

Crossreacting Drugs and Chemicals

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Abstract

Aspirin and nonsteroidal antiinflammatory drugs (NSAIDs) exert their clinical effect through inhibition of prostaglandin H synthases 1 and 2, also known as cyclooxygenase. This shared effect of COX-inhibition is also the mechanism for shared adverse effects. Much of our understanding of cross-reacting drugs and chemicals with aspirin comes from studying asthmatics with aspirin-exacerbated respiratory disease (AERD). Aspirin exacerbated respiratory disease is characterized by recalcitrant sinusitis/polyposis, asthma and precipitation of asthma after ingestion of aspirin and most NSAIDs. Cross-reactions between ASA and NSAIDs occur with first exposure unlike IgE-mediated allergic drug reactions. Cross-reactions between aspirin and other drugs are dependent upon inhibition of the cyclooxygenase-1 isoenzyme. Desensitization to aspirin will result in cross-desensitization to all NSATDs that inhibit COX-1. Despite reports in the literature, there does not appear to be cross-reactions between food coloring, hydrocortisone succinate and monosodium glutamate in individuals with aspirin exacerbated respiratory disease. The new highly selective cyclooxygenase 2 inhibitors are well tolerated in AERD asthmatics who have not been desensitized to aspirin. Because low-dose ASA exerts a cardioprotective effect by irreversible inhibition of COX-1, AERD patients who are at risk for coronary artery disease should be considered for aspirin desensitization.

Index Entries:

Aspirin; nonsteroidal antiinflammatory drugs; cyclooxygenase; desensitization; aspirin-exacerbated respiratory disease.

Introduction

Aspirin and nonsteroidal antiinflammatory drugs (NSAIDs) exert their clinical effect through inhibition of prostaglandin H synthases 1 and 2, colloquially known as cyclooxygenase (COX). The COX pathway converts arachidonic acid to prostaglandins, prostacyclins, and thromboxane A₂ (TXA₂) (1). This shared effect of COX inhibition by aspirin (ASA) and NSAIDs is essential for their efficacy as antiinflammatory, analgesic, and antipyretic agents; it is also the mechanism for shared adverse effects such as gastritis. This section examines drugs that crossreact with ASA. The crossreactivity is a result of the shared mechanism of action—namely, the inhibition of COX. The focus will be on cross-reactions in aspirin-exacerbated respiratory disease (AERD), other articles will deal with urticaria and angioedema. ASA and NSAIDs can also participate in reactions that are drug-specific and are not associated with cross-sensitivity. These include aseptic meningitis, hypersensitivity pneumonitis, single NSAID-induced anaphylaxis, and single NSAID-induced urticaria/angioedema. ASA and NSAIDs induce a number of other adverse reactions, including but not limited to: hepatotoxicity, interstitial nephritis, bleeding disorders, anemia, thrombocytopenia, erythema nodosum, erythema multiforme, fixed-drug eruptions, bullous leukocytoclastic vasculitis, maculopapular eruptions, and Stevens-Johnson syndrome (2).

Cyclooxygenases

The two known isoenzymes, COX-1 and COX-2 or prostaglandin H synthase 1 and 2, have mol wts of 71 Kd and share ~60% homology (3). Genes for COX-1 and COX-2 are found on chromosomes 9 and 1, respectively (4). COX catalyzes the first step of the synthesis of prostanoids by converting arachidonic acid into prostaglandin H₂. The enzyme is bifunctional with COX activity (catalyzing conversion of

