The Pharmacist Activist

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Editorial

The Meningitis Tragedy – More Regulation is Not the Answer

Twenty-nine deaths and 368 people ill with meningitis at the time I prepare this commentary. And the story is far from complete. **Meningitis, Deaths, Compounding Pharmacies, New England Compounding Center (NECC)** have dominated the media headlines in recent weeks. Most of the deaths and illness from meningitis are considered to be attributable to a heretofore obscure fungal organism (*Exserohilum rostratum*) that was a contaminant in presumably sterile formulations of methylprednisolone that were administered by epidural injection for the treatment of back pain. The product was prepared by the New England Compounding Center in Massachusetts and distributed to physicians and hospitals in numerous states.

Tragedy

I do not use the word "tragedy" lightly. It is the strongest word that I think of to describe the consequences of the situation that has occurred. It is an appropriate description for *one* death that was preventable, but this situation is multiplied many times over. In addition, hundreds of patients have been diagnosed with meningitis, and thousands of others have received injections from the same lots of medication and not experienced complications but are fearful that they will. There are many components of this experience that will continue to be examined and discussed in depth. However, none of them should be allowed to diminish the concern and compassion for the families of those who died, and the efforts to accomplish the recovery of those who are ill with meningitis.

The New England Compounding Center

Information provided by the Food and Drug Administration and other agencies, as well as news reports, strongly suggest that there were multiple failures on the part of the NECC with respect to compliance with standards, procedures, and safeguards that are applicable to the preparation of sterile products. I can't explain the reasons for these failures and will not attempt to defend them. Extensive discussion has centered around the questions as to whether NECC should be considered a compounding pharmacy or a pharmaceutical manufacturer, and which regulatory agency is responsible for monitoring its operations.

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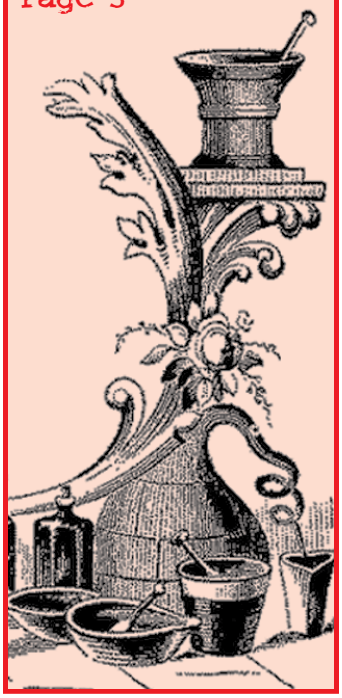

Compounding pharmacies

At one time all pharmacies compounded prescriptions but, at present, many pharmacies do little or no compounding. However, in recent years there has been an increased awareness that the health needs of many patients can be best served by combinations of medications and inactive ingredients and/or special dosage forms that are not commercially available. Compounded prescriptions can be considered to be the original personalized medicines. Accordingly, many pharmacists have emphasized compounding as an important component of their practice and the practices of some pharmacists are entirely committed to the compounding of prescriptions and related services. In addition to being licensed by a state board of pharmacy, there is a voluntary accreditation process in which many of these pharmacies participate and are evaluated.

Some pharmacists limit the extent of their compounding to non-sterile formulations whereas others have the facilities, equipment, and procedures to also prepare sterile products and other specialized formulations. The number of prescriptions dispensed by most compounding pharmacies is relatively small when compared with the number of prescriptions dispensed in traditional pharmacies, and the patients served are in the local community. A smaller number of compounding pharmacies prepare a much larger number of prescriptions for patients in a larger geographical area. However, regardless of whether the number of compounded prescriptions is small or large, a central tenet of a compounding pharmacy practice is that each prescription is prepared for a particular patient.

Manufacturing

The manufacturing of pharmaceutical products has been the responsibility of pharmaceutical companies that then provide the products to pharmacies, physicians, or others that are authorized to provide the medications to patients. The Food and Drug Administration (FDA) is the agency that has the authority to regulate pharmaceutical manufacturers. However, the FDA does not have the authority to regulate the practice of pharmacy or the practice of medicine. This is the responsibility of the state licensing boards.

An important question that has emerged in the tragedy resulting from the use of contaminated injections is whether the NECC functioned as a compounding pharmacy and supplied medications for individual patients, or whether it functioned as a manufacturer that supplied products for subsequent use in individuals for whom it did not have names or records. Three lots of methylprednisolone injection, representing a total of 17,676 vials, have been implicated in the occurrence of meningitis that has been attributed to contamination of the product. This large number of vials coupled with the apparent lack of patient names on the labels of vials, as well as additional information derived from the multiple investigations that are underway, give every appearance that NECC was engaged in manufacturing.

More regulation is not the answer!

State Boards of Pharmacy have regulations that are applicable to the practice of pharmacy and the operation of pharmacies, and the FDA has regulations that are applicable to the companies that manufacture pharmaceutical products. Some of the news reports of the meningitis tragedy have made reference to the "loosely-regulated" area of compounding pharmacy, and some legislators and others are calling for tighter regulations for these pharmacies. However, I would contend that the current regulations are sufficient and provide appropriate authority for the regulatory agencies.

News reports indicate that both the FDA and the Massachusetts Board of Pharmacy had communicated concerns to NECC on previous occasions. Apparently there was an awareness of existing problems or the potential for such. In my opinion, the problem in the current situation is that existing regulations were not adequately monitored and enforced with appropriate actions. I feel that the FDA and boards of pharmacy do not have adequate resources and staffing to appropriately fulfill their responsibilities and this situation must be addressed. More regulation is *not* the answer – instead, we must direct our efforts to increase the monitoring and effective utilization and enforcement of regulations we have now.

