The Pharmacist Activist

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"And without faith it is impossible to please God, because anyone who comes to him must believe that he exists and that he rewards those who earnestly seek him." Hebrews 11:6

Editorial

Consumer Fraud! Call the FDA!

Oh, Wait. The FDA is the Perpetrator!

For more than 20 years pharmacists have known that orally-administered phenylephrine is not effective as a nasal decongestant. However, the phenylephrine follies continue! This does not surprise those of us who have experienced decades of FDA indecision and questionable actions/inactions regarding medications that have been administered orally as nasal decongestants, as well as other issues.

Phenylpropanolamine

Most recent pharmacy graduates are probably not aware of phenylpropanolamine (PPA) because, almost 20 years ago, the FDA requested that drug companies discontinue the marketing of products containing this agent. Prior to that action PPA had been used for many decades as a nasal decongestant, often in OTC combination products for the relief of cold and flu symptoms. In addition, PPA was the most common active ingredient in OTC weight loss products. PPA was considered effective for these uses but questions were raised about its safety because of rare reports of hemorrhagic stroke in young women who had been using the medication.

There were so few reports of hemorrhagic stroke that it was not possible to conclusively demonstrate a cause and effect relationship with the use of PPA. Scientists at Yale University School of Medicine analyzed available case reports and other data, and issued a report that taking PPA increases the risk of hemorrhagic stroke in women (a risk that FDA characterized as very low). It is unfortunate that Yale does not have a college of pharmacy as the expertise and perspectives of pharmacists regarding real-world usage of PPA would have been helpful. Questions were raised about the Yale study that were either unanswered or there were insufficient data to provide an answer. There was reason to think that most of the small number of women who experienced hemorrhagic stroke were taking a PPA-containing product to lose weight, rather than for cold /flu symptoms. There was also speculation that some women were using PPA in higher than recommended dosages in an attempt to lose more weight faster.

The FDA convened its Nonprescription Drugs Advisory Committee to consider the Yale study and other data, and this Committee recommended that PPA be considered not safe for OTC use. The FDA subsequently took regulatory action to remove PPA from the market.

Pseudoephedrine

The removal of PPA from the market left pseudoephedrine and phenylephrine as the remaining OTC orally administered nasal decongestants (ephedrine is a separate story). Most pharmacists recognized and recommended pseudoephedrine as the more effective of the two agents, and single active-ingredient products (e.g., Sudafed) and dozens of cold/flu combination products included pseudoephedrine as the nasal decongestant. During this same time period there was rapidly increasing illicit manufacturing and misuse of methamphetamine. To reduce retail diversion of pseudoephedrine and several related agents that could be used as precursors in the illicit manufacture of methamphetamine and amphetamine, the Combat Methamphetamine Epidemic Act (CMEA) was signed into law in March, 2006.

Administered by the Drug Enforcement Administration, the

CMEA restricts the access and sale of pseudoephedrine-containing products to "behind-the counter (BTC)," requires sellers to confirm the identification of the purchaser and to maintain a logbook of sales, and establishes sales/purchases limits to the amount of pseudoephedrine that can be purchased daily or during a 30-day period. Purchasers must provide their name, address, and other pertinent information and also provide a government-issued photo I.D.

The manufacturers of the pseudoephedrine-containing products correctly anticipated that there would be a marked reduction in sales of these products when limited to BTC availability. In addition to continuing to market selected products for BTC availability, they reformulated most products to include phenylephrine as the nasal decongestant instead of pseudoephedrine to enable continued OTC availability. When they considered it advantageous, the companies exploited the FDA's willingness to permit the use of the same or very similar brand name for products with different active ingredients. As one example, the Sudafed name was continued for the BTC pseudoephedrine-containing product, and the name Sudafed PE was used for the OTC product that now contained phenylephrine as the "active" ingredient. The companies didn't want consumers to know there was any significant difference in the product they purchased based on its brand name, and the FDA apparently didn't care whether consumers knew or understood the difference. Consumers who took note of the additional "PE" following Sudafed could mistakenly think that a second ingredient was added to make the product more effective. The resulting situation is not only confusing but should also be viewed as consumer fraud! The FDA should prohibit the use of the same brand name for products that do not contain the active ingredient with which that brand name is commonly identified. If it does not feel that it has that authority now, it should take action to obtain it, rather than permit the perpetuation of the confusing name games.

Most pharmacists and our professional associations have for decades been unsuccessfully requesting the FDA to establish a "third class" or "pharmacist-only" class of drugs that would be available without a prescription. However, our profession must have experienced collective amnesia or worse in failing to recognize that the BTC availability of pseudoephedrine provided such an opportunity that might be extended to include other medications/products. Pharmacists knew that pseudoephedrine was more effective than oral phenylephrine, had the opportunity to urge customers to discuss and use the most effective product, AND charge an equitable price that would not be influenced by a PBM or insurance coverage. But the majority of pharmacists have ignored this opportunity and some consider the BTC availability of pseudoephedrine as a nuisance rather than an opportunity.

