REVIEW

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Cross-reactivity of triptans and sulfonamide antibiotics – a clinically relevant question?

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After repeated inquiries from patients whether sulfonamide antibiotic allergy should be considered in the context of taking a triptan, we present here the pharmaceutical background, the chemical structure of triptans, and the clinical relevance in a narrative review. In fact, evidence-based cross-reactivity referring to the well-known allergic reaction of sulfonamide antibiotics has not been described so far.

1. Triptans in clinical use

Triptans are serotonin (5-HT) derivatives used as first-line therapy for acute migraine with and without aura and for cluster headache (Diener et al. 2022). They act agonistically at subtypes of 5-HT receptors (Nicolas and Nicolas 2023). Activation of the 5-$HT1_B$ receptor on vascular smooth muscle results in vasoconstriction of intracranial and extracerebral arteries that are dilated during a migraine attack. The release of vasoactive neuropeptides such as substance P or calcitonin gene-related peptide (CGRP) is inhibited by agonism at the 5-$HT1_D$ receptor on the trigeminal nerve. This reduces perivascular inflammation during the migraine attack in the intracranial vessels and the dura mater. Additionally, nociceptive neurotransmission within the brainstem and upper spinal cord is inhibited (Nicolas and Nicolas 2023). Within their drug class, triptans vary in their affinity for the 5-$HT1_F$ receptor, which also suppresses CGRP release and nociceptive modulation (Sacco et al. 2022). Substances which act primarily agonistically at the 5-$HT1_F$ receptor are called ditanes (Diener et al. 2022).

All seven triptans on the market worldwide are approved in Germany and are available in four different forms of administration (tablet, melting tablet, nasal spray, subcutaneous injection). Although triptans are widely used, up to one-third of patients remain inadequately treated with triptans because they do not experience sufficient efficacy after taking them or complain of side effects (Sacco et al. 2022). National guidelines also point out that in case of non-response to triptans, the correct time of intake should be considered, the dose can be increased, the dosage form or the triptan can be changed to achieve sufficient efficacy (Diener et al. 2022). Response to treatment with triptans is highly variable within the drug class, and failure to achieve sufficient efficacy also appears to be associated with concomitant symptoms such as nausea, sensitivity to light and noise or depression (Kourlas and Morey 2007).

Although some triptans are available orally as tablets (in Germany: sumatriptan 50 mg, naratriptan 2.5 mg, almotriptan 12.5 mg) without prescription, there have been only few reports of serious side effects (Diener et al. 2022). Most commonly described are nausea, dizziness, paresthesia, neck pain, and flushing especially after subcutaneous administration, also called "triptan sensations " (Nicolas and Nicolas 2023). Extremely rarely, myocardial infarction (Nicolas and Nicolas 2023), stroke (Diener et al. 2022), or arrhythmias (Nicolas and Nicolas 2023) occur due to vasoconstriction of coronary and limbic arteries. The contraindication for coronary artery diseases such as a history of myocardial infarction or stroke, hypertension, angina pectoris or peripheral arterial disease (Diener et al. 2022) is also based on these events. Other precautions include age > 65 years, hepatic and renal impairment, pregnancy and lactation (Nicolas and Nicolas 2023).

2. Triptans as sulfonamides

Sumatriptan, almotriptan, naratriptan have a sulfonamide structural component in their chemical structure. This structural component is characterized by a nitrogen atom bound to a sulfur atom carrying two double bound oxygen atoms (Fig.1).

