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Indiana Medicaid Drug Utilization Review Board Newsletter

Distinguishing Between "Sulfa" Allergies

Confusion may arise when patients are labeled as having a "sulfa" allergy. This usually refers to an allergy to the sulfonamide antibiotics. However, one cannot assume this is always the case, since other types of sulfur allergies to sulfites and sulfates exist. Many medications contain sulfonamide moieties. A detailed patient history including description of the hypersensitivity reaction is imperative to determine the severity of the allergy and to anticipate the potential for cross-allergenicity with other medications. It is important to distinguish between the different forms of sulfur.

Sulfur (S): An element with antifungal, antibacterial, scabidical, and keratolytic properties. Sulfur is present in the hemoglobin of human blood and body tissue. Cross-allergenicity with sulfonamides has not been reported.

Sulfites (SO₃): Chemicals used as preservatives, antioxidants, and bleaching agents in foods and pharmaceutical preparations. Examples include sodium sulfite, sodium bisulfite, potassium bisulfite, and sulfur dioxide.

Sulfates (SO₄): Usually inactive chemicals that are used to make drugs more soluble. Examples include gentamicin sulfate and morphine sulfate. Allergies to sulfates are rare and these compounds do not appear to cross-react with sulfonamides.

Sulfonamides (SO₂NH): Derivatives of paraminobenzenesulfonamide. A sulfonamide group attached to a benzene ring characterizes antimicrobial sulfonamide structures.

The mechanism of sulfonamide hypersensitivity reactions is believed to differ from that of sulfites. It is thought that a specific metabolite rather than the intact drug may be responsible for most sulfonamide hypersensitive reactions. Sulfonamides are mainly metabolized by acetylation in the liver. Another pathway involves cytochrome P450 oxidation that can metabolize a small portion of the sulfonamide to a potentially toxic hydroxylamine metabolite. The amounts of the hydroxylamine metabolite an individual produces, as well as their ability to detoxify the product, may determine if the patient will have a hypersensitivity reaction.

Cross-allergenicity among the sulfonamides is unpredictable and the incidence has not been well defined. Reactions can occur in the presence of a sulfonamide structure itself. Therefore, other medications that contain a sulfonamide moiety may pose a risk to patients who have had an allergic reaction to sulfonamide antimicrobials. Patients who have had an allergic reaction to one antimicrobial may be at increased risk of experiencing hypersensitivity reactions to other dissimilar compounds. This makes it difficult to distinguish between an individual's sensitivity to multiple chemical agents and a true cross-allergenicity. Approximately 2% of patients who receive a sulfonamide will display a

hypersensitivity reaction immediately or more commonly after 7-10 days of therapy.

Manifestations

| Dermatologic | Non-Dermatologic |
|--------------------------|-------------------------|
| Exfoliative Dermatitis | Headache |
| Urticarial Rash | Drug Fever |
| Stevens-Johnson Syndrome | Liver Necrosis |
| Erythema Multiforme | Nausea/Vomiting |
| Photosensitivity | Malaise |

There have been a limited number of cases of cross-allergenicity reported between sulfonamide antimicrobials and medications with a similar structure. To add to the confusion, the labeling of sulfonamide-containing medications is inconsistent. Theoretically, these medications should be avoided in sulfonamide allergic patients. A list of common drugs that should be avoided or used with caution in sulfonamide sensitive patients is listed in table 7.5. This list may not be all-inclusive. Please refer to the manufacturer’s prescribing information to confirm safe use of other agents in sulfonamide-allergic patients.

Many questions have come up regarding the use of COX-2 inhibitors in sulfonamide-allergic patients. The celecoxib and valdecoxib manufacturer states that these products are contraindicated in patients allergic to sulfonamides, based on the presence of a sulfonamide in the chemical structure. Therefore, it is prudent to avoid these products for these patients. Postmarketing surveillance has described hypersensitivity reactions and angioedema with both agents. There have been reports of fatalities as a result of Stevens-Johnson Syndrome and toxic epidermal necrolysis from valdecoxib use. These adverse reactions have occurred in valdecoxib-treated

patients with or without a documented sulfonamide allergy.

Choosing a diuretic for a sulfonamide-allergic patient can be a challenge. Examples of diuretics that do not contain a sulfonamide moiety include amiloride, triamterene, eplerenone, and spironolactone. Spironolactone does contain a sulfur molecule in the structure but it is not a sulfonamide structure. Therefore, it would not be expected to generate a hypersensitivity reaction.