Phenylephrine

It is well recognized that the intranasal administration (i.e., nasal spray or drops) of phenylephrine provides effective relief of nasal congestion, and this is a likely contributing factor to the assumption that oral administration of the drug is also effective as a nasal decongestant. However, when administered orally, phenylephrine undergoes extensive first-pass metabolism in the gut wall and liver to inactive metabolites. This information has raised questions as to whether the oral use of phenylephrine in the usually recommended dosage is effective as a nasal decongestant. However, there has been little motivation to conduct studies to answer these questions because of the commercial success of the products and the "conventional wisdom" that they are effective.

For several decades, pharmacist Leslie Hendeles of the University of Florida College of Pharmacy has been the most prominent critic of the continued oral use of phenylephrine as a nasal decongestant. At long last a consensus is within reach that his concerns are valid. The FDA convened an advisory panel which concluded that phenylephrine was ineffective when given orally, and the FDA's own analysis indicated that oral phenylephrine is safe but ineffective at recommended or even higher dosages. It is noteworthy that the removal of phenylpropanolamine from the market was because it was considered not safe but effective, whereas the FDA analysis of oral phenylephrine is that it is not effective but safe. In a recent podcast involving two participants from the FDA and one from the American Pharmacists Association, the current data and opinions were summarized with the observation that there were no questions regarding the safety of oral phenylephrine.

The emphasis on the safety of oral phenylephrine is curious because it can't be assumed that a lack of effectiveness also means that there is a lack of risk. I am not aware of any recent studies that definitively conclude that oral phenylephrine is safe. Although it undergoes extensive first-pass metabolism, part of the oral dose is absorbed in a pharmacologically active form, although not in an amount sufficient to provide effectiveness. It is known that phenylephrine can interact with monoamine oxidase inhibitors with serious consequences. However, to my knowledge, there are no data that identify a specific quantity of oral phenylephrine that retains activity and is small enough to avoid the risk of this interaction. Therefore, an FDA statement that oral phenylephrine is safe is not based on evidence or science.

Although the FDA is not obligated to take actions that are consistent with recommendations of its Advisory Committees, it usually does so, but there have been exceptions. The FDA may decide to take no action regarding the availability of oral phenylephrine products but, even if it announces a proposed action to remove these products from the market or require reformulation to remove phenylephrine, it could take months or years for the action to be implemented.

CVS responded to the recent concerns of the FDA about the lack of effectiveness of oral phenylephrine by announcing that it would no longer sell certain common decongestant products. It was clearly stated and reported that the decision involved products that contained oral phenylephrine as the only active ingredient, and CVS continues to sell OTC brand-name and store-brand combination products that contain phenylephrine and other active ingredients. But why? The presence of other active ingredients certainly does not make phenylephrine effective! CVS apparently justifies the continued marketing of ineffective phenylephrine in OTC combination products because they include other active ingredients, while ignoring the fact that including phenylephrine contributes to a higher cost for the product and may increase the risks, notwithstanding the FDA's characterization of oral phenylephrine as "safe." In addition, stopping the sale of dozens of brand-name and store-brand combination products containing phenylephrine would at least temporarily result in lost revenues for CVS. Therefore, CVS's efforts to attain favorable publicity and

perhaps to demonstrate that it can make decisions more quickly than the FDA, are exposed as self-serving. In fact, CVS contributes to the consumer fraud that has been enabled for decades by the FDA in permitting the continued marketing of an agent that has been recognized by many as ineffective. Several law firms have announced plans to file class-action lawsuits against CVS for misleading consumers regarding phenylephrine and claims that the products are "maximum strength."

Intranasal decongestants

The previous discussion is applicable only to the oral administration of phenylephrine. When phenylephrine and other decongestants (e.g., oxymetazoline) are administered as nasal sprays or drops, they have a rapid onset of action in effectively reducing nasal congestion. However, unlike effective oral decongestants such as pseudoephedrine, the continuation of intranasally-administered decongestants for more than 3 days is likely to be associated with rebound congestion (rhinitis medicamentosa) and related complications. Although pharmacists are well aware of this precaution, many consumers aren't, and it should be discussed in the consideration of products that are alternatives to less effective products currently being used.

Stop the Fraud!

Pharmacists, consumers, and their advocacy groups must no longer tolerate the misrepresentation and fraud that is perpetrated by pharmaceutical companies and the FDA. The FDA has had decades to take action regarding oral phenylephrine-containing products but has failed to do so. Even with the recent recommendations of its Advisory Committee and other health professionals, there is no assurance that FDA will do so, even now. I propose the following recommendations:

1. Community pharmacists should discontinue the sale of orally-administered single- and multiple-active ingredient products that contain phenylephrine, return the products to the company from which purchased, and insist on a full refund. Don't be concerned if other pharmacies and retailers in your area do not take the same action. Use their decision to your advantage by urging consumers to come to your pharmacy for effective products and valuable counseling that might also include a footnote such as "Products with ineffective ingredients can still be obtained at (insert the name of your closest competitor)."
2. The FDA should initiate actions to prohibit the sale of oral phenylephrine-containing products, including those with multiple active ingredients.
3. The FDA should prohibit the use of a brand-name that is commonly identified/associated with a particular medication, in the brand name of any product that does not contain that medication.

