Volume 18, Number 7

SHANDS at the University of Florida

July/August 2004

Drugs & Therapy BULLETIN

FORMULARY UPDATE

The Pharmacy and Therapeutics Committee met June 15, 2004. 3 drugs were added in the *Formulary* and 3 drugs were deleted and designated not available.

◆ ADDED

Extended-Release Divalproex Sodium (Depakote® ER by Abbott Pharmaceuticals)

Rimantadine (Flumadine® by Forest Pharmaceuticals)

Tiotropium (Spiriva® by Boehringer Ingelheim/Pfizer)

◆ DELETED

Bacitracin + Polymyxin B Topical Powder (Polysporin® Topical Powder by Pfizer)*

Clotrimazole Vaginal Tablets (Femcare® by Schering Plough)*

Salsalate (Disalcid®)*

*Nonformulary and Not Available

Tiotropium is a quaternary ammonium derivative that is structurally related to ipratropium. It acts as an anticholinergic bronchodilator and is indicated for the maintenance treatment of chronic obstructive pulmonary disease (COPD). Although similar to ipratropium, tiotropium possesses a unique pharmacodynamic profile allowing for once daily administration. The improved dosing schedule is a major advantage over ipratropium, which requires dosing up to 6 times daily. Tiotropium is the first anticholinergic drug approved for COPD-associated bronchospasm since the approval of ipratropium in 1986.

In clinical trials, tiotropium demonstrated superior sustained

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DRUG INFORMATION FORUM

NSAIDS + ASA = CONFUSION

Patients are seeing advertisements promoting the use of acetaminophen instead of traditional nonsteroidal anti-inflammatory drugs (NSAIDs), like ibuprofen, when they are taking low-dose aspirin for the prevention of cardiovascular events. The premise of these warnings is that traditional NSAIDs could negate the beneficial cardiovascular effects of low dose aspirin. The advertisements suggest that acetaminophen is the preferable analgesic because it has fewer drug interactions.

Is acetaminophen preferable to traditional NSAIDs in patients taking aspirin? Are COX-2 inhibitors preferable to traditional NSAIDs when acetaminophen does not work? Does low-dose aspirin cancel the lower gastrointestinal effects of COX-2 inhibitors?

What is the science behind these warnings? Is acetaminophen preferable to traditional NSAIDs in patients taking aspirin? Are COX-2 inhibitors preferable to traditional NSAIDs when acetaminophen does not work? Does low-dose aspirin cancel the lower gastrointestinal effects of COX-2 inhibitors? These are all related questions received by the Drug Information & Pharmacy Resource Center. This article will summarize what we know about these issues…and what we do not know.

ASA and Traditional NSAIDs

Concern about the use of traditional NSAIDs with low-dose aspirin can be traced to a study that shows that ibuprofen binds to the COX-1 receptor on platelets and prevents the binding of aspirin to platelets.[1] This led to the recommendation that aspirin should be given before administering ibuprofen. It also led to observational studies that suggest that chronic use of ibuprofen (and possibly other NSAIDs) may decrease the effectiveness of low-dose aspirin.[2-3] However, a recently done case-control study showed that the combination of aspirin and ibuprofen did not increase the incidence of myocardial infarctions.[4]

Intermittent use of ibuprofen (and other NSAIDs) has not been shown to alter the cardiovascular protective effects of low-dose aspirin. Chronic use of ibuprofen alone (without aspirin) may be cardioprotective compared with nothing. However, if there is concern that ibuprofen decreases aspirin's effectiveness, acetaminophen is a good option for chronic pain.

Acetaminophen at doses of less than or equal to 4 grams per day (eg, 500 mg 4 times a day) is a first-line agent for mild to moderate joint pain associated with osteoarthritis. It is a first-line therapy because it is inexpensive, has few adverse effects, and does not have many drug interactions. Patients treated with acetaminophen do not have to worry about mitigating the cardioprotective benefits of low-dose aspirin.

Unfortunately, acetaminophen may not provide sufficient pain relief. Many patients have already tried over-the-counter acetaminophen before seeking medical attention and it did not provide adequate relief. Also, many patients find it difficult to adhere to the 4-times-a-day dosage.

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effects on pulmonary function tests compared to ipratropium. Tiotropium reduced beta-agonist use, the number of COPD exacerbations, the time to exacerbation, the overall number of hospitalizations, and number of days spent in the hospital when compared to ipratropium. Significant increases in bronchodilation, dyspnea, and health-related quality of life scores were seen with tiotropium versus twice-daily salmeterol use. However, tiotropium has not been shown to reduce the number of exacerbations or hospitalizations compared with salmeterol.

