The Pharmacist Activist

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Editorial

The Assault on Compounding Must be Rejected!

If there is any activity that can be identified as being responsible for the emergence, many years ago, of pharmacy as a profession that is different from the other health disciplines, it is the compounding of medications. This responsibility might be considered a "birthright" of our profession and predates the development of large pharmaceutical companies that now make the vast majority of both prescription and nonprescription drug products.

Over the years, the rapid growth of the pharmaceutical companies and the approval of many new therapeutic agents in formulations supplied by these companies resulted in a situation in which only a very small percentage of prescriptions required compounding by pharmacists. Today, many practicing pharmacists do not compound any prescriptions.

Notwithstanding the very important advances in the development of new medications and formulations for which the pharmaceutical companies deserve great credit, there has been a growing recognition that these companies don't and won't supply their medications in enough potencies and formulations that will provide the best therapy for all patients who are candidates for treatment with a particular medication. In other words, one (or even several) potency(ies) or formulation(s) doesn't fit all. This is not a criticism of the pharmaceutical companies, but rather a recognition of the practical limitations on the number of potencies and formulations of a medication that are commercially feasible.

An increasing number of pharmacists and physicians have identified patients for whom treatment with certain medications is less than optimal because of the limited options and/or flexibility with respect to the commercially-available formulations of these medications. This has resulted in a significant increase in the extent to which some pharmacists have become involved in compounding prescriptions and, indeed, the practices of some pharmacists are devoted exclusively to compounding. The compounding of prescriptions provides an excellent professional opportunity for pharmacists to contribute to personalized and improved drug therapy for patients, as well as a financial opportunity to be equitably compensated for their services. However, I would contend that the increased number of compounded prescriptions is not just an opportunity, but is a responsibility of the profession of pharmacy which is uniquely prepared to optimize drug therapy in this manner. This responsibility will become all the more important as we become even better positioned to personalize drug therapy as a result of the rapid advances in pharmacogenomics and in identifying patient factors that influence the type and extent of responses to medications.

The need for compounding

The situations that presently create the need to compound prescriptions are numerous. Many medications are available in dosage forms and potencies that are intended only for use in adult patients. When physicians identify a need to use these medications in children, there is often a need for a dosage and formulation (e.g., oral liquid) that are not commercially available. Many individuals have medical problems associated with current or anticipated nutritional deficiencies for which mixtures of the appropriate nutritional supplements are compounded for oral or parenteral use. To provide optimal use of medications, there is sometimes a need to use a dosage, route of

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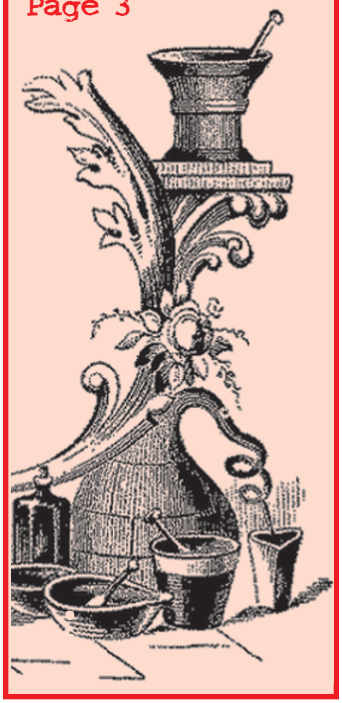

administration, and/or formulation that cannot be met with the commercially-available formulations. Some patients are allergic to an "inactive" ingredient in a formulation, such as a preservative, necessitating the compounding of a prescription that does not include the agent causing the problem. Other circumstances in which compounding is required also exist and the number of such situations will continue to grow as expanding knowledge and technology provide the opportunity to personalize drug therapy to a much greater extent. In addition to meeting the needs of humans for compounded prescriptions, some pharmacists have developed veterinary compounding practices.

Crossing the line

The increase in compounding, as well as the promotion and publicity surrounding it, has not been without debate and some controversy. Some pharmacists have "crossed the line" by engaging in activities such as manufacturing rather than compounding medications for individual patients, compounding products that essentially duplicate formulations that are commercially available, failing to have the appropriate facilities and procedures that will provide confidence in the quality, potency, and safety of the compounded prescriptions, or making unsubstantiated claims regarding the compounded prescriptions. These actions are inappropriate and it is important that the profession of pharmacy, in conjunction with state boards of pharmacy, have appropriate standards and the ability to take prompt and effective action to prevent the continuation of such situations. The establishment of the Pharmacy Compounding Accreditation Board is a positive step in this direction.

