What medicines should be avoided by patients suffering from "sulfa allergy"?

Prepared by UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals
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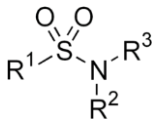
Background



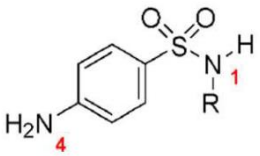
"Sulfa-allergy" is a general term to refer to patients who have displayed an allergy to one or more drugs containing the sulfonamide chemical group, displayed at right (1-3). However, concerns about potential cross-sensitivity between sulfonamide drug classes are not supported by published data. For this reason, many experts have advocated abandoning the term "sulfa-allergy" on the basis that it is "imprecise, incorrect and misleading" (1), and limits prescribing options. Instead, the precise drug and reaction should be noted, as would be done for any other allergy or adverse reaction.

A distinction should first be made between "sulfa-" and "sulphur". Many incorrectly assume "sulfa-allergy" to mean an allergy to all sulphur-containing compounds, which is not the case, and leads to unnecessary worry and inappropriate restrictions on therapeutic options. Although patients may suffer from adverse reactions to inorganic sulphate (e.g. in morphine sulphate) or products containing sulphites (often added to fresh produce to control browning (3)), this is unrelated to any adverse reaction to a sulfonamide.

Adverse reactions to sulfonamides are a common problem, occurring in about 3% of cases, about 3% of which are true hypersensitivity reactions (4). Approximately 3% of the general population in the United States have an allergy to sulfonamide antimicrobials, while incidence among the HIV-infected population is estimated to be 60% (3, 5). Patch testing is not considered to be of value, as the allergies generally occur *after* metabolism of the offending drug, when immune complexes have formed (1).

Answer

Drugs containing the sulfonamide moiety can be divided into 2 groups; sulfonamide antibiotics and sulfonamide non-antibiotics. Although all sulfonamides contain the NH_2-SO_2 moiety shown above, sulfonamide antibiotics also contain an arylamine at the N4 position and a nitrogen-containing ring at the N1 position (see below). It is these additional groups that are believed to be the main determinant of "sulfa-allergy" as opposed to the NH_2-SO_2 moiety contained in all sulfonamides (6).



Because of this, there is an overwhelming lack of evidence that supports the existence of cross-sensitivity between sulfonamide antimicrobials and sulfonamide nonantimicrobials and studies have shown that sulfonamide nonantibiotics are often tolerated by patients with allergy to sulfonamide antibiotics (1).

It has been suggested that any supposed cross-sensitivity arises from a "predisposition to general immunologic drug reactions", rather than an allergy to the sulfonamide moiety (1, 7, 8). In one retrospective cohort study, Strom et al examined patients with a presumed allergy to a sulfonamide antibiotic and how they reacted when they received a sulfonamide nonantibiotic. The study found that

patients with a history of an allergy to sulfonamide antibiotics were more likely to react to sulfonamide nonantibiotics (9.9% vs 1.6%; adjusted odds ratio [AOR] 2.8; 95% Confidence Interval [CI]: 2.1 – 3.7). However, the authors found that the rates of reaction were even higher when patients with a sulfonamide antimicrobial received pencillin (14%; AOR 3.9; 95% CI: 3.5 – 4.3). The authors concluded that patients allergic to sulfonamide antibiotics are predisposed to further allergic interactions with other drugs irrespective if they contain the sulfonamide moiety or not (9).

Where evidence exists, it is generally in the form of case reports involving only one or two patients. (8). A comprehensive review of the literature between 1966 through 2011 performed by Wulf et al identified 9 case reports indicating cross-reactivity. However, in most cases, adequate patient testing was not conducted to firmly establish either sulfa allergy or sulfonamide cross-sensitivity (10). It would be inappropriate to extrapolate this amount of data to an entire population.

In spite of this, significant discrepancies exist between prescribing information and monographs in tertiary resources, with many manufacturers contraindicating the use of their products in patients with hypersensitivity to sulfonamide derivatives even in the absence of supporting data. Other authors simply state that there is insufficient evidence to support a lack of cross-sensitivity.(11) The advice can also vary between the different manufacturers of the same medicine. For example, a manufacturer of a particular drug may list sulfonamide allergy as a contra-indication, whereas a different manufacturer of the same drug may not list this as a contra-indication or indeed a cause for concern at all.