To date, the literature has not identified a cross-sensitivity between sulfite sensitive patients and sulfonamide-allergic patients. In addition, sulfates have a structure different from that of sulfonamides and sulfites and would not be expected to cross-react. Three potential mechanisms appear to be responsible for sulfite hypersensitivity, which are distinct from that of sulfonamide hypersensitivity reactions. It is important to note that if a sulfonamide-allergic patient is also sensitive to sulfites, they may be at increased risk of developing an allergic reaction to compounds related to both agents.

Hypersensitivity reactions generally occur when a sulfite-sensitive individual ingests 20-50mg of sulfite. Parenteral products often contain sulfites as preservatives in small enough quantities not likely to elicit a reaction, unless the individual is highly sensitive. Approximately 5% of asthmatic patients are sensitive to sulfites. Most metered dose inhalers have been reformulated to remove the sulfites once present in these products. Controversy surrounds the use of anaphylactic kits, which often contain sulfite-preserved epinephrine products. These products should not be withheld from an individual experiencing an anaphylactic reaction if no sulfite-free products are available.

Clinical Pearls:

1. Cross-allergenicity among sulfonamide medications is unpredictable.
2. A documented sulfonamide allergy does not imply that all molecules containing sulfur in the structure are contraindicated.
3. Labeling a patient as “sulfonamide” or “sulfite” allergic is preferred over “sulfa” due to the confusion surrounding this term.
4. Patients with advanced HIV are often slow acetylators and glutathione deficient and therefore may be at increased risk of developing a hypersensitivity reaction.
5. To date, the literature has not identified a cross-sensitivity between sulfite sensitive patients and sulfonamide-allergic patients.
6. Generic versions of brand-name sulfite-free medications may contain sulfites as inactive ingredients.
7. Check all food and medication labels for inactive ingredients.
8. Sulfates are generally considered inactive and hypersensitivity reactions are very rare.

Evidence-Based Pharmacotherapy for Asthma

The National Asthma Education and Prevention Program (NAEPP) guidelines provide up-to-date asthma management recommendations, which are stratified according to the level of research evidence. The guidelines recommend inhaled corticosteroids as the preferred controller therapy for patients of all ages with persistent asthma of any severity.¹ Evidence indicates that regular use of inhaled corticosteroids, even at low doses, could prevent a large proportion of asthma-related hospitalizations and deaths.

Unfortunately, most patients do not use sufficient amounts of inhaled corticosteroids. The risk of exacerbations declines as the use of

Table 7.1 Stepwise Approach for Long-Term Asthma Pharmacotherapy (for adults and children older than 5 years of age)¹

| Severity Class | Medications Required To Maintain Long-Term Control |
|----------------------------|---|
| Step 4 Severe Persistent | High dose inhaled corticosteroid AND long-acting beta ₂ -agonist AND, if needed, Systemic corticosteroid long-term |
| Step 3 Moderate Persistent | Low-to-medium dose inhaled corticosteroid and long-acting beta ₂ -agonist OR Increase inhaled corticosteroid to medium dose range OR Low-to-medium dose inhaled corticosteroid and either leukotriene modifier or theophylline |
| Step 2 Mild Persistent | Low dose inhaled corticosteroid OR Cromolyn, leukotriene modifier, nedocromil, OR sustained-release theophylline |
| Step 1 Mild Intermittent | No daily medication needed (a course of systemic corticosteroids is recommended for severe exacerbations) |

Listed below are some commonly prescribed drugs that have similar sounding or look-alike names.

- Lamictal-Lamisil
- Atarax-Ativan
- Diovan-Zyban
- Vioxx-Zyvox
- Benylin-Benadryl
- prochlorperazine-trifluoperazine

Any and all medication mishaps should be reported to the FDA Medwatch Program (1-800-FDA-0178) or the U.S. Pharmacopeias Medication Errors Reporting Program at 1-800-23-ERROR.

inhaled corticosteroids increases. Analysis of medication claim databases show that patients receive an average of only 2.2 canisters annually. To improve adherence, providers can educate patients about the benefits of long-term inhaled corticosteroid use.

