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Secundum Artem

Current & Practical Compounding Information for the Pharmacist.

Need for Extemporaneous Formulations in Pediatric Patients

The number of new drugs being marketed in the U.S. appears to be increasing; 27 new agents reached the market during the first 6 months of 1998.[1] However, most new drugs are not labeled for certain populations e.g. infants and children. It has been estimated that over 80% of the drugs approved by the FDA have not been labeled for use in infants and children. Only 5 of the 80 drugs most commonly used in newborn infants were labeled for use in this population.[2] When a drug is not approved by the FDA for infants and children, it is usually not available in a suitable dosage form for the pediatric population.

"Off label" use of drugs is common in pediatric patients. In fact, it would be unethical to not use a potentially better therapy, just because it is not yet approved by the FDA. In such cases, the alternatives are to refuse or delay access to a promising drug or provide an extemporaneous formulation to the patient. Examples of some orally used medications not available commercially in liquid dosage forms appear in Table 1.

Extemporaneous formulations have an important role especially in infants and young children (below 6 years of age), who are unable to swallow tablets or capsules. In addition, these patients require doses based on body weight, and fixed doses in tablets or capsules intended for adults cannot be given to infants and children. For example, captopril is available only as tablets containing 12.5 mg, 25 mg, 50 mg and 100 mg each.

The dose in an infant is 0.1-0.3 mg/kg; thus, the dose in a patient weighting 5 kg could be 1 mg. The only practical solution to this problem would be to prepare a liquid (e.g., 1 mg/mL) to provide the desired dose. However, the stability of captopril in aqueous medium was unknown for several years after its initial use began. In fact, the manufacturer indicated that it underwent oxidation in the presence of water. Thus, powder packets of captopril were prepared with lactose, to be administered by the caregiver just prior to the dose. The powders are time consuming and cumbersome to make, and errors may occur in preparing and administering the doses. Our efforts in preparing captopril solution in the presence of water and ascorbic acid (as antioxidant) led to a liquid formulation stable for at least 8 weeks.[3] (See Table 2, next page)

TABLE 1. EXAMPLES OF DRUGS NOT AVAILABLE IN LIQUIDS

• Acetazolamide	• Allopurinol	• Amiodarone
• Amlodipine	• Azathioprine	• Caffeine
• Captopril	• Clonazepam	• Clonidine
• Dapsone	• Enalapril	• Gabapentin
• Granisetron	• Indinavir	• Isradipine
• Lamotrigine	• Levodopa/carbidopa	
• Levofloxacin	• Mexiletine	• Nifedipine
• Omeprazole	• Propylthiouracil	• Pyrazinamide
• Rifampin	• Sertraline	• Spironolactone
• Spironolactone/hydrochlorothiazide		• Sumatriptan
• Topiramate	• Ursodiol	• Verapamil
• Vigabatrin	• Zidovudine/lamivudine	

This formulation is now routinely used in infants and young children with hypertension or congestive heart failure at our institution.

Intravenous drugs not approved for infants and young children are often not available in appropriate (low) concentrations for accurate and precise measurement of small doses. For example, phenobarbital is commercially available at a concentration of 65 mg/mL. The dose in an infant may be 2.5 mg/kg to be given every 12 hours. Thus, the dose in a premature infant weighing 1 kg would be 2.5 mg and 0.038 mL would need to be measured to administer each dose. Errors may occur in measuring doses less than 0.1 mL. Such errors with potent drugs like morphine and digoxin have led to intoxication in pediatric patients.[4,5] One solution would be to dilute these concentrated drugs intended

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for adults. We dilute commercially available morphine injection, 10 mg/mL to 0.5 mg/mL in 0.9% sodium chloride injection (normal saline), and phenobarbital injection, 65 mg/mL to 10 mg/mL in bacteriostatic water for injection.[6] However, the stability and sterility of the diluted drug were documented before any dilutions were performed. It should be realized that the diluted drugs may be stable for varying periods of time, as the dilutions can lead to lower than desired concentrations of stabilizing agents e.g., antioxidants or preservatives. Thus, stability, sterility and pyrogen tests should be done to assure the quality of the modified extemporaneous formulation.

TABLE 2

GENERIC NAME: Captopril

DOSAGE FORM: oral solution

MADE FROM: tablets

CONCENTRATION: 1 mg/mL

STABILITY: 56 d

STORE: refrigerate

LABEL: shake well

- Captopril tablets 50 mg, 2 tablets
- Sodium ascorbate injection or asorbic acid tablets 500 mg,
- Distilled water qs ad 100 mL

Instructions: Allow 2 tablets of captopril 50 mg to dissolve in 50 mL of water in a graduate. Add the contents of a 500-mg ampul of sodim ascorbate or a 500-mg ascorbic acid tablet to the mixture and qs with distilled water. Shake well to disperse. Do not filter.