Based on current evidence, prescribers should understand that patients with a history of allergic reaction to sulfonamides may be at increased risk for reactions to other drugs in general (4). A history of sensitivity to sulfonamide antimicrobials should not be considered an absolute contraindication to subsequent use of non-antimicrobial sulfonamides (11), with a couple of possible exceptions that will be discussed below. Except for those patients with serious allergic reactions and/or multiple drug allergies, all other patients with a sulfa allergy might be given sulfonamide-containing drugs provided there is no alternative drug available and they were appropriately monitored while on treatment. Others have suggested giving a test dose, preferably orally and in a monitored environment (4), and desensitisation protocols exist for some important sulfonamides, for instance co-trimoxazole.

The following list contains classes of medication that contain a sulfonamide in their chemical structure, and examples of individual drugs in the class. No increased risk should be inferred from the ordering of the medications, and this list does not include those drugs unlikely to be encountered in clinical practice in the UK. (Please note, it is beyond the scope of this Q&A to check all Summaries of Product Characteristics, and individual SPCs may need to be checked for specific contraindications.)

Sulfonamide Antibiotics
Sulfamethoxazole, sulfadiazine

Although the importance of the sulfonamides has decreased as a result of increasing bacterial resistance and their replacement by antibacterials which are generally more active and less toxic, they may still be encountered in clinical practice. The commonest example is sulfamethoxazole, which is a component of co-trimoxazole.

The sulfonamide antibiotics are said to be one of the commonest reported causes of adverse drug reactions, second only to the penicillins (1, 12). This group of sulfonamides seems to be associated with most true allergies, due to the presence of the arylamine at N4 (4), hence the existence of a true cross-sensitivity between the different sulfonamide antimicrobials seems likely. The use of any sulfonamide antimicrobial is therefore contraindicated in patients who have demonstrated previous hypersensitivity to other sulfonamide antimicrobials (7).

Silver sulfadiazine cream (eg *Flamazine*™) contains the silver salt of the sulfadiazine. Up to 10% of this sulfonamide may be absorbed after topical use, which will be of particular concern if used over a large area; this can produce systemic effects similar to those caused by oral sulfonamides. (13, 14)

Desensitisation protocols exist, although should only be used if considered essential. One study demonstrated that AIDS patients may be desensitized to sulfadiazine, when its use for the treatment of toxoplasmosis was considered necessary in patients who had hypersensitivity reactions to the drug (7, 15). Similar protocols have been used for co-trimoxazole in patients requiring treatment for *Pneumocystis carinii* (3). Specialist resources must be consulted before initiating any such desensitization, however, as it is not always effective or guaranteed safe (1, 16).

Aminosalicylates

Sulfasalazine is a sulfonamide prodrug; it is activated in the bowel by cleaving sulfapyridine from 5-aminosalicylic acid (5-ASA or mesalazine) (17). The sulfapyridine portion contains a sulfonamide arylamine, as do the sulfonamide antimicrobials, leading to the potential for cross sensitivity with these drugs. As such, sulfasalazine is generally contra-indicated in patients with hypersensitivity to sulfonamides (18, 19).

Although the sulfapyridine portion is thought to have some effect in patients with rheumatoid arthritis, different aminosalicylates are available which lack the sulfonamide moiety, including mesalazine, balsalazide and olsalazine, and may be preferable for use in other patient groups (20). If sulfasalazine is the only viable option, various desensitisation protocols have successfully been used in some patients with known mild to moderate sulfonamide allergy (7, 20, 21). Desensitisation should not be considered for patients with anaphylaxis or severe reactions (e.g. Stevens-Johnson Syndrome).

Sulfonylureas

Gliclazide, glipizide, glibenclamide and glimepiride

The sulfonylureas can also cause adverse reactions presumed to be immune-driven in nature, usually developing in the first 6-8 weeks of therapy (22). It is thought unlikely that these reactions occur via the same mechanism as sulfonamide hypersensitivity, as the sulfonylureas do not contain an aromatic nitrogen-containing ring system (3) and the nature of the reactions differ from the reactions typical to the sulfonamide antibiotics (1).