In an area such as compounding pharmacy, it is unlikely that the officials and investigators of the FDA or a board of pharmacy will have significant experience and expertise in the operations and responsibilities being evaluated. I recommend that these agencies appoint advisory panels of pharmacists, and others as appropriate, with pertinent experience and expertise who can provide objective recommendations that will be of value to the agencies in making the most appropriate decisions. The current use of advisory committees by the FDA to make recommendations regarding the approval of new drugs provides a model that can be considered.

Daniel A. Hussar

New Drug Review

Elvitegravir/cobicistat
(with 2 other agents in Stribild – Gilead)

Antiviral Agent

New Drug Comparison Rating (NDCR) = 4

(significant advantage[s]) in a scale of 1 to 5 with 5 being the highest rating

Indication:
A complete regimen (combination formulation Stribild includes elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate) for the treatment of HIV-1 infection in adults who are antiretroviral treatment-naïve.

Comparable drug:
Raltegravir (Isentress).

Advantages:
- Is administered once a day (whereas raltegravir is administered twice a day);
- Is supplied in a combination formulation that facilitates convenient use (one tablet once a day);
- May have less risk of causing severe skin and hypersensitivity reactions (included as a warning in the labeling for raltegravir).

Disadvantages:
- Use is limited to patients who are antiretroviral treatment-naive;
- Is not indicated for use in patients less than 18 years (whereas raltegravir is indicated for children as young as 2 years);
- Is only supplied in a combination formulation and is not available as a single agent;
- Product interacts with more medications (primarily attributable to cobicistat).

Most important risks/adverse events
(including those attributable to the emtricitabine and tenofovir components of the formulation):
Lactic acidosis and severe hepatomegaly with steatosis (boxed warning); risk of exacerbation of hepatitis B virus (HBV) infection in patients who are coinfected with HIV and HBV; redistribution/accumulation of body fat; immune reconstitution syndrome; decreases in bone mineral density; new onset or worsening renal impairment (estimated creatinine clearance, urine glucose, and urine protein should be determined prior to treatment; therapy should not be initiated in patients with estimated creatinine clearance below 70 mL per minute; treatment should be discontinued in patients whose estimated creatinine clearance is below 50 mL per minute; should not be used concurrently with medications that are nephrotoxic); should not be used concurrently with other antiretroviral agents (because the combination formulation is a complete regimen) or with adefovir dipivoxil (Hepsera); elvitegravir is a substrate for CYP3A pathways, and cobicistat is an inhibitor of CYP3A, CYP2D6, and P-glycoprotein; increases the action of other drugs that are CYP3A substrates and concurrent use with alfuzosin, lovastatin, simvastatin, ergot derivatives, cisapride, pimozide, and sildenafil [for pulmonary arterial hypertension] is contraindicated; strong inducers of CYP3A (rifampin, St. John's wort) may reduce efficacy resulting in the loss of virologic response, and concurrent use is contraindicated; action may be reduced by the simultaneous use of antacids, and the administration of the products should be separated by at least 2 hours; may interact with numerous other medications and concurrent therapy should be closely monitored.

Most common adverse events
(with the combination formulation):
Nausea (16%), diarrhea (12%), abnormal dreams (8%), headache (7%), fatigue (5%).

Usual dosage:
One tablet once a day with food.

Product:
Stribild tablets – elvitegravir – 150 mg, cobicistat – 150 mg, emtricitabine – 200 mg, tenofovir disoproxil fumarate – 300 mg.

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New Drug Review (cont.)

Comments:

Elvitegravir is the second antiretroviral agent that acts as an HIV-1 integrase strand transfer inhibitor to be approved for the treatment of HIV-1 infection, joining raltegravir. The new drug is not supplied as a single agent but rather in a combination formulation that also contains three other agents including another new drug, cobicistat, that inhibits the metabolism of elvitegravir via the CYP3A metabolic pathways, as well as emtricitabine (Emtriva), a nucleoside reverse transcriptase inhibitor, and tenofovir disoproxil fumarate (Viread), a nucleotide reverse transcriptase inhibitor. Cobicistat has been designated as a pharmacokinetic enhancer and increases/prolongs the action of elvitegravir in a manner analogous to the use of ritonavir (Norvir) to "boost" the action of the HIV protease inhibitors by inhibiting their metabolism. However, in contrast to ritonavir, cobicistat does not exhibit antiviral activity. The use of elvitegravir, cobicistat, emtricitabine, and tenofovir together in a combination formulation (Stribild) provides a complete regimen for the treatment of HIV-1 infection in adult patients who are antiretroviral treatment-naïve.

The effectiveness of Stribild was demonstrated in two clinical trials in adult patients who had not previously been treated for HIV infection. In one study it was compared with Atripla (a combination of emtricitabine, tenofovir disoproxil fumarate, and efavirenz) and administered once a day and, in the other study, it was compared with Truvada (a combination of emtricitabine and tenofovir disoproxil fumarate) plus atazanavir (Reyataz) and ritonavir, administered once a day. The studies were designed to identify the percentage of patients who had an undetectable amount of HIV in their blood at 48 weeks. Treatment with Stribild attained this outcome in 88% and 90% of the patients in the two studies, compared with 84% of the patients treated with Atripla and 87% of the patients treated with Truvada plus atazanavir and ritonavir.

Like raltegravir, elvitegravir appears to be well tolerated. Many of the risks associated with the use of the combination formulation in which it is included have previously been associated with the use of other antiretroviral agents such as emtricitabine and tenofovir that are also included in the formulation. Cobicistat has an important role in inhibiting the CYP3A metabolism of elvitegravir and prolonging its duration of action to the point that it may be administered just once a day. However, many of the interactions that may occur with the use of Stribild are attributable to the inclusion of cobicistat.

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