Excessive responses of the FDA and some legislators

Although there have been some valid concerns, the Food and Drug Administration (FDA) has been excessive in its challenges to compounding pharmacists. The FDA has viewed compounded prescriptions as new, unapproved drugs, a position that would place paralyzing restrictions on the practices of medicine and pharmacy, and that was rejected last year by a federal district court judge. The FDA has also attempted to prevent the promotion or advertising of the compounding of medications, restrictions that were ruled unconstitutional by the U. S. Supreme Court in 2002. In addition, there have been some situations in which the FDA has intruded into areas in which state boards of pharmacy have authority and, in some cases, has inappropriately alleged that certain pharmacies were manufacturing rather than compounding. In certain of these latter situations, the FDA appears to have mistakenly tried to correlate a large number of compounded prescriptions and/or large quantities of compounded products with its allegation of manufacturing. However, just as a pharmacy would not be suspected of inappropriate activity based just on a large number of prescriptions for commercially-available products that are dispensed, a pharmacy that dispenses a large number of compounded prescriptions should not be suspected of inappropriate activity for that reason.

The FDA should cease and desist with respect to its excessive responses and look for ways in which it can work with compounding pharmacists, and support and enhance their efforts to address patient needs and personalize and optimize drug therapy.

Some legislators have overreacted to infrequent reports of problems related to compounding and, under the banner of Safe Drug Compounding, have proposed legislation that would give too much authority to the FDA and excessively restrict pharmacists and physicians. These legislative initiatives must be rejected.

Excessive responses of some pharmaceutical companies

Some pharmaceutical companies have been highly critical of the compounding of certain products. Although this criticism is voiced in the context of a concern for patient safety, close evaluation usually reveals a priority of wanting to avoid the loss of even a small fraction of the company's sales of its product to compounded prescriptions. One noteworthy example is Wyeth's filing in 2005 a "Citizen Petition Seeking FDA Actions to Counter Flagrant Violations of the Law by Pharmacies Compounding Bio-Identical Hormone Replacement Therapy Drugs that Endanger Public Health." Although this petition raises some valid questions, Wyeth's lengthy discourse does not identify even one patient who has been harmed by a compounded hormonal prescription (in marked contrast to the experience with Wyeth's hormonal products). The petition also ignores the benefits that many women say they have experienced with the use of these compounded prescriptions.

The filing of this citizen petition has reportedly prompted more than 30,000 responses from patients, physicians, and pharmacists, many of whom are concerned that the FDA may restrict the availability of the compounded hormonal prescriptions which they have found beneficial. The extent of the response has been so overwhelming that, almost two years later, the FDA is still reviewing this matter and has not yet taken action on the petition. In my opinion, Wyeth is wasting the time of the FDA staff in filing this citizen petition that is viewed by many as self-serving rather than addressing a situation that has placed patients at risk.

Wyeth should withdraw its citizen petition. If it doesn't, the FDA should reject it.

Should Premarin remain on the market?

The bioidentical (better designated as human) hormones about which Wyeth has raised concerns are actually present in the human body, and compounded prescriptions include them in specific amounts. In sharp contrast, Wyeth's Premarin is described as containing "...a mixture of conjugated estrogens...occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine." The actual composition of Premarin, as well as the amounts and pharmacologic roles of the individual components (some of which were designated for many years as "impurities") continue to raise questions. Indeed, Wyeth has exploited this confusion for its own financial advantage by blocking the approval of generic products for many years.

Products such as Cenestin and Enjuvia that contain synthetic conjugated estrogens in specific amounts are now available, as are the bioidentical hormones that can be used in compounded prescriptions for patients who need more personalized dosages. Why should products derived from the urine of horses and for which the exact quantities of ingredients are not identified continue to be used? Should those who have these concerns adopt the Wyeth strategy of filing a citizen petition to request that Premarin and the combination products in which it is included be withdrawn from the market?

Daniel A. Hussar

New Drug Review

Bismuth subcitrate potassium (Pylera [with metronidazole and tetracycline] – Axcan)

Antiulcer Agent

New Drug Comparison Rating (NDCR) = 3 (no or minor advantages/disadvantages, or advantages and disadvantages of similar importance)

in a scale of 1 to 5, with 5 being the highest rating

Indication:

In combination with omeprazole for the treatment of patients with Helicobacter pylori infection and duodenal ulcer disease (active or history of within the past five years) to eradicate H. pylori.