Advice for this group is reasonably consistent; some sources have advised that since oral sulfonylureas differ in structure from sulfonamides, they are not contraindicated in patients with an allergy to sulfonamides unless the reaction was severe (4). Likewise, no reference to hypersensitivity to sulfonamides is made in the BNF or individual monographs in Martindale. Drugdex only mentions a contraindication in the monographs of glipizide and glimepiride (23, 24). In spite of this, many UK manufacturers do contraindicate their use in such patients.

Prescribers should be aware that cross-sensitivity may exist within the sulfonylurea group itself (1).

Fosamprenavir

Although it contains an arylamine, fosamprenavir is not contraindicated in patients with sulfonamide allergy, but should be used with caution (25, 26), and the manufacturer of the UK licensed product notes than the potential for cross-sensitivity between sulfonamides and fosamprenavir is unknown (27).

It has been suggested that because of the close structural similarity with sulfonamide antibacterials, cross-sensitivity is likely, but this has so far not been borne out by the published evidence. In one

small study, in patients receiving fosamprenavir with ritonavir there was no evidence of an increased risk of rashes in patients with a history of sulfonamide allergy versus those who did not have a sulfonamide allergy (27). In another study of fosamprenavir calcium alone, rash was reported in 20% of patients with a sulfonamide allergy history compared with 33% of patients without a history of sulfonamide allergy. When fosamprenavir calcium was used in combination with ritonavir, rash was reported in 16% of patients with a sulfonamide allergy history compared with 12% of patients without a history of sulfonamide allergy (26).

Diuretics:
Includes thiazide and related diuretics (e.g. bendroflumethiazide, indapamide, metolazone), and loop diuretics (e.g. furosemide, bumetanide).

Although the thiazides and loop diuretics are known to contain a sulfonamide moiety, and may be chemically very similar, there is very little consistency in advice given for these drugs, either collectively for the sulfonamide-containing diuretics as a group, or for each individual drug.

No mention of sulfonamide hypersensitivity is made for either group in the BNF (28), nor in Martindale (4). Some experts suggest that a history of sensitivity to sulfonamide antibacterials should not be considered an absolute contraindication to non-antibacterial sulfonamides such as thiazides (8).

Difficulty arises when the licensing status of individual drugs is considered. For instance, all UK manufacturers contraindicate the use of indapamide or furosemide in patients with documented hypersensitivity to sulfonamides but for bendroflumethiazide there is variation in recommendations between different manufacturers. Some manufacturers contra-indicate its use in patients who are allergic to sulfonamides whereas other manufacturers do not list this as a caution or contra-indication, highlighting the lack of standardised advice for this particular area (29, 30).

The authors of one paper list furosemide and indapamide in the same group as sulfamethoxazole, describing the drugs as “mostly unsafe – warning for cross-sensitivity” (5). This appears to be primarily based on warnings found in drug compendia rather than practice, however, which themselves derive from advice from the manufacturers and is in marked contrast to many other publications, where furosemide is noted as a sulfonamide often taken without consequence by patients with known allergy to other sulfonamides (1).

One study examined the safety of furosemide when used during nuclear diuretic renography. Out of 1103 patients, 83 (7.5%) had a documented sulfonamide allergy. There were 2 cases of rash documented; one patient had no prior exposure to sulfonamide and history of sulfonamide exposure was not documented in the second case. The authors concluded that furosemide is associated with an ‘extremely low risk’ of skin reactions in patients with a sulfonamide allergy (31)

A few case reports discussing cross-sensitivity between individual diuretics and other sulfonamides exist, but these appear to be the exception to the rule (32-34). Some of these patients have subsequently been successfully desensitised (32).

Different diuretics can cause hypersensitivity reactions in their own right, but this does not appear to be related to their sulfonamide content. As with sulfonylureas, it has been suggested that cross-sensitivity may exist between individual diuretics (35).

Carbonic anhydrase inhibitors:
Acetazolamide, brinzolamide and dorzolamide

Administered as eye-drops, both dorzolamide and brinzolamide may be systemically absorbed, and

hence have sulfonamide-like side effects, although this is rare (36). No evidence could be found for the existence of any cross-sensitivity between them and other sulfonamides. Regardless, preparations containing brinzolamide are contra-indicated in their respective SPCs in patients hypersensitive to sulfonamides.

