare no conflict of interests.

Streszczenie

Pod koniec czerwca 2018 roku w niektórych lekach z grupy antagonistów receptora AT_1 dla angiotensyny II (sartanów) stosowanych w nadciśnieniu tętniczym wykryto niewielkie ilości silnie rakotwórczego zanieczyszczenia N-nitrozodimetyloaminą (NDMA) z grupy N-nitrozoamin. Do lipca 2019 zidentyfikowano łącznie cztery N-nitrozoaminy stanowiące zanieczyszczenia sartanów — NDMA, N–nitrozodietyloaminę, N–nitrozodiizopropyloaminę oraz kwas N-nitrozo-N-metylo-4-aminomasłowy, a także siedmiu wytwórców trzech skażonych substancji czynnych (walsartanu, losartanu, irbesartanu) pochodzących z Chin, Indii oraz Meksyku. Związki te przedostawały się do produktów leczniczych prawdopodobnie wskutek nieprzemyślanych modyfikacji syntezy. Liczbę osób, którym przepisano sam skażony walsartan, w skali światowej szacuje się na około 20 milionów.

W pracy omówiono miejsce sartanów w leczeniu w kontekście fizjologicznego znaczenia układu renina–angiotensyna–aldosteron oraz rolę ugrupowania tetrazolowego w mechanizmie ich działania receptorowego. Scharakteryzowano syntezę ugrupowania tetrazolowego oraz jej modyfikacje jako możliwe przyczyny pojawienia się zanieczyszczeń nitrozoaminowych w sartanach. Pokrótce przedstawiono także toksykologiczne właściwości nitrozoamin. Fakt, że związki te przedostawały się do leków przez co najmniej 5 lat niewykryte i bez wiedzy organów odpowiedzialnych za bezpieczeństwo leków, obnażył rażące niedostosowanie do rzeczywistości systemu mającego gwarantować bezpieczeństwo produktów leczniczych. Dlatego „afera walsartanowa" wymusiła zmiany niektórych regulacji dotyczących leków, zwłaszcza wymagania dotyczące procedur analitycznych.

Słowa kluczowe: sartany, zanieczyszczenia substancji czynnych leków, nitrozoaminy, chemizm pochodnych tetrazolu

Folia Cardiologica 2019; 14, 6: 564–571

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