How soon should inhaled corticosteroids be started in patients with mild persistent asthma? In patients with mild persistent asthma of recent onset, early intervention with an inhaled corticosteroid was shown to significantly decrease the risk of exacerbations, reduce the need for systemic corticosteroids, and improve asthma control. However, it remains to be determined whether inhaled corticosteroids or any other controller therapy can prevent irreversible airway obstruction associated with the natural progression of asthma. For patients with mild persistent asthma, leukotriene modifiers are an alternative controller medication to inhaled corticosteroids.

For patients with moderate persistent asthma, the preferred therapy is a low to medium dose of inhaled corticosteroid plus a long-acting beta₂-agonist. Evidence

suggests that adding a long-acting beta₂-agonist may be more effective than raising the corticosteroid dose and helps to reduce the potential for corticosteroid-related adverse effects.

A stepwise approach for long-term asthma pharmacotherapy in adults and children (age > 5 years) is included in table 7.1.

Medication Mishaps

Accupril and Accutane. Both sound similar and look similar but are indicated for different uses. Medication errors partially arise from similar drug names, packaging, poor handwriting, misinterpretation of an abbreviated drug name, or incorrect data entered into a computer.

Look-alike drugs can cause up to 25 percent of medication errors. The FDA reported a recorded number of 400 deaths in January, 2002 due to medication errors. Sixteen percent (16%) of these errors were directly attributed to drugs with similar names.

Program Assistance

All questions regarding brand medically necessary should be directed to the ACS Pharmacy Services Helpdesk at 1-866-645-8344.

PDL Listing

The fee-for-service PDL listing may be found at the following website:
<http://www.indianapbm.com/Downloads/PDL%20update%207-09-04.pdf>.

Top 25 Drugs for First Quarter 2004

The following tables (7.2 and 7.3) list the drugs ranked by total amount paid and ranked by the total number of prescriptions for the first quarter of 2004.

**Table 7.2
Top 25 Drugs 1st Quarter 2004
By Total Amount Paid**

| Drug | Total Paid | Total Claims |
|------------|--------------|--------------|
| Zyprexa | \$11,338,368 | 35549 |
| Risperdal | \$7,035,884 | 38184 |
| Seroquel | \$5,231,315 | 27787 |
| Novoseven | \$3,726,823 | 30 |
| Depakote | \$3,671,243 | 31512 |
| Neurontin | \$3,569,013 | 28662 |
| Zoloft | \$3,424,636 | 38472 |
| Lipitor | \$3,340,385 | 39026 |
| Duragesic | \$2,896,138 | 14761 |
| Abilify | \$2,767,218 | 9261 |
| Protonix | \$2,763,279 | 26632 |
| Plavix | \$2,515,302 | 21700 |
| Oxycontin | \$2,455,151 | 9584 |
| Zocor | \$2,296,108 | 18836 |
| Allegra | \$2,237,128 | 35246 |
| Effexor | \$2,221,059 | 19011 |
| Topamax | \$2,152,348 | 11283 |
| Advair | \$1,769,354 | 12861 |
| Singulair | \$1,732,399 | 21375 |
| Aricept | \$1,710,511 | 13389 |
| Lexapro | \$1,681,972 | 26277 |
| Wellbutrin | \$1,675,093 | 15944 |
| Actos | \$1,599,756 | 9719 |
| Strattera | \$1,459,853 | 15041 |
| Zithromax | \$1,444,363 | 34919 |

**Table 7.3
Top 25 Drugs 1st Quarter 2004
Ranked by Claims Paid**

| Drug | Total Claims | Total Paid |
|---------------------|--------------|--------------|
| Hydrocodone/APAP | 100194 | \$1,209,166 |
| Furosemide | 60709 | \$392,623 |
| Albuterol | 53882 | \$731,204 |
| Ranitidine | 47376 | \$476,941 |
| Amoxicillin | 41418 | \$453,081 |
| Lipitor | 39026 | \$3,340,385 |
| Lisinopril | 38581 | \$469,696 |
| Zoloft | 38472 | \$3,424,636 |
| Risperdal | 38184 | \$7,035,884 |
| Alprazolam | 37434 | \$284,024 |
| Aspirin | 36167 | \$28,867 |
| Zyprexa | 35549 | \$11,338,368 |
| Allegra | 35246 | \$2,237,128 |
| Zithromax | 34919 | \$1,444,363 |
| Docusate | 32853 | \$79,733 |
| Propoxyphene N/APAP | 31625 | \$320,575 |
| Depakote | 31512 | \$3,671,243 |
| Potassium | 30839 | \$570,997 |
| Neurontin | 28662 | \$3,569,013 |
| Seroquel | 27787 | \$5,231,315 |
| Synthroid | 27470 | \$453,127 |
| Protonix | 26632 | \$2,763,279 |
| Lexapro | 26277 | \$1,681,972 |
| Norvasc | 25472 | \$1,389,618 |
| Lorazepam | 23239 | \$237,717 |

