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TALKING POINTS

Comments on Drugs Difficult to Compound and the Quality of Chemicals to Be Used in Compounding

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ABSTRACT

These comments are minor modifications to the material submitted by the author to the docket for the FDA Pharmacy Compounding Committee that met on October 15 and 16, 1998.

SUSTAINED-RELEASE PRODUCTS

I have recently read that it takes companies with a business that is solely the design of sustained-release oral products from five to seven years to develop a new product successfully, the longer time being necessary for molecules that are more water soluble. Then, why can a compounding pharmacist make any drug into a sustained-release product in 10 minutes regardless of water solubility, pharmacokinetic parameters, and the like from a general formula (Fig. 1) provided by a supply company?

Mixing with hydroxymethyl cellulose or related substance and lactose and placing in a capsule is the preferred method, with no testing of total drug content or rate of dissolution. The most common drugs sold by compounding pharmacists in this way are morphine sulfate, oxycodone hydrochloride, and verapamil, although theophylline, a drug on many negative formularies, has been compounded.

I have already written that such sustained-release products can be expected to release the active ingredient far too quickly and may not release all the active ingredient. This has been confirmed by data for verapamil sent to my graduate student from a pharmacy school, receiving support from a supply company, that teaches students how to compound sustained-release capsules and determine their dissolution characteristics. This data also confirmed reports on national television using data obtained in a commercial laboratory regarded as the leader in evaluating sustained-release products. The featured pharmacist was a past president of the Florida Pharmaceutical Association, his former partner was a member of the Florida House of Representatives, who pushed any bill to support compounding activities.

I know of two pharmacies that make sustained-release methylphenidate capsules. Parents have told me that they can tell how much water their child has consumed by the behavior of the child. Isn't this also predictable? That the release of the active ingredient from a manufactured

SUGGESTED FORMULA FOR TIME-RELEASE CAPSULES (#1):

Methocel (E4M) 100 mg
(this will occupy 40% of the volume of a #1 capsule)
Active Ingredient
(up to 60% of the volume of a capsule may be occupied by the active ingredient)
Lactose or Corn Starch
(if a filler is needed to complete the bulk of the capsule)

SUGGESTED COMPOUNDING PROCEDURE

1. Weigh a medium packed #1 capsule full of the active ingredient (weigh against a blank capsule).
2. Express as a percentage the ratio of the desired amount of the active ingredient to the weight obtained in item 1 above. Example: a medium packed #1 capsule contains 200 mg progesterone; 100 mg is the desired amount of active ingredient; 100 mg/200 mg = 50%.
3. Add the percentage obtained in item 2 above to 40% of the volume occupied by the methocel and subtract this total from 100% to find the amount of filler needed.

Figure 1.

sustained-release product must be independent of food and water intake is never mentioned at the cult meetings of compounding pharmacists. Compounders also make sustained-release fen-phen products with both drugs in the same capsule.

The main target of compounding pharmacists is the vulnerable elderly, who are targeted by sales of sustained-release morphine and oxycodone to nursing homes, hospices, and the like in the Sun Belt. These sales result in huge profits, helped by the overpricing by the legitimate manufacturer, for the nursing homes and compounding pharmacists.

In any other industrialized nation and in most of the third world, pharmacists who make their own sustained-release products would lose their licenses for life; in the United States, they become leaders of the profession. Compounding pharmacists also make slow-release estrogen implants using pellet machines. No slow-release product should ever be compounded.

PRODUCTS MANUFACTURED TO BE RECONSTITUTED BY THE PHARMACIST

Manufactured products to be reconstituted by the pharmacist are mostly pediatric suspensions and injections. It costs the manufacturer much more to produce these products for reconstitution than it would if they sold a finished drug. So, why do compounders totally ignore the stability problems of antibiotics? The worst case is that of Augmentin®. The pH profiles and solubilities of molecules are never looked at by compounding pharmacists; the patient's parent is simply asked about the child's favorite flavor. I have had telephone calls from parents who have had several products reflavored, and their child has become very sick. The child has recovered when the original drug was correctly reconstituted in a chain pharmacy. Such small numbers of calls prove nothing, but any thoughtful pharmacist should see a red flag when reconstitution is involved. The matter is not simply one of pH, as has been stated to compounders, but also involves potential catalysis by all added components and, most important, the solubility of the hydrolyzable molecule; this solubility is also influenced by pH and the presence of all other ingredients. In some compounding pharmacies, seats are provided for children to watch their medicine being made (or more probably mutilated).

All products supplied by the manufacturer to be reconstituted should be reconstituted as directed by the manufacturer. The active ingredient, whether obtained from the powder for reconstitution or from a solid dosage form such as a tablet or capsule, should never be reformulated in a pharmacy.