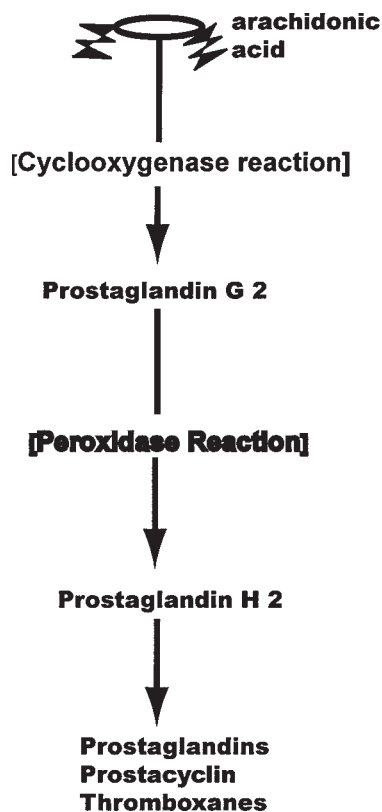


Fig. 1. Dual function of COX (prostaglandin H synthase).

arachidonic acid to prostaglandin G₂) and prostaglandin hydroperoxidase activity (converting prostaglandin G₂ to prostaglandin H₂) (5) (Fig. 1). COX-1 is constitutively expressed in most cell types, including platelets, and is involved in physiologic protective functions such as gastric mucosal protection. COX-2 expression is limited to inflammatory cells, and is induced by pro-inflammatory stimuli leading to the generation of prostaglandins associated with inflammation, pain, and pyresis (6,7). COX has three independent folding units or domains: an N-terminal epidermal growth-factor-like domain, a membrane-binding motif, and a C-terminal catalytic domain that contains the COX and peroxidase active sites (8,9). COX integrates into a single leaflet of the nuclear or endoplasmic reticulum-membrane lipid bilayer in such a manner that arachidonic acid gains access to the active site from the interior of the lipid bilayer (8,9). The COX

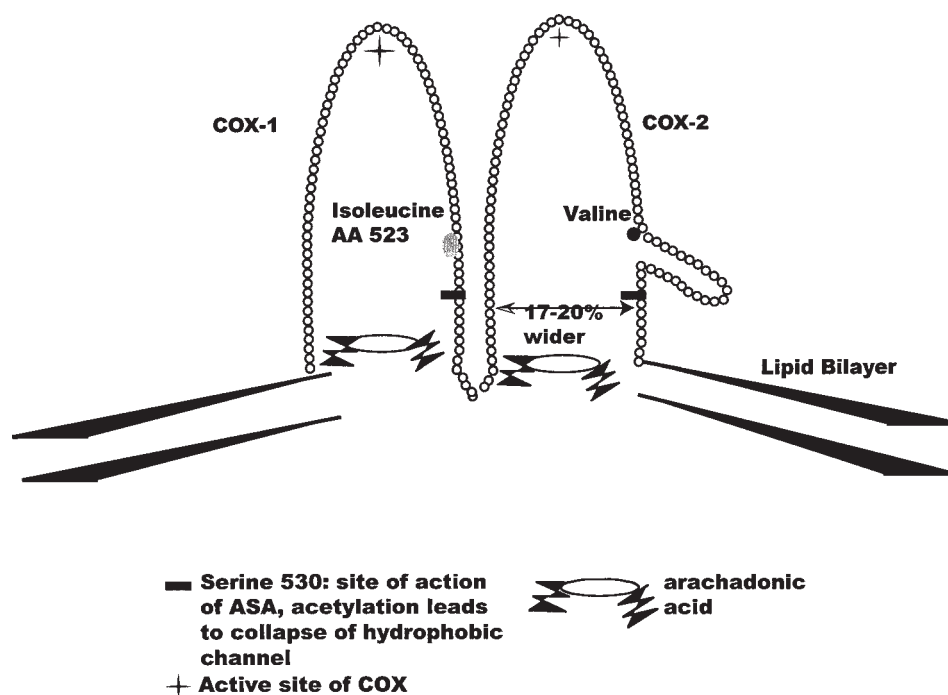


Fig. 2. Comparison of COX-1 and COX-2 C-terminal catalytic domains. COX-2 differs from COX-1 at amino acid 523 (valine substituted for isoleucine) allowing for access to side pocket in COX-2, site of action of COX-2-specific inhibitors.