One study showed that rates of adverse reactions to carbonic anhydrase inhibitors (CAIs) were similar between patients with a self-reported history of sulfonamide allergy and patients with non-sulfonamide allergy; both groups had more ocular ADRs after the initiation of topical antiglaucoma medications when compared to those patients with no reported allergies. Additionally, self-reported sulfa-allergic patients had similar rates of adverse reactions to different drug classes (topical CAIs and topical prostaglandin analogues). The authors suggest it may be safe to use a topical CAI in patients who report a history of a sulfa allergy (37).

Acetazolamide is contraindicated by the manufacturer in patients with sulfonamide hypersensitivity (38, 39). Anaphylaxis has been reported in a patient who had not previously received acetazolamide but was hypersensitive to “sulfonamides” (40); however, a study of 34 patients reporting sulfa-allergy were treated with either furosemide or acetazolamide for intracranial hypertension, and no adverse reactions to those drugs were documented (1).

COX2 antagonists

Celecoxib and parecoxib

Although little distinction is sometimes made between COX2 antagonists and the implication may arise that all contain the sulfonamide moiety (3), only celecoxib and parecoxib contain it.

Although available data suggests that cross-sensitivity between sulfonamide antibiotics and these drugs is unlikely, serious skin reactions (including Stevens-Johnson Syndrome) have been seen in patients with a history of allergic reactions to sulfonamides (41, 42). As such, licensed product information contraindicates the use of these drugs in such patients as they “may be at greater risk of skin reactions”. It should be noted that patients with a history of other types of allergy may also be at greater risk of skin reactions, but the drug is not contraindicated in these patients (43, 44).

However, in a prospective trial of 28 patients (26 women, mean age of 60 years, 6 of whom tested positive via skin prick or in vitro to sulfamethoxazole) who reported an allergy to sulfonamide antimicrobials, all tolerated oral celecoxib 10 mg followed one hour later by 100 mg with no adverse reactions. This supports the theory that hypersensitivity (and hence cross-sensitivity) is due to the aromatic amine in the sulfonamide antimicrobial, which is not present in the COX2 (42).

$5HT_1$-receptor agonists

The sulfonamide moiety is present in sumatriptan, almotriptan and naratriptan. Use of these drugs is not routinely contraindicated in patients with sulfonamide hypersensitivity, but rather it is listed as a caution in use – a few exceptions exist among OTC products (45). The potential for cross-sensitivity has not been tested and no case reports supporting an association could be found. A chart review of 15 patients with sulfonamide allergy who later received sumatriptan found no adverse effects reported (46).

Other triptans (eletriptan, frovatriptan, rizatriptan and zolmitriptan) are free of the sulfonamide group and may be considered as alternatives if necessary.

Alpha blockers

Tamsulosin is the only alpha-blocker containing a sulfonamide moiety. None of the current UK manufacturers of tamsulosin products contraindicate use of their product in patients with allergy to

sulfonamides, and no case reports of cross-sensitivity could be found. However, its use is cautioned by the US manufacturer (47).

None of the other alpha blockers (alfuzosin, doxazosin, indoramin, terazosin, and prazosin) contain sulphur in the active drug molecule, and could be considered as alternatives.

Probenecid and cidofovir

Probenecid contains a sulfonamide moiety, and while some texts advise that caution should be exercised when prescribing to patients with known sulfonamide allergy (48), no mention is made in others (49, 50). No case reports of cross-sensitivity could be found.

Although it is not available in the UK as a licensed product, probenecid must be prescribed alongside cidofovir. Cidofovir is not itself a sulfonamide, however its use is contraindicated in patients "unable to receive probenecid or other sulfa-containing medication" as probenecid must be used concomitantly to reduce cidofovir's pronounced nephrotoxicity (51).

Zonisamide

The antiepileptic zonisamide is a benzisoxazole derivative, which contains a sulfonamide, and is contra-indicated in patients with a history of hypersensitivity to sulfonamides (52, 53). No case reports of cross-sensitivity between zonisamide and other sulfonamides could be found.

HIV Protease Inhibitors

Darunavir and tipranavir both contain a sulfonamide moiety, and should be used with caution in patients with sulfonamide hypersensitivity (54-56). Their potential for cross-sensitivity with other sulfonamides is unknown, but it is important to note that the rate of allergic reactions to sulfonamide antibiotics is 10 times higher among HIV-positive patients than the general population (1).