Note: A sulfur-like odor is not indicative of captopril degradation.

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REQUIRED STUDIES FOR EXTEMPORANEOUS FORMULATIONS

The physicochemical properties of the drug and the characteristics of the available dosage form (e.g. tablet or capsule) should be considered in preparing the extemporaneous dosage form. Most drugs are not completely water soluble. Thus, a suspension is generally prepared to yield a uniformly dispersed oral formulation. Carboxymethylcellulose or methylcellulose are commonly used suspending agents. We frequently use commercially available carboxymethylcellulose in a ready-to-use suspension (Ora-Plus, Paddock Laboratories, Minneapolis, MN) and an extemporaneously prepared 1% methylcellulose suspension[6] at our hospital (See Table 3, next column).

The pH of Ora-Plus is about 4.4 while that of 1% methylcellulose is nearly 6.8. We routinely mix the suspending agent with equal volume of commercially available simple syrup or Ora Sweet (sugared or sugar free). Flavors and preservatives may be added, as necessary. The commercially available intravenous drugs are normally diluted in sterile or bacteriostatic water for injection or 0.9% sodium chloride injection.

The physical and chemical stability of drugs in extemporaneous formulations is determined at clinically simulated conditions e.g., desired drug concentration, storage container and temperature, and duration of use. For example, about an ounce of the prepared formulation is stored in each of 10 plastic prescription bottles. Five bottles are stored at 4ºC in a refrigerator and five at 25ºC. Small aliquots are collected and normally studied on day 0 (soon after preparation) and on days 3, 7, 14, 28, 42, 56, 70 and 91 during storage. On each study day, the physical stability is assessed by visual appearance against a white and black background to rule out any changes in color and appearance; odor is also evaluated. The chemical stability is determined by measuring the concentration of the drug using an accurate, specific, reproducible, and stability-indicating analytical method e.g. high performance liquid chromatographic technique on each day of study. The pH is also measured on each study day. The stability-indicating nature of the method is confirmed by subjecting samples of the extemporaneous formulation to extremes of temperature by heating, and to low and high pH by mixing with an acid and a base. The degradation products should not interfere with the measurement of the drug for a method to be stability-indicating.[7] The drug is considered stable, if its physical characteristics have not changed and its concentration has remained above 90% of the initial concentration.

TABLE 3

GENERIC NAME: Methylcellulose

DOSAGE FORM: oral suspension

MADE FROM: powder

CONCENTRATION: 1%

STABILITY: 6 mo

STABILITY REFERENCE: experience

- Methylcellulose powder 4000cps 10g,
- Methylparaben 200mg,
- Propylparaben 100mg,
- Purified water USP qs 1000mL

Instructions: Heat 200 mL of purified water to boiling. Add the parabens and mix well. Wet the methylcellulose powder and add it. Allow to stand for 15 minutes, then remove from heat. Then Qs with cold purified water while mixing well with a magnetic stirrer. Keep mixing until a clear, homogeneous solution results.

The palatability of an extemporaneous formulation should also be assessed. A palatable formulation is more likely to improve compliance and minimize spillage during administration of doses. A 5-point scale or facial expressions are used to assess palatability of formulations in pediatric patients.[8] Sterility and pyrogen tests are done by using USP methods.

In general, pharmacokinetics, pharmacodynamics, efficacy and

safety studies are rarely conducted with extemporaneous formulations. The pharmacokinetics can be somewhat different for a drug in an extemporaneous versus a commercially available formulation. The tablets and capsules containing sustained or timed release drug products should not be used to prepare liquid dosage forms, as the sustained release property may be lost in preparing an extemporaneous formulation. Since performance of pharmacokinetic studies is expensive and limited resources are available for these studies, patients receiving a new extemporaneous formulation should be carefully monitored to document efficacy and safety of the drug. Excessive use of sorbitol or propylene glycol should be avoided as the former can lead to diarrhea[9] and the latter to hyperosmolality.[10]

NEW REGULATIONS

The FDA has issued new regulations requiring manufacturers to conduct pediatric studies and seek labeling for new drugs in pediatric patients. However, the requirement can be waived for a number of reasons including difficulty in developing a pediatric formulation, as long as "reasonable efforts" were made.[11] It is unclear what would be sufficient as "reasonable efforts."