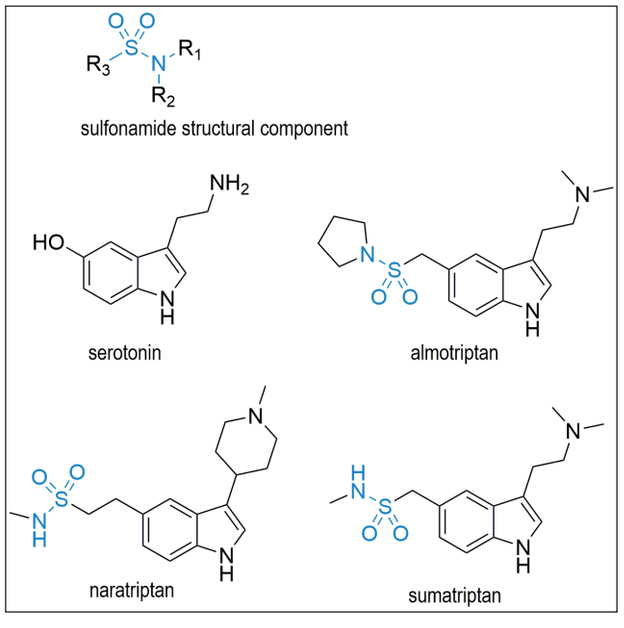

Fig. 1: Triptans as serotonin derivatives with a sulfonamide structural component (Gelbe Liste)

This structural component is also known from other drug classes (Fig. 2), with sulfonamide antibiotics being the best known due to their allergenic properties (Kourlas and Morey 2007). Sulfonamides can be structurally classified into three groups. For

example, the para-aminobenzenesulfonamides with a substituent at the nitrogen atom of the sulfonamide structural component are sulfonamide antibiotics (**A**)(Kourlas and Morey 2007). Here, the sulfur atom of the sulfonamide structural component additionally carries an aromatic with a nitrogen atom in para position to the sulfur atom. The nitrogen atom of the sulfonamide structural component is bound to at least one other structural component. The second group of sulfonamides looks structurally the same, but the nitrogen atom of the sulfonamide structural component remains unsubstituted such as in carbonic anhydrase inhibitors, cyclooxygenase 2 (COX-2) inhibitors, loop diuretics, thiazides, sulfonylureas, and protease inhibitors (**B**). Agents of the third group of sulfonamides are characterized only by the sulfonamide structural component such as the triptans (**C**)(Kourlas & Morey, 2007) (Fig. 2).

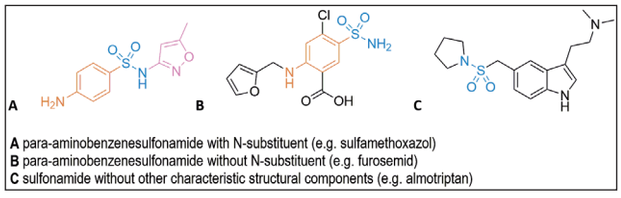

Fig. 2: Structural classification of the sulfonamides (Kourlas and Morey 2007)

3. Sulfonamide antibiotics allergy

It is suggested that 3-6 % of the population are affected by sulfonamide antibiotic allergy (Wulf and Matuszewski 2013), which could only be diagnosed by provocation tests (Dorn et al. 2018) and by patient's medical history (Chow and Khan 2022). Its symptoms are varied and manifest e.g. as urticaria, angioedema or even anaphylactic shock (Wulf and Matuszewski 2013). Especially the differentiation from an adverse reaction that is not based on an immunological reaction as well as the insufficient sensitivity and specificity of provocation tests are a challenge in the diagnosis (Dorn et al. 2018). For causal therapy, a well-tolerated and effective desensitization is available, while the immediate allergic reaction is treated only symptomatically (Chow and Khan 2022).

Two predominant mechanisms for the development of the allergic reaction to sulfonamide antibiotics such as trimethoprim-sulfamethoxazol (TMP-SMX), sulfisoxazole or sulfathiazole are described: The immediate allergic reaction is mediated by immunoglobulin E (IgE) antibodies (Wulf and Matuszewski 2013) and rarely causes sulfonamide antibiotic allergy (Dorn et al. 2018). The sulfonamide antibiotics often carry an aromatic of 5 or 6 carbons containing one or more nitrogen atoms as a substituent at the nitrogen atom in the sulfonamide structural component (Fig. 2, pink). IgE antibodies are known to recognize especially these nitrogen substituents as well as a CH_3 group in proximity to the nitrogen substituent (Wulf and Matuszewski 2013) as epitops (Chow and Khan 2022) that may trigger an immunological response in sulfonamide antibiotic allergy (Wulf and Matuszewski 2013). Which role the aromatic, bound to the sulfur atom of the sulfonamide structural component with the nitrogen atom in para position (Fig. 2, orange), plays as an allergy-triggering epitope for the activation of IgE antibodies is inconsistently reported in literature. It is described by Wulf and Matuszewsky (2013) as a possible recognition structure for IgE antibodies, whereas Khan et al. (2019) did not observe any influence of the structural component on IgE activation. However, the literature agrees that the sulfonamide structural component itself (Fig. 1) can be excluded as an allergenic epitope (Dorn et al. 2018).