active site lies at the end of a hydrophobic channel that runs from the membrane-binding surface of the enzyme to the interior of the molecule. NSAIDs act through at least three mechanisms within the hydrophobic channel to inhibit COX activity. ASA is unique among the NSAIDs because it irreversibly acetylates a serine residue in the COX channel (serine 530), leading to collapse of the COX channel (10). Reversible competitive inhibitors such as mefenamate and ibuprofen compete with arachidonic acid for the active site. A third class cause a slow, time-dependent reversible inhibition of COX, which results from the formation of a salt bridge between the carboxylate of the drug and arginine 120 followed by conformational changes (5).

COX-2 is very similar to COX-1, but a single amino acid substitution in position 523—valine for isoleucine—allows access to a “side pocket” for COX-2-selective drugs. The total NSAID-binding site is ~17% larger in COX-2 (11), and allows for binding of larger inhibitors than

COX-1 (12). Fig. 2 is a schematic of the differences between COX-1 and COX-2 in the catalytic domain.

ASA Crossreactions in ASA-Exacerbated Respiratory Disease

Aspirin-exacerbated respiratory disease (AERD), formerly referred to as aspirin-induced asthma (AIA) or aspirin-intolerant asthma, is characterized by recalcitrant mucosal inflammation of the upper and lower respiratory tract combined with precipitation of asthma and rhinitis attacks after ingestion of ASA and most NSAIDs (13). It is associated with progressive sinusitis, nasal polyposis, and asthma, despite avoidance of ASA and NSAIDs. In sensitive individuals, even small, single doses of ASA may cause rhinorrhea, bronchospasm, and shock symptoms, related to a non-IgE-mediated pharmacological hypersensitivity reaction. COX-1 is constitutively expressed in most tissues, including respiratory epithelial

and endothelial cells. Prostaglandins derived from COX-1 are involved in cellular housekeeping functions, and serve a cytoprotective role (14). Because of the sheer number of cells that synthesize prostaglandins, COX-1 is the main enzyme responsible for generation of prostanooids, including prostaglandin E₂ (PGE₂) in all organ systems (15). PGE₂ is a prostanoid that is essential in the protection of the airways, reducing leukotriene synthesis by inhibiting 5-lipoxygenase (5-LO), particularly in subjects with AERD (16,17). By inhibiting the COX pathway, ASA and NSAIDs divert arachidonic acid metabolites to the lipoxygenase pathway. As PGE₂ levels decline, the inhibitory effect on mast cells and eosinophils is lost, allowing the release of preformed mediators such as histamine and tryptase as well as synthesis of cysteinyl leukotrienes (18). This ultimately leads to bronchoconstriction as well as the histamine-mediated upper-respiratory reactions.

COX-1 Inhibitors in AERD

As early as 1967, crossreactivity between aspirin and indomethacin was reported by Vanselow and Smith (19). Subsequently, Samter and Beers identified a number of NSAIDs that crossreact with ASA (20). It is now known that all NSAIDs, which preferentially inhibit COX-1, crossreact with ASA upon first exposure to the new NSAID. The degree of crossreactivity is roughly equivalent to the concentration of NSAID required to inhibit COX-1 in vitro, so that those NSAIDs that produce crossreactions after exposure to the smallest dose of the drug tend to most effectively inhibit COX-1 (21,22). Crossreaction occurs upon first exposure, unlike IgE-mediated reactions, which require prior sensitization (2,21,23,24). Asthmatics and their physicians must be aware that even ophthalmic NSAID preparations can precipitate asthma attacks (25). Table 1 provides a list of the NSAIDs that crossreact on first exposure with ASA in patients with AERD.

