

# PEDIATRIC PHARMACOTHERAPY

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## Alternative Forms of Oral Drug Delivery for Pediatric Patients

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The lack of an appropriate dosage form limits the use of many medications that may potentially benefit children. While this has been a long-standing problem for pediatric healthcare providers, little attention has been paid to remedying it until recently. In 2005 the Eunice Kennedy Shriver National Institute for Child Health and Human Development, joined by representatives from the Food and Drug Administration (FDA), academic medicine, and the pharmaceutical industry, formed the United States (US) Pediatric Formulations Initiative in an effort to stimulate research in pediatric formulation technology.<sup>1</sup> Similar work by the European Medication Agency (EMA) led to the development of the European Pediatric Formulation Initiative.<sup>2</sup> In addition, the World Health Organization launched a global initiative in 2007 entitled "Make Medicines Child Size" to foster development of pediatric dosage formulations.<sup>3</sup> These groups continue to guide research in the field of pediatric drug delivery and champion technologic advances.

### Limitations with Current Products

One of the greatest challenges in pediatric pharmacology has been optimization of oral drug delivery. Although most children over 6 years of age can be taught to swallow solid dosage forms, many remain uncomfortable with it until adolescence. In a recent study 54% of children between 6 and 11 years told study investigators that they were unable to easily swallow a tablet.<sup>4</sup> While altering oral tablets to create formulations suitable for children has long been a part of pediatric healthcare, it is clearly a less than ideal option.<sup>5</sup>

Crushing tablets to mix them with food or water may change the rate or extent of drug absorption. Best and colleagues recently found that crushing lopinavir/ritonavir (Kaletra®) tablets, a common practice for children with HIV-1 infection, resulted in a significant change in drug bioavailability.<sup>6</sup> The authors conducted a pharmacokinetic study in 12 children between 10 and 16 years of age after administration of whole and crushed tablets. The use of crushed tablets resulted in a median decrease in the area under

the concentration versus time curve (AUC) of 45% for lopinavir and 47% for ritonavir ( $p = 0.003$  and  $0.006$ , respectively).

Cutting tablets, another common practice, may be acceptable for some drugs, however this practice can introduce considerable variability between doses. In drugs with a narrow therapeutic index, such as levothyroxine, this variability may be enough to produce clinically significant changes in clinical response.<sup>7</sup> When cutting a tablet is necessary, family members should receive specific instructions on the process, including the proper use of a tablet splitter. Family members involved in dose preparation should also understand how to dispose of unused drug and the need to avoid repeated exposure to drugs that have carcinogenic or teratogenic properties.

Having a pharmacist prepare an extemporaneous oral suspension or solution can minimize these issues, but even a relatively simple change in the process, such as conversion to a sugar-free suspending agent, addition of a flavoring, or use of a different brand, may alter the stability of the final product or the absorption characteristics of the drug. While the availability of extemporaneous formulations is widespread in most developed countries, it may be limited in parts of the world lacking necessary resources such as a source of clean water.<sup>5</sup>

Commercially available oral liquid medications provide a more reliable, ready-to-use preparation for infants and children, but bioequivalence with solid oral dosage forms is still not assured. In 2012, Kasirye and colleagues published the results of a pharmacokinetic study comparing oral solutions and solid dosage forms of three antiretrovirals in 19 children between 1 and 4 years of age.<sup>8</sup> Oral solutions of zidovudine and abacavir produced similar AUC values to tablets, but lamivudine AUC values were 45% lower with the solution. The authors concluded that administration of lamivudine solution based on dosing guidelines developed for the tablets may result in subtherapeutic serum concentrations.

A new oral liquid formulation of levothyroxine available in Europe was recently shown to produce lower rates of normalization of thyroid function than a tablet given at the same dose.<sup>9</sup> Levothyroxine, digoxin, hydrocodone, and phenobarbital are just a few examples of drugs that cannot be easily formulated as liquids because of their relative insolubility in water. The traditional method of preparing liquid formulations of these drugs has been as alcohol-based elixirs. The concentration of alcohol in elixirs varies from 5% to as much as 40%. The long-term effects of repeated exposure to the alcohol in these products, particularly in infants and toddlers, are not known.

The problems encountered with currently available formulations highlight the need for the development of new products that are both easy to administer and capable of providing reliable serum drug concentrations. Several alternatives to traditional dosage formulations have been introduced in the US over the past decade that may fill this need. Extended release oral suspensions, as well as orally disintegrating tablets and films are ideally suited for children unable to swallow tablets and capsules.