The recommended dosage of tiotropium is the inhalation of one 18-mcg capsule once daily using the HandiHaler® device. The most commonly reported adverse effect with tiotropium use in clinical trials was dry mouth, followed by other anticholinergic effects (ie, constipation, increased heart rate, blurred vision, glaucoma, urinary difficulty, and urinary retention).

Depakote® ER is a once-daily version of valproic acid. Valproic acid is available in several different formulations. Divalproex sodium (Depakote®) was introduced as a sustained-release formulation of valproic acid that allowed for twice-daily dosing. The extended-release version of divalproex (Depakote® ER) was developed to permit once-daily administration. Valproic acid is also available as a liquid, as Depakote Sprinkles®, and for intravenous administration.

Similar to other antiepileptic medications, the exact mechanism by which valproic acid exerts its anticonvulsant activity is unclear. It is believed that its anticonvulsant activity results from inhibition of GABA (gamma-amino-butyric acid), an inhibitory neurotransmitter.

Depakote® ER has labeled indications for the treatment of seizures in adults and children at least 10 years old and for the prophylaxis of migraine headaches. The advantage of Depakote® ER is a simplified dosing regimen. The manufacturer's claims of more stable serum concentrations have not been shown to translate into meaningful differences in clinical outcomes.

Conversion from the regular release Depakote® to Depakote® ER requires approximately a 20% increase in dose. For example, 1750 mg of regular release Depakote® is equivalent to 2000 mg of Depakote® ER.

Depakote® ER has a black box warning for hepatotoxicity, teratogenicity, and pancreatitis. Administration of Depakote® ER is contraindicated in patients with hepatic disease or significant hepatic dysfunction.

Rimantadine belongs to the adamantane class of antiviral agents. It has activity against influenza A viruses but not influenza B viruses.

Rimantadine is FDA approved for the treatment of influenza A in adults and for the prophylaxis of influenza A in children at least 1 year of age. However, the American Academy of Pediatrics recommends rimantadine be used in the treatment of influenza A in children. Rimantadine is dosed at 100 mg twice a day for adults and children over 10 years of age.

Rimantadine has shown superior efficacy to placebo and comparable efficacy to amantadine. Symptomatic and virological improvements are the efficacy markers used in trials. Treatment appears to reduce the duration of symptoms by approximately 1 day.

Rimantadine has a significantly better adverse effect profile than amantadine. Amantadine is associated with severe gastrointestinal and central nervous system adverse effects, especially in the elderly. These effects occur less frequently with the use of rimantadine.

Salsalate is a traditional nonsteroidal anti-inflammatory drug (NSAID) that lacks antipyretic properties. Salsalate has not been dispensed in over a year and, therefore, was deleted from the *Formulary*. Other available NSAIDS include: aspirin, ibuprofen, indomethacin, and naproxen.

The manufacturer of **clotrimazole vaginal tablets** discontinued their production in 1999. Thus, it was deleted from the *Formulary*. Clotrimazole vaginal cream (eg, Mycelex®-G) is an alternative therapy.

Bacitracin and Polymyxin B Topical Powder (Polysporin®) is a topical anti-infective. It has been removed from the *Formulary* because of low utilization. Alternatives to this product include neomycin-bacitracin-polymyxin (Neosporin®) ointment, mupirocin (Bactroban®) cream or ointment, and bacitracin ointment.

by Wendy D. Smith, PharmD

PRESCRIBING

Tracking physicians' prescribing patterns: If HIPAA protects patients, then who protects physicians?

When prescriptions are dispensed in community pharmacies, an enormous database is created. When a patient brings a prescription to be filled, the pharmacist attempts to submit an electronic claim for payment by the patient's insurer. The information is transmitted online by community pharmacies to independent companies, known as "switch" companies. The switch companies provide information about the patient's third-party prescription coverage and required copayments back to the pharmacy at the time of dispensing. Each transaction submitted to the switch company contains the drug dispensed, the date, the quantity, the location where the prescription was filled, and most surprisingly, the identity of the physician writing the prescription. This process leaves the switch companies in possession of a huge amount of data. Unknown to most pharmacists, these data are then sold to an information company known as IMS America (IMS). IMS, in turn, organizes the prescription information and these data are sold to pharmaceutical companies.