Most important risks/adverse events (associated with the new drug, bismuth subcitrate potassium):

Neurotoxicity (associated with excessive doses); may interfere with diagnostic imaging of the gastrointestinal tract (because bismuth absorbs X-rays); contraindications, warnings, and precautions with metronidazole and tetracycline must also be observed.

Most common adverse events:

Stool abnormality (16%; e.g., black stool attributable to bismuth), diarrhea (9%), abdominal pain (9%), dyspepsia (9%), darkening of the tongue.

Usual dosage:

Three capsules (representing 420 mg of bismuth subcitrate potassium, 375 mg of metronidazole, and 375 mg of tetracycline) four times a day after meals and at bedtime for 10 days; used in conjunction with omeprazole for which the recommended dosage is 20 mg twice a day after the morning and evening meals for 10 days.

Product:

Capsules containing 125 mg of tetracycline in an inner capsule and a blend of 140 mg of bismuth subcitrate potassium and 125 mg of metronidazole in the outer area of the larger capsule.

Comparable drugs:

Helidac regimen (bismuth subsalicylate [Pepto-Bismol], metronidazole, and tetracycline, in conjunction with an H_2-receptor antagonist); regimen including omeprazole, amoxicillin, and clarithromycin; regimen including lansoprazole, amoxicillin, and clarithromycin (PrevPac).

Advantages:

- Shorter duration of treatment (10 days compared with 14 days with the Helidac regimen);
- Bismuth salt is swallowed in capsule (compared with tablet in the Helidac regimen that is chewed);
- May be used in patients who are allergic to penicillins (compared with amoxicillin-containing regimens).

Disadvantages:

- Less convenient dosage regimen (administered four times a day compared with twice a day with the amoxicillin/clarithromycin-containing regimens).

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New Drug Review (cont.)

Comments:

Bismuth subcitrate potassium, also known as biskalcitrate, is a soluble, complex bismuth salt of citric acid. It is not available as a single agent but is included in a combination formulation (Pylera) that also contains metronidazole and tetracycline. This formulation is used in conjunction with omeprazole in a "quadruple" regimen that is most similar in content to the Helidac regimen (bismuth subsalicyclate, metronidazole, and tetracycline, in conjunction with an H2-receptor antagonist [e.g., famotidine, ranitidine]). In the clinical studies, the Pylera regimen was compared with an omeprazole/amoxicillin/clarithromycin regimen and was at least as effective as the latter regimen in eradicating Helicobacter pylori in patients with duodenal ulcer disease. The Pylera regimen may be particularly useful in patients who are allergic to penicillins and in patients in whom clarithromycin-containing regimens have not been effective.

The adverse events experienced most frequently with the Pylera quadruple regimen are gastrointestinal effects such as stool abnormality (e.g., black stool), diarrhea, abdominal pain, dyspepsia, and nausea. Some patients experience a temporary and harmless darkening of the tongue, which is known to be associated with bismuth salts. Although bismuth is presumed to reduce the absorption of tetracycline, the clinical importance of reduced tetracycline systemic exposure is not known because the relative contribution of systemic versus local antimicrobial activity against H. pylori has not been established. Bismuth subcitrate potassium and tetracycline are physically separated in the capsule formulation in which they are supplied by placing tetracycline in an inner capsule that is contained within a larger capsule that contains a blend of the bismuth salt and metronidazole in the outer area.

The focus of this review is on bismuth subcitrate potassium, which is the new molecular entity. However, the appropriate precautions also must be observed with respect to the other agents with which it is used in combination (i.e., metronidazole [e.g., avoidance of alcoholic beverages, neurologic adverse events], tetracycline [e.g., photosensitivity reactions, drug interactions], omeprazole [e.g., interactions with medications that require an acid medium for adequate absorption]).

The recommended dosage of Pylera capsules is three capsules four times a day after meals and at bedtime for 10 days. Patients should swallow the capsules whole with a full glass of water. Omeprazole is administered separately twice a day for 10 days. The need to administer the new product four times a day is less convenient than the omeprazole or lansoprazole/amoxicillin/clarithromycin regimens that are administered twice a day. The recommended 10-day duration of treatment with the new product is shorter than the 14-day course of treatment that is recommended for some of the previous regimens.

Daniel A. Hussar