#### Extended Release Oral Liquids

One of the disadvantages of oral liquid preparations has been the need to give multiple doses throughout the day. Until recently, extended release products have been available only as tablets, capsules, or sprinkles. On June 10, 2005 the first extended release oral suspension, Pfizer's azithromycin product (Zmax<sup>®</sup>), was approved by the FDA for the treatment of community acquired pneumonia in adults and children over 6 months of age and acute bacterial sinusitis in adults.<sup>10</sup> It is administered as a single 60 mg/kg dose (with an adult dose of 2 grams).

On September 27, 2012, the FDA approved an extended release oral suspension of methylphenidate (Quillivant XR<sup>™</sup>) developed by NextWave Pharmaceuticals, a subsidiary of Pfizer.<sup>11</sup> The suspension consists of cationic polymer matrix particles that bind racemic methylphenidate via ion exchange. Variation in the thickness of the coating applied to the particles results in 20% of the drug being released immediately, with the remaining 80% of the drug released over 12 hours. It is shipped as a powder to be reconstituted with water prior to dispensing to make a 5 mg/mL suspension.

In the February 2013 issue of the *Journal of Child and Adolescent Psychopharmacology*, Wigal and colleagues published the results of a two-week double-blind, randomized, placebo-controlled trial of extended release

methylphenidate suspension in children with attention-deficit/hyperactivity disorder (ADHD).<sup>12</sup> Forty-five children between 6 and 12 years of age were enrolled. Following an open-label dose optimization period, patients were randomized to receive either active drug or placebo for 1 week, followed by the alternative. Use of the extended release methylphenidate suspension resulted in improvement in scores on ADHD rating scales and a standardized math test similar to that reported with methylphenidate in other studies. The new suspension has not yet been evaluated in a comparison study with other extended release methylphenidate dosage forms.

#### Orally Disintegrating Tablets

Orally disintegrating, or orodispersible, tablets (ODTs) are designed to dissolve in the presence of saliva within one minute. The primary advantage of ODTs is that no external source of liquid is needed for consumption.<sup>13</sup> For patients with dysphagia or children too young to swallow tablets or capsules, ODTs provide a useful alternative. There are a variety of methods for preparing ODTs, including freeze drying, molding, compaction, granulation, spray drying, flash heat processing, sublimation to increase porosity, and direct compression. Disintegrating aids, binding agents, and sweeteners are added to the active drug moiety during production to improve the feel of the product in the mouth, making the dissolved drug smooth and creamy. Several companies have patented technologies for manufacturing ODTs, such as Zydis<sup>®</sup> (Catalent, Inc.) Flashtab<sup>®</sup> (Prographarm), Orasolv<sup>®</sup> (Cima), and Wowtab<sup>®</sup> (Yamanouchi Pharma Technologies).<sup>1,13</sup>

Although the development of ODTs began in the 1970s, the first product to reach the US market, Claritin<sup>®</sup> Reditabs, was not approved by the FDA until December 1996. Since that time the number of ODT products has grown rapidly to include more than two dozen prescription and non-prescription drugs (Table).

#### **Table. Examples of Drugs Available as ODTs**

Acetaminophen	Loratadine
Alprazolam	Metoclopramide
Aripiprazole	Mirtazapine
Carbidopa-levodopa	Olanzapine
Cetirizine	Ondansetron
Citalopram	Prednisolone
Clonazepam	Risperidone
Clozapine	Rizatriptan
Desloratadine	Selegiline
Diphenhydramine	Tramadol
Donepezil	Vardenafil
Fexofenadine	Zolmitriptan
Lansoprazole	Zolpidem
Lamictal	

While most currently available ODTs have been designed for adolescents and adults, some have been formulated specifically for younger patients, such as Children's Tylenol® Meltaways. These grape punch or bubble gum flavored tablets, designed for children 2-11 years of age, contain 80 mg acetaminophen and may be chewed or allowed to melt in the mouth.

An ODT formulation of prednisolone (Orapred ODT®) has proven to be very useful in pediatric patients with asthma or allergic conditions such as atopic dermatitis.<sup>14</sup> Glucocorticoids are extremely bitter and the taste is difficult to mask, particularly in oral liquid products. The ODT product uses a triple layer polymer formulation to minimize the taste. Grape-flavored Orapred ODT® is currently available in 10 mg, 15 mg, and 30 mg strengths. In 2007, the manufacturer conducted a survey of 973 children; 89% reported a preference for the ODT product over prednisolone oral liquid.<sup>15</sup> The primary disadvantage of this product is the cost; at \$6 to \$10 per tablet, it is considerably more expensive than other prednisolone preparations.

Ondansetron ODT (Zofran ODT® and generics) has been well accepted for the prevention or treatment of nausea and vomiting in the pediatric population.<sup>16</sup> As with standard oral tablets, children 4-11 years of age may be given a 4 mg ODT three times daily. The dose for older children and adults is 8 mg taken three times daily. In 2008, Davis and colleagues enrolled 221 children (5-16 years of age) into a randomized, double-blind, placebo-controlled trial of ondansetron ODT after tonsillectomy.<sup>17</sup> The incidence of emesis within the first 3 days after surgery was significantly lower in the ondansetron ODT group than in the placebo group (14.6% versus 32%,  $p = 0.004$ ).