Data and information are essentials of decision-making in any industry. The large amount of documentation used in health care creates a data-rich environment. Prescription databases are extremely useful in analyzing patterns of utilization.

The pharmaceutical industry uses the IMS prescription information to define marketing targets for their sales force, a practice known as "detailing." The pharmaceutical companies use the IMS data to identify physicians in specific practice areas prescribing the drugs they are interested in. The reports contain information for all drugs, not just those manufactured by that particular company. They contain prescription-writing information for all drugs within a class. This educates

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the industry on which physicians are prescribing what drugs. This would also provide insight to determine if another company is outselling them on a particular drug. Determining prescription-writing patterns allows companies to monitor the success of their sales force.

Pharmaceutical sales jobs are unlike many occupations because the representatives do not report to their "office" for work. Most of their time is spent in the community. Therefore, market share data provide a tool for the industry to monitor the activities and success of their sales representatives. If IMS data contained only information about individual drug utilization, it would be impossible to measure the success of a sales force in relative terms. For example, if the pharmaceutical company only knew that sales for their new ACE inhibitor in the Gainesville area generated $50,000 per month, it might think the marketing of the drug was successful. However, if the data showed the total market share for all ACE inhibitors in Gainesville was $500,000 per month, it would stimulate the company to increase its marketing efforts. Determining the percentage of the total market share a drug has provides a measuring tool to monitor improvement and failure of sales efforts.

IMS data are also used to help sales teams target physicians who have the largest potential to affect their market share. Physicians who prescribe large quantities of the class of medication they are interested in are identified and targeting for marketing. This allows streamlining of the marketing efforts in order to gain the largest increase in market share. Representatives of the pharmaceutical industry are often rewarded for increasing their market share above a predetermined quota.

The data provided by IMS are very specific. They identify physicians by DEA numbers writing prescriptions for the drug of interest. Approximately 10 years ago, the information could only be drilled down to the zip code for the area where the drug was being prescribed. During this time, drug representatives visited community pharmacies and asked the pharmacists about the prescribing habits of local physicians. Technology has allowed the IMS information to become much more precise by identifying the DEA number of the physician.

Within the institutional setting, a similar database is created describing the usage patterns for the entire hospital. The difference here is that the data cannot identify individual physicians.

Detailed reports of physicians' prescribing-patterns allow the pharmaceutical industry to focus their marketing efforts to receive the largest capital return. It also allows companies to "research" the success of new or innovative marketing strategies. However, in order for "research" to occur, consent from the "subject" is required, right? Not in the case of prescribing data.

Under current federal law, physicians, unlike patients, have no specific right to privacy. Neither the switch companies selling the information nor the company buying the information are required to obtain consent from physicians or patients. They are not required to obtain consent from patients because the information in the database does not identify the patient. Even though the physicians' identities are contained in the data, the data are not considered protected. This practice may change in the future.

Prescription-tracking information provides a very clear picture of prescribing patterns of physicians. This information is not considered privileged and, therefore, consent is not required for the information to be sold in an effort to target marketing.

The California Medical Association has proposed a bill to the state Senate granting physicians the ability to stop companies from using information about their prescription-writing habits in marketing campaigns. The group states that detailing is harmful to patients because it encourages physicians to use expensive brand-name drugs when cheaper, generic equivalents exist. The bill, AB 262, would create a "do-not-sell list" modeled after "do-not-call lists" for telemarketers. It would prohibit switch companies from selling prescription data for physicians who ask that their information not be used for marketing. The bill would not block the information for public health research.

The pharmaceutical industry contends that IMS data are helpful to patients because it directs the industry to physicians that can be contacted for clinical trials and physicians to notify when a drug is recalled or to distribute important safety information.

Most physicians and pharmacists are unaware this process even occurs. There is no official documentation or reference describing the process of prescription tracking. One of the services offered by IMS is "Brand Management." The IMS website (http://www.imshealth.com/ims/portal/front/indexC/0,2773,6599_43089764_0,00.html) states that "Brand Management contributes to our customers' [the pharmaceutical industry] success by providing tools, business intelligence, services and expertise at every phase of a product's lifecycle. Our goal is to ensure maximum market share while minimizing the effects of product maturity, generic erosion and other factors contributing to a decline in market share." Providing the pharmaceutical industry with prescription-tracking information earned the IMS company $1.4 billion in revenue in 2003.[1]

Prescription-tracking information provides a very clear picture of prescribing patterns of physicians. This information is not considered privileged and, therefore, consent is not required for the information to be sold in an effort to target marketing. This may change in the future as more physicians become aware of this practice. For more information on IMS, visit http://www.imshealth.com.

by Wendy D. Smith, PharmD

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1. http://www.ims-america.com/ims/portal/front/articleC/0,2777,6599_18731_40198214,00.html (accessed June 23, 2004).