It can be anticipated that the companies that market the products that would be discontinued or need to be reformulated will strongly oppose such actions, which would include some of the most widely-sold cold/flu combination products. But their efforts to justify the continued marketing of oral phenylephrine-containing products that only add to the cost and risk of the products will be exposed as fraudulent and self-serving.

Bonus OTC Coverage – ACETAMINOPHEN

Acetaminophen is the most widely used of all medications. It is also one of the safest medications when it is used in the recommended dosage. However, when it is used on a continuing basis in dosages that exceed the recommended dosage, it can cause severe hepatotoxicity that may necessitate a liver transplant, if available, or could be fatal. Acetaminophen overdosage is the most common cause of acute liver failure, and results in tens of thousands of hospitalizations, or worse, each year. Although some overdosages are intentional (i.e., attempted suicide), most are accidental and usually attributable to insufficient consumer awareness of the recommended dosage, as well as the inclusion of this analgesic in OTC and prescription products that contain multiple active ingredients. When individuals experience a cold or the flu in which pain and fever are not the most prominent symptoms, they focus more on the most bothersome symptoms (e.g., cough, nasal congestion, runny nose) and, unless they read the listing of ingredients, often do not realize that acetaminophen is one of the 3 or more active ingredients in the product they are using.

The maximum recommended dosage of acetaminophen for most adults is 4,000 mg during a 24-hour period. The most common dosage regimens that reach or approach the maximum dosage are 2 extra-strength (500 mg) tablets every 6 hours and 2 longer-acting (650 mg) tablets every 8 hours. A lower maximum recommended daily dosage would be appropriate for individuals with hepatic impairment or who are otherwise more vulnerable (e.g., alcoholism) to hepatotoxicity. Many individuals use acetaminophen, or another OTC analgesic, on an occasional basis for the treatment of conditions such as headaches. However, others experience conditions characterized by chronic pain such as osteoarthritis or back pain, and these are the individuals who would be using acetaminophen on a continuing basis with which there is a greater possibility of overdosage.

Accidental acetaminophen overdosage with severe consequences occurs often enough that it is well recognized by health professionals and public health personnel. Specific educational and other initiatives have been developed to increase the public's awareness of the importance of knowing the active ingredients in all medicinal products they are taking and the appropriate dosage for each. However, these programs have had limited success in reducing the number of accidental acetaminophen overdosages.

It is reasonable to think that consumers will have a better understanding of the content, use, and appropriate dosage of a product in which acetaminophen is the one and only active ingredient. The amount of the drug taken during a 24-hour period can also

be quickly determined. It is the combination products containing acetaminophen along with other active ingredients that are the most important causative factor in accidental acetaminophen overdosages.

Some consider the frequency and severity of acetaminophen overdosage to be sufficiently important to recommend that the availability of acetaminophen be restricted to prescription-only status. I do not consider this action to be necessary, but will provide the following recommendations:

1. Community pharmacists should discontinue the sale of multiple active-ingredient products that include acetaminophen, and only provide acetaminophen in products that include it as a single active ingredient. This will facilitate consumer understanding, pharmacist monitoring, and the use of acetaminophen in an appropriate dosage that should significantly reduce the number of accidental overdosages.
2. The FDA should initiate actions to prohibit the inclusion of acetaminophen in OTC products that contain other active ingredients. In monitoring the anticipated success of this action, taking the same action with prescription combination products that include acetaminophen (e.g., hydrocodone/acetaminophen) should be considered

CAUTION: Even if FDA officials quickly agree that this action should be taken, it should be anticipated that it will take at least 20 years for laws, rules, regulations, etc. to be finalized, during which time many avoidable overdosage tragedies will occur. Therefore, pharmacists, other health professionals, and public health personnel must assume the leadership in establishing effective interventions that will increase the safety of the public.

As noted in the discussion of the discontinuation or reformulation of oral phenylephrine-containing products, it can be expected that the companies that market OTC combination products that contain acetaminophen will strongly oppose this recommendation. However, for OTC products that include phenylephrine , acetaminophen, and other active ingredients, reformulating once to remove both phenylephrine and acetaminophen will be more cost effective than having to reformulate the products on two occasions.

Community pharmacists have the opportunity to implement these recommendations quickly. I look forward to learning of your experiences in doing so.

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ADDENDUM:

The following is an acetaminophen quiz that pharmacists can give to student pharmacists employed or participating in rotations at your pharmacy.

1. What is the generic designation for the active ingredient in Tylenol?

2. What is the generic designation for this active ingredient in Canada and numerous other countries?

3. What abbreviation is commonly used for the active ingredient in Tylenol?

4. What is the chemical name for this active ingredient from which the abbreviation is derived?

5. What is the origin of the brand-name Tylenol?

Answers:

1. acetaminophen
2. paracetamol
3. APAP
4. N-acetyl-para-aminophenol
5. "Tyl" are the last 3 letters in acetyl, and "enol" are the last 4 letters in phenol

Editor's note: You can determine the passing grade for your students. I would not expect them to know the answer to question 5, and possibly not to question 2, unless they are going to a great school of pharmacy.

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