INJECTABLES

By law, injectables should be sterile and pyrogen free. The Millipore filters and generic equivalents used by compounding pharmacists are excellent for helping maintain sterility during transfer of one sterile solution to another; they are not designed as a primary method of sterilization, and they do not remove pyrogens. Of the several injections made by compounding pharmacies, the worst example is morphine sulfate for intrathecal use, sometimes with the addition of clonidine. It is well documented that the spinal fluid is very much more susceptible to pyrogens than is blood. I have been told by a very reliable person, in Washington, that if someone knowingly takes advantage of loopholes in Medicare payment methods, then they are guilty of Medicare fraud. Thus, Medicare fraud is the reason for compounders who make morphine sulfate injections for intrathecal use. The Merck Index gives a water solubility of morphine sulfate as around 64 mg per milliliter at room temperature. A commercial product (i.e., one proved to be sterile and pyrogen free) of 50 mg per milliliter is available. There is absolutely no need to compound morphine sulfate in-

trathecal products other than to take advantage of the ridiculous amount paid by Medicare for the compounding of morphine sulfate injection.

A method of making these injections is to be found in an early issue of the *International Journal of Pharmaceutical Compounding*. No analysis of the finished product is recommended in the article, but occasional testing of sterility and freedom from pyrogens are recommended. This journal accepts advertising from supply companies. The editor has been involved with a supply company for years, and another supply company has recently proudly announced his appointment as a consultant, yet he is supposedly representing the USP on this committee. This is a major conflict of interest in the eyes of many people, but apparently not in the eyes of the Food and Drug Administration (FDA) or USP.

There is a need to make injections occasionally in an institutional setting, but these should never be released until a sterility test, pyrogen tests, and chemical analysis have been conducted. It is criminal to make injections for intrathecal use without at least testing for pyrogens and sterility. Testing drugs using caveman-type technology (i.e., using the five senses, as suggested on national television by a prominent member of the Florida affiliate of the American Pharmaceutical Association) is hardly adequate as we approach the third millenium.

INHALATION FLUIDS

I personally would only use a sterile inhalation fluid provided in a sealed unit dose container. The active ingredients of inhalation fluids are notoriously fragile molecules. Their decomposition can be accelerated by filter materials, plastic, glass, and the metals used during production. Every new supply of filters and containers has to be tested by the manufacturer for compatibility with each active ingredient and any preservative to be added. One type of cheap container cannot be used for all inhalation fluids, as is done by compounding pharmacists. I have been told by students that benzalkonium solutions are produced in plastic milk cartons in a pharmacy making 30,000 vials a day. Apparently, no one considers that the surface-active benzalkonium can remove plasticizers from the carton. The same pharmacy also used already yellowing albuterol manufactured in a third world country and obtained from a well-known supply company. Using chemicals manufactured in third world countries and of unknown quality is common in compounding pharmacies.

Mixing two active ingredients is not a good idea. For example, I have a patient (a Medicaid patient) who talked to me about a mixture of ipratropium and albuterol containing benzalkonium. At first, she used commercial products (i.e., separate active ingredients in sealed vials) (the best). Then, she was persuaded to have the prescription compounded in a single vial, with benzalkonium added. This very sick patient now found that the interval between doses was shortened considerably, and what once was a prescription for a month now left her several days short. On returning to the original chain pharmacy and obtaining the manufactured separate drugs, the problem disappeared. The potency was thus reduced in the compounded mixture. This is not due to any pharmacological activity of benzalkonium, a problem that has been overstated. The problem is due to poor weighing or stability, probably the latter.

Others have told me, and will publish information, that their laboratories have found a loss of potency in the mixture of albuterol and ipratropium when certain benzalkoniums are added. This can occur even if all three ingredients are of USP quality, which emphasizes the point that the USP allows a considerable range of ingredients in the mixture called benzalkonium; ethical manufacturers carefully screen every batch of benzalkonium to see if it satisfies the problems in their particular environment.

Clinical pharmacy representatives and physician specialists using inhalation fluids have told me that they see no reason to compound inhalation fluids as the range of proven manufactured products is adequate. Why are inhalation fluids compounded? Again, the answer is Medicare fraud. Some pharmacies make as many as 100,000 vials a day using 1940s techniques for the delicate molecules of the 1990s. In their minds, this proves that they are compounding, not manufacturing. Again, the ridiculous fees paid for compounded inhalation fluids by the Health Care Financing Administration are the reason for the compounding. Many pharmacies receive several million dollars a year from the Health Care Financing Administration for compounded inhalation fluids. The total figure seems to amount to over half a billion dollars a year nationally. The figures are in the public domain and make interesting reading; many prominent pharmacists (i.e., officers in the state affiliates of the American Pharmaceutical Association) are involved.

All inhalation fluids should be sterile; the FDA is dragging its heels on this issue following pressure from the leading manufacturer using outdated containers. We read of the increased treatment of asthma in emergency rooms. Is it not possible that this is associated with the increased usage of homemade inhalation fluids of un-

proven quality? This is probable, when you see the poor quality of the containers presented at the emergency rooms.

COPYING OF COMMERCIAL PRODUCTS

Compounders have long ignored patents, orphan drugs statuses, and so on. This must be stopped. Excuses such as ''The child must be allergic to an ingredient'' are just excuses to compound. There is absolutely no literature to support these statements, and of course, no tests are ever conducted on the patient. The copying of commercial products is not allowed in any other industrialized nation and must be stopped in the United States.