POLICIES AND PROCEDURES

Alcoholic beverages and patients

Alcoholic beverages (beer, whiskey, and wine) were deleted from the *Formulary* in March of 2003. Since that time, there have been requests to allow patients to bring their own alcohol into the hospital similar to patients bringing their home medications to use while they are in the hospital. It is against hospital and university policy to bring alcoholic beverages to campus. The rationale for eliminating alcoholic beverages from the *Formulary* was because the effectiveness of using alcohol to prevent alcohol withdrawal is uncertain. Appropriate therapeutic uses of alcohol in the hospital setting are for the treatment of ethylene glycol and methanol poisonings. A review on the treatment of alcohol withdrawal may be found at http://www.shands.org/professional/drugs/bulletins/0204.pdf.

by Wendy D. Smith, PharmD

Drugs & Therapy
B · U · L · L · E · T · I · N

Volume 18, No. 7 July/August 2004

This publication is produced by the Drug Information and Pharmacy Resource Center under the direction of the Department of Pharmacy Services and the Pharmacy and Therapeutics Committee.

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Drug information forum, from page 1

This leaves prescribers and patients wondering whether a traditional NSAID and low dose aspirin is acceptable. Of course, both aspirin and the NSAID can cause gastrointestinal effects. Ideally, they would not be used together. If the NSAID cancels part of the therapeutic benefit of aspirin, the additive toxicity would result in an even worse benefit versus risk ratio.

There is some evidence that not all traditional NSAIDs have the same blocking effects with low dose aspirin. Therefore, if a traditional NSAID is chosen to treat chronic pain (ie, because of the low cost of the generic versions of these products), a traditional NSAID other than ibuprofen (eg, naproxen, diclofenac) could be considered. Also, aspirin should be given 2 hours before the dose of the NSAID.

ASA and COX-2 Inhibitors

Another alternative is to use a COX-2 specific inhibitor (eg, celecoxib) for patients with chronic pain receiving low-dose aspirin. This appears to make sense because COX-2 inhibitors are associated with less gastrointestinal effects and they do not block the COX-1 receptor on platelets. COX-2 inhibitors should not mitigate the cardioprotective effects of low-dose aspirin.

Unfortunately, there is some evidence that the gastrointestinal effect of low-dose aspirin cancels the favorable gastrointestinal profile of COX-2 inhibitors.[5] Rates of GI events in patients on a COX-2 inhibitor and low-dose aspirin approach rates expected with a traditional NSAID.

A traditional NSAID plus a gastrointestinal protective agent (eg, misoprostol) would be another reasonable alternative in a patient on low dose aspirin. Of course, this assumes that the patient has failed acetaminophen.

If low-dose aspirin is avoided in patients on a COX-2 inhibitor, there is some evidence that the rate of cardiovascular events may be higher than with a traditional NSAID.[6] This is not surprising, since traditional NSAIDs do bind to the COX-1 receptor on platelets and have been shown to confer cardioprotective effects.[7] Unlike aspirin, however, this inhibition is reversible and does not appear to be equally effective.

Summary

If acetaminophen is effective, it should be considered a first-line agent for patients on low-dose aspirin being treated for mild to moderate chronic pain (eg, osteoarthritis).

If acetaminophen is ineffective and traditional NSAIDs are used for intermittent pain, the interaction between low-dose aspirin and traditional NSAIDs has not been shown to be clinically significant.[3] However, it would be prudent to administer the low dose aspirin first and wait a period (eg, 2 hours) before administering a traditional NSAID (eg, ibuprofen).

If a patient requires chronic therapy with a traditional NSAID and low-dose aspirin, an alternative to ibuprofen could be considered. A gastrointestinal protective agent, like misoprostol or a proton-pump inhibitor could be added to the regimen.

Data suggest that chronic use of low-dose aspirin with a COX-2 inhibitor increases the risk of gastrointestinal adverse effects. A COX-2 inhibitor alone appears to have inferior cardioprotective effects compared with a traditional NSAID. How these risks and benefits of a COX-2 inhibitor balance is not clear.

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