Table 1 NSAIDs that Crossreact with Aspirin in Respiratory Reactions	
Piroxicam	Feldene
Indomethacin	Indocin
Sulindac	Clinoril
Tolemetin	Tolectin
Zomepirac	Zomax
Ibuprofen	Motrin, Rufen, Advil
Naproxen	Naprosyn
Naproxen sodium	Anaprox, Aleve
Fenoprofen	Nalfon
Meclofenamate	Meclomen
Mefenamic acid	Ponstel
Flurbiprofen	Ansaid
Diflunisal	Dolobid
Ketoprofen	Orudis, Oruval
Diclofenac	Voltaren
Ketorolac	Toradol
Etodolac	Lodine
Nabumetone	Relafen
Oxaprozin	Daypro

By contrast, sodium salicylate, salicylamide, choline magnesium trisalicylate, benzydamine, chloroquine, azapropazone, and dextropropoxyphene do not inhibit COX-1 enzymes and do not induce respiratory reactions in subjects with AERD (Table 2). Unfortunately, these drugs are poor analgesics and have fewer antiinflammatory effects than the crossreacting NSAIDs.

Asthmatics with AERD can be desensitized to ASA (26–28). Desensitization is accomplished by giving incremental doses of ASA until a reaction occurs. After a reaction occurs, ASA doses are suspended for that day. After reactions stop, the next highest dose of ASA is given, and is repeated until further reactions cease (26). The process of escalating ASA doses continues until the patient can tolerate 650 mg with no reactions. At this point, the patient can take any dose of ASA or NSAID without adverse respiratory reactions. After ASA desensitization, in the absence of further exposure to ASA, the desensitized state persists for 2–5 d, with full sensitivity returning after 7d (28). In addition, cross-desensitization between ASA and other NSAIDs occurred routinely for all

NSAIDs tested (28,29). From a practical standpoint, an AERD patient with concomitant arthritis or need for anti-platelet therapy can be desensitized to ASA and then take daily ASA (at least ASA 81 mg daily) indefinitely or the patient can be switched to any cross-reacting NSAID as long as ASA or NSAID is continued daily. Silent desensitization to ASA in AERD patients can be conducted by very slowly increasing the dose of ASA each day (30,31).

Weak COX-Inhibitors: Acetaminophen and Salsalate

Acetaminophen is a weak COX-1 inhibitor. Cross-sensitivity between ASA and acetaminophen in AERD has been reported, with frequencies ranging from 0-34% (32-36). When carefully controlled acetaminophen challenges were performed in proven AERD patients, 6% experienced naso-ocular reactions at 1000 mg acetaminophen, 15% naso-ocular reactions at 1500 mg. Bronchospastic reactions occurred in 28% of AERD asthmatics at 1000 mg acetaminophen and 32% at 1500 mg acetaminophen, showing a dose-response effect. Interestingly, the respiratory reactions were generally mild and easily treated, and only occurred in a 34% of AERD asthmatics challenged (35). AERD asthmatics should avoid doses of acetaminophen greater than 650 mg. Most asthmatic patients tolerate 650 mg acetaminophen or less with only a small risk of bronchospasm (35).

Salsalate is a partially effective antiinflammatory agent that is used in the treatment of arthritis. Salsalate is also a weak inhibitor of COX-1. When 10 subjects with AERD were challenged with large doses of Salsalate (2 g), 2 of the 10 experienced mild bronchospastic reactions (24), again suggesting that the majority of asthmatics can safely tolerate lower doses of a weak COX-1 inhibitor.

Selective Inhibitors of COX-2

COX-2 selective inhibitors are usually safely tolerated in AERD asthmatics because of the continued synthesis of COX-1-mediated products. With the nonselective COX-inhibitors, COX-1 inhibition leads to a rapid decline in PGE₂. PGE₂ modulates airway inflammation and bronchoconstriction in part by inhibiting the 5-LO pathway, cholinergic transmission, and release of histamine and other preformed mediators from mast cells. The COX-2-selective agents are also better tolerated by the gastric mucosa. The relatively COX-2-selective NSAIDs, meloxicam and nimesulide, are tolerated in AERD asthmatics in low doses. At higher doses COX-1 inhibition occurs, and crossreactions are observed (2,37-41).