In one of the few prospective randomized pediatric studies to compare ODT products to standard formulations, Çorapçıoğlu and Sarper evaluated IV and ODT ondansetron products in 22 children (ages 3-17 years) with cancer.<sup>18</sup> The children were randomized to receive either 5 mg/m<sup>2</sup> IV ondansetron or a 4 or 8 mg ondansetron ODT 30 minutes before and 12 hours after chemotherapy. The percentage of patients experiencing a complete treatment response, defined as no nausea or vomiting, was no different between the groups (82% of the IV group and 85% of the ODT group,  $p = 0.981$ ). Response rates remained similar when a subgroup of children receiving highly emetogenic regimens was analyzed (75% of the IV group and 80% of the ODT group,  $p = 0.931$ ).

The ODT formulation is not without disadvantages. Most products are available in a

single strength, often one that is too large for use in younger children. Because of their fragility, breaking, cutting, or splitting ODTs is not recommended. For some drugs, the rapid absorption from an ODT may result in a brief exposure to very high, potentially toxic, drug concentrations. New microencapsulation techniques provide a slower, more controlled release of drug from an ODT. Li and colleagues at the Shanghai Eighth People's Hospital have developed a scopolamine ODT that contains microparticles embedded with the drug.<sup>19</sup> It dissolves within 45 seconds, but the drug itself is not completely absorbed into the bloodstream until 90 minutes after administration.

Another important concern is the potential for toxic ingestions of ODTs, particularly acetaminophen. Without the need to swallow, ODTs can be consumed in large numbers, even by very young children. In 2011, Ceschi and colleagues conducted a retrospective study of acetaminophen ingestions in children  $\leq 6$  years of age reported to the Swiss Toxicological Information Center between June 2003 and August 2009.<sup>20</sup> The authors compared 187 tablet ingestions and 16 cases involving ODTs. The mean ingested dose was 59% greater in the ODT group ( $157.3 \pm 147.6$  mg/kg compared to  $98.7 \pm 77.7$  mg/kg in the tablet group,  $p = 0.085$ ). The authors suggest that the rapid dissolution of the ODT, as well as its sweet taste and candy-like feel in the mouth may encourage children to ingest more drug than what they would be able to swallow if tablets were involved.

#### Orodispersible Films

Orodispersible films (ODFs) offer another option for rapid drug delivery.<sup>21</sup> These thin films or strips are often more acceptable to patients with dysphagia or a fear of choking than solid dosage forms or ODTs. Films consist of hydrophilic polymers that dissolve in the mouth within seconds. They may be placed on the tongue for oral absorption, under the tongue for sublingual absorption, or along the buccal surface for transmucosal absorption directly into the systemic circulation. The latter route bypasses gut absorption and delivery into the hepatic portal system, thus avoiding first pass metabolism and increasing drug bioavailability.

The ODF formulation has already proven to be a popular means of delivering over-the-counter products such as breath fresheners (Listerine Pocketpaks® Breath Strips), simethicone (Gas-X Thin Strips®), and multivitamins. Several of the first ODFs to reach the market (Benadryl®, Children's Triaminic®, and TheraFlu® thin strips), however, have been subsequently discontinued. The reasons for the removal appear to include production issues as well as poor sales. The latter

may reflect the declining use of cough and cold products in children over the past several years. The first prescription ODF, a new formulation of ondansetron (Zuplenz<sup>®</sup>), was approved by the FDA on July 2, 2010.<sup>22</sup> It is available in both 4 mg and 8 mg strengths and is approved for use in children 4 years of age and older. A month after the release of this product, a buprenorphine ODF (Suboxone<sup>®</sup> sublingual film) was approved for the treatment of opioid dependence in adults. Several ODFs are currently in development, including films for levocetirizine, rizatriptan, and rotavirus vaccine.<sup>23</sup>

### Summary

Many medications with the potential to benefit children are not available in a formulation appropriate for them. Innovations in drug delivery technology are leading to new alternatives better suited to the pediatric population. The stability of ODTs and ODFs and their ability to deliver drugs without a source of clean water make these formulations ideal for both developing and developed countries and have made them a focus for the US and European Pediatric Formulations Initiatives. As a result, it can be expected that there will continue to be considerable growth in this area in the future.

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### Formulary Update

The following actions were taken at the February meeting of the Pharmacy and Therapeutics Committee:

1. the restrictions on prescribing of bosentan (Tracleer<sup>®</sup>) were amended to include initiation of therapy in the neonatal population.

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