Before Viagra, we had a prostaglandin injection. Caverject was a protected product, but was copied immediately by compounding pharmacists, who shipped prefilled syringes and multidose vials around the country. There were many complaints about ineffectiveness and of the subsequent prescription being of different potency than the first. Much of the active ingredient was made in the Czech Republic and was of unproven quality.

Why did the FDA take no action against the supply companies providing the prostaglandin or the pharmacies that shipped their products around the country? Why did the state boards of pharmacy totally ignore the problem? The answer is the political protection the compounding pharmacists have carefully built up in their state governments and Washington, D.C. I suspect many that many of the right wing politicians will be embarrassed when they learn that the small businesses they protected are involved in Medicare fraud.

OTHER

Currently, there is a growing business of compounding mixed estrogens, with the composition apparently frequently being determined by the pharmacist. The patients are told that the components are natural; I think they are synthetic or at least semisynthetic. These are molecules that have limited water solubility, and some skill in the formulation of mixed estrogen products is necessary to obtain an adequate dissolution rate. You can read how to make these products in an issue of the *International Journal of Pharmaceutical Compounding*; no dissolution or stability data are included.

Reflavoring of antibiotics should not be done, not only for the stability reasons mentioned above, but also for safety reasons. The danger of cross contamination involving antibiotics is huge in compounding pharmacies and is probably in violation of various laws. Manipulation of antibiotics must be stopped. I believe that pharmacists have contributed to what has been interpreted, in a given microenvironment, as bacterial resistance, with the possibility that the local pharmacist has destroyed the antibiotic never considered.

As in the other cases, the compounding pharmacist hides behind reasons such as the provision of individualized doses, the practice of pharmaceutical care, and being part of the triad. Does the compounding pharmacist ever tell the patient and physician that the product has not been tested for quality or performance and that the active ingredients have been manufactured in a third world country? Just what does individualized dosing mean? For example, 18.75 mg of sustained-release methylphenidate. What appropriate measurements are made to determine this dose? Do all compounders just observe the patient like the pharmacist from Oklahoma featured on television?

QUALITY OF CHEMICALS USED IN COMPOUNDING

The USP monograph on compounding is embarrassing, the worst section being on quality of chemicals used. No pharmacist is trained to make a judgment on the quality of chemicals to be used in drugs. I suspect only two members of this committee, one an internationally respected technologist and the other a practicing pharmacist, have the necessary experience to make these judgments. To suggest that buying a chemical from a chemical supply company is satisfactory is nonsense; experience has taught me that the impurities are invariably not the same, and certainly not in the same concentrations, as the form sold for the manufacture of drugs.

The certificate of analysis suggestion is also stupid. Just what does a certificate of analysis originating with a minor nonapproved company in a third world country mean? Nothing. Representatives of supply companies have been heard to say, ''We check the melting point and run an infrared on all our chemicals.'' This is meaningless and shows a complete lack of understanding of the problem. Incidentally, certificates of analysis can be purchased for any chemical through the Internet; I suspect compounding pharmacists are or will be the main clients for this service.

The quality of chemicals to be used to make drugs must be as accepted in the original New Drug Application

unless legally modified. USP specifications are no longer satisfactory.

CONCLUSIONS

Sustained-release products and inhalation fluids should never be compounded. Injections should only be prepared in an institutional environment and only in extenuating circumstances. Before release, they should be assayed for content and pass sterility and pyrogen tests. Active ingredients supplied in forms for reconstitution should never be reformulated. A new set of standards or improved USP monographs must be produced to stop the use of low-quality ingredients in drugs.

Technology has been downplayed in pharmacy schools for the last 25 years; we are not training pharmacists to make value judgments on what can and cannot be compounded, and yet compounding is the fastest growing branch of the profession. We certainly do not train pharmacists to make value judgments of the quality of chemicals used in the preparation of drugs.

The U.S. public has been very poorly served by the FDA and the boards of pharmacy; the FDA has had the information necessary to stop the supply of chemicals of questionable quality and of unproven drugs, but has taken no action. Why? Even worse is the situation in the states with the boards of pharmacy. The boards seem intimidated by compounding pharmacists, their supply companies, and the politicians supporting both. There has been no leadership from the (admittedly of no legal consequence) National Association of Boards of Pharmacy, although the head spoke out recently on the ABC Evening News. I am hoping he will continue to do so and lead the committee to make decisions that are in the best interest of the U.S. public, not just to keep 3000 unnecessary pharmacies in existence.

Many compounding pharmacies have been inspected by the Joint Commission on Health Care Organizations (JCHO). Some of the worst photographs I have seen, taken in pharmacies producing inhalation fluids, are of pharmacies that have been JCHO inspected, including one owned or partially owned by a JCHO inspector. Some photographs taken in compounding pharmacies show dirty, crowded conditions with chemicals and containers stored anywhere, including under active toilet bowls. Other pharmacies are meticulously clean and to the unknowing suggest total professionalism.