Small size of the pediatric market for most drugs is perhaps the leading reason for the lack of investment in drug development for this population by the industry. The FDA will provide incentives to the industry (6 month extension of exclusivity and waiver of fees for the supplemental new drug application) for pediatric drug development.[9] This may lead to increased availability of pediatric formulations of new drugs; however, extemporaneous formulations would still be needed for the generic drugs and for marketed drugs of little interest to the sponsor. In addition, the potential use of a new drug in infants and children may not be apparent at the time of seeking initial approval for adults.

The FDA Modernization Act of 1997 (FDAMA) also has provisions for bulk drug substances. Effective November 21, 1998, FDA must develop and publish regulations to address various aspects of pharmacy compounding. The compounding law stipulates that the bulk substances used in compounding should be 1) components of an FDA-approved drug product; 2) in a USP or National Formulary monograph; or 3) included in a list developed by the FDA, with the input from its Pharmacy Compounding Advisory Committee.[12] (Table 4, next page) A request for inclusion of substances on this list was published by the FDA in April, 1998. It is unclear what may happen if the list is incomplete and whether the efficacy and safety of the substances would have to be assured before placing them on the list.

SUMMARY

Extemporaneous drug formulations play an important role for pediatric patients. As an example, many frequently used drugs are available only as tablets or capsules, but not in suitable liquid dosage forms. Thus, such medications cannot be used in patients unable to swallow tablets or capsules. Pharmacists must extemporaneously compound these medicines. However, stability data are often lacking for these products. In such cases, physical and chemical stability must be determined using clinically simulated conditions (e.g., concentration, storage temperature and containers) for the drugs. Palatability and microbiological studies also may be needed in certain situations. Pharmacokinetics/pharmacodynamics, efficacy and safety studies are usually not done, but may be necessary in some cases. Recent regulations of the U.S. Food and Drug Administration were proposed to increase the labeling of new drugs for pediatric patients. The implementation of these regulations should also increase the availability of suitable dosage forms of some new drugs. It should be realized, however, that the need for extemporaneous formulations of many existing drugs and some new ones will continue. Thus, pharmacists have a unique role in compounding these medicines for use in pediatric patients.

Increased funding by the universities, government, industry and foundations would be required to develop stable formulations, conduct studies, and publish results. Joint efforts by various groups including practitioners, academia, industry, government and professional associations is required for making extemporaneous formulations accessible to the most vulnerable populations e.g. infants, young children and the elderly unable to take commercially available dosage forms.

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TABLE 4:

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Verapamil HCl-Am J Health-Syst Pharm. 1996; 53: 2304-9

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- Captopril
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- Cisapride
- Clonazepam
- Diltiazem HCl
- Dipyridamole
- Enalapril Maleate
- Flecainide Acetate
- Flucytosine
- Hydralazine HCl
- Ketoconazole
- Labetalol
- Metolazone
- Metoprolol Tartrate
- Metronidazole
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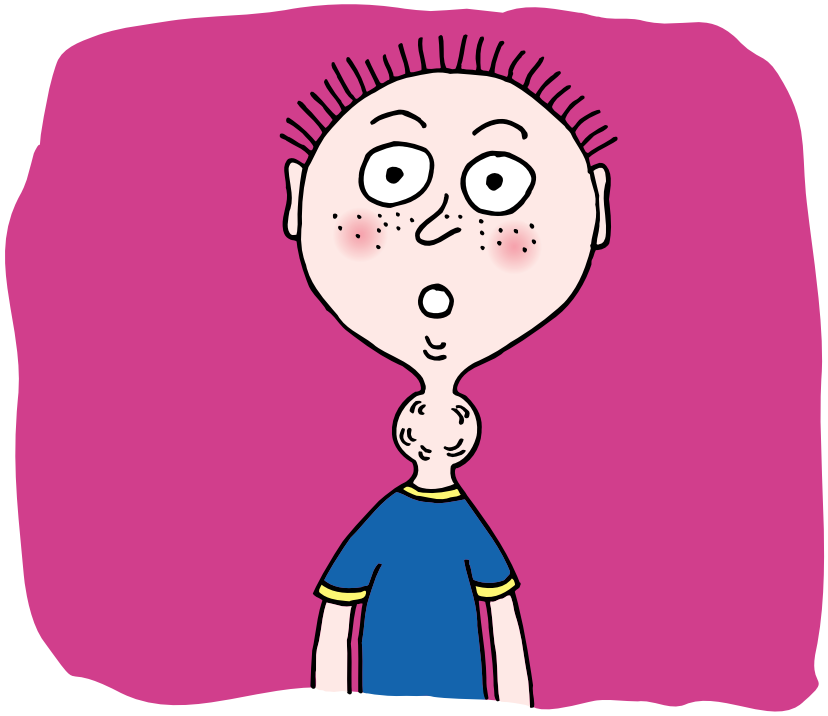

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