The newer, highly selective COX-2 inhibitors—rofecoxib and celecoxib—have not been shown to crossreact with ASA. Shortly after rofecoxib was released, Szczeklik et al. challenged 12 AERD asthmatics with rofecoxib in a double-blind placebo-controlled study over a period of 5 d (42). During rofecoxib challenges, none of the patients experienced any symptoms or changes in lung-function parameters (42). Subsequently Stevenson et al. challenged 60 AERD asthmatics with rofecoxib in a blinded, placebo-controlled study, and again did not identify any crossreactivity (43). Two letters to the editor reported the tolerability of celecoxib in AERD asthmatics (44,45). More recently, Woessner et al. challenged 60 AERD asthmatics with celecoxib. In contrast to the dose-response reactions seen with relative-COX-2 selective NSAIDs, such as nimesulide, and meloxicam, no reactions to celecoxib (either naso-ocular or drops in forced expiratory volume in 1 second [FEV₁] values) were seen as the dose was increased from 100 mg to 200 mg (46). Taken together, the data for the COX-2-selective inhibitors in AERD demonstrates their relative safety in this disease.

As with any medication, drug-specific reactions have been reported for celecoxib and rofecoxib, including gastric intolerance, hives,

angioedema, and renal impairment and anaphylaxis (47). Anaphylaxis with celecoxib has also been reported in an individual following her third dose of celecoxib, consistent with a classic IgE-mediated immune response (48). A recent letter to the editor reported a case of an anaphylactoid reaction to rofecoxib 40 min after what was suggested to be the first exposure to the medication in an individual with a known sensitivity to diclofenac and no history of AERD (49).

Non-COX Inhibitors and AERD

Other chemicals, dyes, and additives have been reported to crossreact with ASA although they do not possess COX-inhibitory activity (20,50–53). There is little evidence to support cross-sensitivity with ASA, as presented in the following section.

Tartrazine

Tartrazine, or Yellow #5, is an azo dye used to color foods, drinks, cosmetics, and pharmaceuticals, and has been purported in older reports to crossreact with ASA in AERD asthmatics (20,50–52). However, in 1979, Weber et al. reported that in their AERD asthmatics, reductions in lung function following tartrazine challenge were actually caused by withholding of anti-asthmatic controller medications and not by tartrazine sensitivity (54). More recently, extensive and well-controlled studies indicate that tartrazine intolerance is extremely rare among AERD subjects (55,56). There is the possibility that IgE-mediated sensitivity to tartrazine may occur in any individual, including those with AERD (16,57). In general, it is not necessary to recommend routine avoidance of azo dyes for AERD patients.

Hydrocortisone and Methylprednisolone Succinate

It has been reported that patients with AERD sporadically react to intravenous (iv) hydrocortisone and methylprednisolone succinate (58,59). As COX inhibition does not occur

with these agents, the mechanism for cross-sensitivity was obscure. Feigenbaum et al. identified one of 45 known ASA-sensitive asthmatics, who experienced angioedema and a respiratory reaction to iv hydrocortisone succinate (60). Unlike crossreactions between the NSAIDs, cross-desensitization could not be achieved between hydrocortisone succinate and ASA in this patient. The same reaction also occurred after the administration of iv methylprednisolone, which also has a succinate base. It is generally believed that succinate can function as a drug hapten in inducing IgE-mediated reactions that must be distinguished from cross-sensitivity (60). As asthma tends to be more severe in the AERD, there is greater exposure to iv corticosteroids, and thereby an increased risk of sensitization to succinate.