Dapsone

Although often listed as a drug of concern, and structurally similar to a sulfonamide, dapsone is a *sulfone* (57). It is known to cause similar hypersensitivity reactions to the sulfonamides (a condition known as sulfone or dapsone syndrome) (58), but pre-existing sensitivity to sulfonamides is not a reliable indicator of patients that will go on to develop dapsone syndrome, and vice versa.

Little data exists on the risk of cross-sensitivity between dapsone and sulfonamide antibiotics, with some authors suggesting no cross-reactivity has been documented (59). Although a cross-sensitivity to dapsone has been reported in HIV-positive patients who are sensitive to co-trimoxazole, a recent report suggests that dapsone is often tolerated in these patients (58, 60).

The British Association of Dermatologists recommends that dapsone (used in dermatological conditions such as dermatitis herpetiformis, pyoderma gangrenosum, Sweet's syndrome and vasculitis) should be avoided in patients who are sensitive to other sulfonamides (61).

Desensitisation protocols have been published. (1)

Other drugs of note:

Other drugs contain the sulfonamide moiety and have been included in some lists of drugs to use with caution, but no information could be found except a reference to a sulfonamide in their chemical structures. They are not contraindicated in patients with previous hypersensitivity to sulfonamides, nor is hypersensitivity listed as a caution in use. These include: sotalol (16), pipothiazine (62), dronedarone (63), bosentan (64), mafenide (65) and topiramate (which is a sulfamate-substituted monosaccharide) (66).

Summary

Patients with documented allergy to sulfonamide antibiotics may be at increased risk of all drug-induced reactions that appear to be allergic in nature, irrespective of drug class. The term “sulfa-allergy” is misleading, restrictive, and should be avoided. Healthcare professionals should instead document the exact drug and the nature of the reaction as they would an adverse reaction to any other drug.

The existence of a cross-sensitivity between sulfonamide antibiotics and sulfonamide non-antibiotics is not supported by theory or clinical data (with the exception of sulfasalazine). Many experts do not agree with the contraindication of drugs simply on the basis of their chemical structure, but a large number of manufacturers still contraindicate the use of their drugs in patients with a documented hypersensitivity to sulfonamides.

Prescribers should be aware that this is a subject on which there is extreme variability, even in advice given for the same drug. Where a non-sulfonamide containing option is available, it would be prudent for prescribers to consider this before a sulfonamide-containing alternative.

In cases where it would be detrimental to the patient’s health to avoid using a particular therapy, consideration should be given to using one of the drugs listed above. Clinicians should conduct a careful risk-benefit assessment before prescribing, taking into account the history and nature of the allergy and any other drugs the patient may have taken, as it is possible they will have taken another sulfonamide in the interim period without it being realised. Patients will need to be counselled and monitored. Any decision to prescribe needs to be in the knowledge that if use of a drug is contraindicated, the prescriber is taking responsibility.

For patients with a convincing history of significant sulfonamide hypersensitivity reaction, for whom no acceptable alternative medications exist, desensitisation procedures may be attempted, in an environment where appropriate monitoring can be carried out.

Limitations

This is not an exhaustive list of all sulfonamides currently available on the global market. Sulfonamide-containing drugs that are not currently available in the UK have been excluded, and only those which are most likely to be encountered in UK clinical practice have been listed.

In a number of references, no distinction is made between a true Type 1 hypersensitivity reaction, and an adverse drug reaction being inaccurately reported as an “allergy”.

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Quality Assurance

Prepared by

Tim Meadows, East Anglia Medicines Information Service

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Checked by

Abigail Scott, East Anglia Medicines Information Service

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Search strategy
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Embase (exp SULFONAMIDE/ and '"DRUG HYPERSENSITIVITY"/ OR ALLERGY/ OR "ALLERGIC REACTION"/) – results limited between 2018 - 2020

Medline (SULFONAMIDES/ and "DRUG HYPERSENSITIVITY/") – results limited between 2018 - 2020

NHS evidence search: 'sulphonamide allergy' – results limited between 2018 – 2020. Accessed via https://www.evidence.nhs.uk/

In-house database / resources (including MI Databank, Martindale: the Complete Drug Reference, AHFS Drug Information, Drugdex, UpToDate and Meyler's Side Effects of Drugs)