New Drugs Approved by FDA for 1Q and 2Q 2004

Table 7.4 lists some of the new drugs approved by the FDA. The list does not include new dosage forms. New approvals with new dosage forms include: Acetadote, Apidra, Caduet, DepoDur, Enjuvia, Iquix, LidoSite, Menostar, Myfortic, Vitrase, Zegerid, and Zyprexa IntraMuscular.

**Table 7.4
New Molecular Entities/Significant Biologicals**

| Drug | Generic Name | Description |
|----------|---------------|---|
| Alimta | Pemetrexed | An agent used in combination with cisplatin for mesothelioma |
| Apokyn | Apomorphine | A dopamine agonist for episodes of hypomobility in Parkinson's patients |
| Avastin | Bevacizumab | A monoclonal antibody for metastatic colorectal cancer |
| Erbitux | Cetuximab | A monoclonal antibody for metastatic colorectal cancer |
| Ketek | Telithromycin | A ketolide antibiotic for treatment of respiratory tract infections |
| Sanctura | Trospium | An antispasmodic/antimuscarinic agent for treatment of overactive bladder |
| Sensipar | Cinacalcet | A calcimimetic for hyperparathyroidism in dialysis patients and hypercalcemia secondary to parathyroid cancer |
| Spiriva | Tiotropium | Inhaled anticholinergic for once-daily maintenance treatment of COPD |
| Tindamax | Tinidazole | An antiprotozoal for treatment of trichomoniasis, giardiasis, intestinal amebiasis, and amebic liver abscess |
| Vidaza | Azacitidine | An antineoplastic for treatment of myelodysplastic syndrome |
| Xifaxan | Rifaximin | A non-systemic antibiotic for treatment of travelers' diarrhea |

| Table 7.5 Drugs to Avoid in Sulfonamide -Sensitive Patients | | |
|--|---|---|
| Drug Class | Examples | Mfr Labeling |
| Sulfonamides (systemic, ophthalmic, vaginal) | Silver sulfadiazine | Warning (topical preparations) |
| | Sulfamethoxazole | Contraindication |
| | Sulfacetamide | Contraindication |
| | Sulfadiazine | Contraindication |
| | Sulfadoxine | Contraindication |
| | Sulfapyridine | Contraindication |
| | Sulfasoxizole | Contraindication |
| | Sulfasalazine | Contraindication |
| | Sulfanilamide | Contraindication (topical preps) |
| Sulfonylureas | Chlorpropamide | No warning of precaution |
| | Glipizide | No warning of precaution |
| | Glyburide | No warning of precaution |
| | Tolazamide | No warning of precaution |
| | Tolbutamide | No warning of precaution |
| | Glimepiride | No warning of precaution |
| Carbonic Anhydrase Inhibitors | Acetazolamide | Warning |
| | Dorzolamide | Warning (topical preps) |
| | Methazolamide | Warning |
| | Dichlorphenamide | No warning or precaution |
| | Brinzolamide | Warning (topical preps) |
| Diuretics (loop) | Furosemide | Precaution |
| | Bumetanide | Warning |
| | Torsemide | Contraindicated in patients with hypersensitivity to sulfonylurea |
| Diuretics (thiazide diuretics) | Hydrochlorothiazide | Contraindication |
| | Benzthiazide | Contraindication |
| | Chlorothiazide | Contraindication |
| | Chlorthalidone | Contraindication |
| | Indapamide | Contraindication |
| | Metolazone | Warning |
| NSAIDs | Celecoxib | Contraindication |
| Anticonvulsants | Zonisamide | Contraindication |
| HIV Agents | Amprenavir | Precaution |
| Sunscreens | PABA (para-aminobenzoic acid containing agents) | May vary with preparation used |
| Miscellaneous | Tamsulosin | No warning or precaution |

¹ National Heart, Lung, and Blood Institute. *National Asthma Education and Prevention Program, Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma (Update on Selected Topic 2002)*. <http://www.nhlbi.nih.gov/guidelines/asthma/asthmafullrpt.pdf>