Monosodium Glutamate (MSG)

Questions regarding MSG and provocation of asthma were raised in the 1980s when Allen et al. published the results of MSG challenges in 32 asthmatics, of which 14 were reported to have reacted with drops in peak expiratory flow rates (53). Allen also suggested that because 13 of the 14 patients were ASA-sensitive asthmatics, this subpopulation of asthmatics were at greater risk for MSG-induced asthma exacerbations (53). Because the non-essential amino acid glutamate is found naturally in high levels in common foods (tomatoes, mushrooms, and parmesan cheese) and is added as a flavor enhancer in the form of L-monosodium salt of glutamate (MSG), Allen's report generated considerable interest as a possible explanation for intrinsic or non-allergic asthma. Moneret-Vautrin also published data suggesting a causal relationship between MSG ingestion and bronchospasm (61). However, both studies have been criticized because of uncontrolled challenge protocols and discontinuation of essential anti-asthmatic medications (62). This theory has not gained support in the scientific community, as subsequent studies with placebo-controlled

oral MSG challenges in aspirin-sensitive asthmatics—both with and without histories of restaurant-associated asthma exacerbations—failed to elicit MSG-induced bronchospasm in any asthmatics (63–66).

Sulfites

Sulfite salts of potassium or sodium were commonly used as antioxidants to prevent browning and spoiling of foods, and were found in significant amounts in food and drinks such as lettuce at salad bars, shrimp and other seafood, cut potatoes, wine, and beer. In 1981, Stevenson and Simon confirmed that sulfites induced asthma in six patients with a history of severe, life-threatening asthma attacks after eating restaurant meals containing sulfites (67). Since 1986, the number of severe reactions to sulfites has declined as the use of sulfiting agents in raw fruits and vegetables has been banned, and packaged foods containing greater than 10 ppm of sulfur dioxide equivalents must provide proper labels. To date, sulfite sensitivity has not been identified in any AERD asthmatics, with more than 200 consecutive sulfite challenges in known AERD subjects at the Scripps Clinic (personal communication).

Salicylates That do not Inhibit COX

Sodium and choline salicylates and a number of natural food-derived salicylates do not inhibit COX and do not crossreact in AERD asthmatics (2,68). As a result, adhering to a “salicylate-free” diet in order to control AERD is not effective.

Special Considerations of ASA and NSAID Interactions

Low-dose ASA exerts a cardioprotective effect by irreversible inhibition of platelet COX-1, resulting in decreased production of thromboxane A₂. As platelets are anuclear, the effect lasts the duration of platelet lifespan, 8–10 d (69,70). The nonselective NSAIDs have not yet been shown to be definitively cardioprotective, and thus the recommendation remains

that high-risk patients taking NSAIDs should also take low-dose ASA (71). Both in vitro and human in vivo studies have shown that ibuprofen and indomethacin can block platelet COX-1 inhibition by low-dose ASA, so that co-administration may compromise the cardioprotective effect of the ASA (72–75). Because the selective COX-2 inhibitors have been shown to also bind to COX-1, albeit weakly, there are theoretical concerns of potential interference of ASA acetylation of the COX-1 channel in platelets (76,77). This is a genuine concern because near-complete platelet COX-1 inactivation is required for the cardioprotective effect. If there is as little as 5–10% activity, platelets can still aggregate (78). Ouellet et al. have demonstrated, using in vitro methodology, the ability of coxibs to interfere with the ASA inhibition of platelets (79). The degree of interference correlated directly with their potency against COX-1—e.g., low affinity for COX-1 and a high degree of COX-2 selectivity confers a low potential to block ASA action in platelets—(79). Their data suggests that the highly COX-2-selective coxibs—rofecoxib and etoricoxib—would not interfere with ASA at therapeutic doses, but that there was a potential for celecoxib to do this (79). This correlates with in vivo human studies in which rofecoxib showed no interference with COX-1 inhibition by ASA, even at supratherapeutic doses (75,80). Therefore, AERD patients who are at risk for coronary artery disease should be considered for ASA desensitization.

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