Allergic delayed reactions occur a few days after the first treatment with sulfonamide antibiotics and represent the more common cause of sulfonamide antibiotic allergy (Dorn et al. 2018). It usually manifests as skin exanthema to Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), eosinophilia (Wulf and Matuszewski 2013) and drug rash with eosinophilia and systemic symptoms (DRESS)(Dorn et al. 2018). The allergic reaction is triggered via stimulation of T-cell receptors, activation of T-lymphocytes and activity as haptens (Dorn et al. 2018). The sulfonamides themselves or their metabolites are responsible for this (Wulf and Matuszewski 2013). The latter are formed by endogenous degradation processes at the substituent of the nitrogen atom of the sulfonamide structural component (Fig. 2, pink) by the enzyme CYP2C9 and subsequent conversion to reactive nitroso compounds(Khan et al. 2019), which can bind e.g. to endogenous proteins or directly to T cells (Wulf and Matuszewski 2013). Sulfonamides without substitution at the nitrogen atom of the sulfonamide structural component, as in compounds of the second and third group, can therefore not form the allergenic metabolites (Wulf and Matuszewski 2013).

4. Cross-reactivity

Cross-reactivity, defined as such, between sulfonamide antibiotics and other drug classes with sulfonamide structural component has not yet been described in the literature. Single case reports of allergic reactions to sulfonamides without antibiotic activity are reported, such as to sulfonylureas, carbonic anhydrase inhibitors or diuretics with and without provocation test on the skin for comparison with allergic reaction to sulfonamide antibiotics (Wulf and Matuszewski 2013). The cross-reactivity of COX-2 inhibitors was also comparable to placebo and to other NSAIDs without sulfonamide structural component (Lee et al. 2021). A study of cross-reactivity by Strom et al. (2013) revealed a minimally increased risk of allergic reactions after exposition to non-antibiotic sulfonamides in the presence of a previously diagnosed sulfonamide antibiotic allergy (17.0 %) compared to people without a sulfonamide antibiotic allergy in medical history (15.3 %). However, they also observed that the risk for an allergic reaction after exposition to non-antibiotic sulfonamides was lower than after exposition to penicillin, which has no structural similarity to sulfonamide antibiotics. Likewise, the risk of allergic reaction after exposition to non-antibiotic sulfonamides was lower for a previously diagnosed sulfonamide antibiotic allergy than for a previously diagnosed penicillin allergy (Strom et al. 2003).

Regarding cross-reactivity to triptans, 15 patients with a medical history of sulfonamide antibiotic allergy were studied and no allergic reaction was observed in any patient taking sumatriptan (Wulf and Matuszewski, 2013). Since allergic reactions to triptans have generally been reported rarely, a single case report of an 18-year-old female patient with anaphylactic reaction to sumatriptan is notable. However, when the provocation test was performed on the skin, she did not react positively to the sulfonamide naratriptan, but to rizatriptan, which does not contain a sulfonamide structural component (Lee et al. 2021).

5. Conclusion

Some triptans are structurally similar to sulfonamide antibiotics as they also contain a sulfonamide structural component. However, allergic reactions to triptans are very uncommon. Nevertheless, evidence-based cross-reactivity referring to the well-known allergic reaction of sulfonamide antibiotics has not been described so far (Wulf and Matuszewski 2013). This could be due to the fact that the sulfonamide structural component is not essential for the immediate and delayed allergic reaction and the presumably allergenic structural components of sulfonamide antibiotics are absent (Wulf and Matuszewski 2013). Associations between single case reports of allergic reactions after exposition to non-antibiotic sulfonamides may be due to a general predisposition for allergic reactions, also called "multi-drug allergy syndrome" (Strom et al. 2003). Allergic reactions to triptans have not been described except for a single case report (Lee et al. 2021). To rule out cross-reactivity in an evidence-based manner, controlled studies and reliable provocation tests are needed to determine the allergic reaction.

Conflicts of interest: None reported.

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