

# Pediatric Pharmacotherapy

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## **Improving Compliance with Medication Regimens** **Marcia L. Buck, Pharm.D.**

**P**atient compliance, the degree of adherence to medical advice necessary for therapeutic benefit, is of increasing concern to health care professionals. The trend towards promoting outpatient therapy and self-treatment has led to placing greater responsibility on patients for their own health outcomes. While compliance has been well studied in adults over the past several decades, it has only lately begun to be evaluated in children.<sup>1-19</sup>

Medication compliance is a complex issue in the pediatric population. It involves not only the patient, but also parents and other care providers. Compliance is dependent on the family's health belief system: their beliefs in susceptibility to disease, their perception of disease severity, and their understanding of the benefits of treatment.<sup>1,5,12</sup>

In addition to the family's belief system and those factors known to affect compliance in adults (such as regimen complexity), specific pediatric factors must be considered. Different developmental stages can have a profound impact on behaviors related to medication compliance. In young children, their inability to comprehend the benefit to be gained from treatment affects their willingness to accept medications.<sup>12</sup> In adolescents, compliance may be affected by the need to demonstrate independence, denial of illness, and unwillingness to accept cosmetic side effects such as hirsutism or gingival hyperplasia.<sup>5</sup>

Family dynamics also impact therapy. Parental anxiety and the placing of restrictions on the patient's activities appear to have a greater impact on compliance than more traditional factors such as frequency of dose administration or palatability.<sup>13</sup>

The type of illness being treated also plays a role in determining compliance in children. Issues to address with families in order to ensure

compliance with short-term therapy are often quite different than those which may be discussed in the face of chronic therapy.

### Compliance During Acute Illness

While estimates vary considerably in the medical literature, the rate of compliance in the treatment of acute illness in children is believed to be approximately 50%. This value has been reported both in patients treated for acute otitis media and in those with streptococcal pharyngitis who receive a one or two week treatment course.<sup>6,7</sup> Similar rates have been reported in adults.<sup>1</sup>

### Compliance During Chronic Illness

For children receiving chronic therapy, compliance is slightly improved compared to acute illness, with most studies reporting a rate of approximately 70%.<sup>1</sup> Compliance is rarely static for any given patient; it fluctuates over time, depending on variables such as the severity of symptoms, external stressors, and family support.<sup>4,5,12</sup>

Children with asthma have been the most frequently studied pediatric population.<sup>8-12</sup> As in all cases of chronic illness, complexity of the regimen is directly related to compliance. The use of inhalers, although considered a cornerstone of disease management, is associated with the least compliance of all therapeutic interventions. Inability to use the inhaler properly and misunderstanding regarding the appropriate time to administer treatment are cited as the two primary reasons for noncompliance.<sup>8,9,11</sup>

Other investigators have found significant noncompliance in children following renal transplantation and in those with sickle cell disease, hemophilia, epilepsy, and diabetes mellitus.<sup>13-18</sup>

### Assessing Compliance

There are both direct and indirect methods to assess patient compliance. Direct methods, such as serum, urine, or saliva concentration sampling and the use of tracer substances, provide accurate information, but are costly and time-consuming. Indirect methods, including patient/family interviews, records of refills, and pill counts, are often more feasible.<sup>1,5,8</sup>

Clinicians should keep in mind, however, that many of these methods of assessment can be circumvented by the patient. For example, the “toothbrush effect,” markedly improved compliance immediately preceding a medical visit, can easily confound drug concentration sampling.<sup>1,4</sup> The “parking lot” phenomenon, dumping of medication prior to a medication check, can invalidate pill count or checks of metered dose inhalers.<sup>8</sup>

Estimates by health care providers, even those who have an on-going relationship with the family, are not an accurate means of determining compliance. Several studies have demonstrated that the ability of the patient’s physician to predict compliance is no better than chance. It has also been shown that experienced senior faculty are no more accurate than residents in predicting compliance. The inability to ignore biases and the wish to believe that their recommendations are followed hamper accurate assessments.<sup>1,4,13</sup>

Several methods have been proposed to facilitate more accurate indirect assessment. Daily journals and charts are simple, inexpensive methods to remind patients and families. More technologically sophisticated methods are used in clinical research and may be appropriate for some patients. The Medication Event Monitoring System (Apex Corp.) uses a microprocessor in the medication bottle cap to record each time the bottle is opened.<sup>1,17</sup> Similar devices have been developed to measure use of metered dose inhalers.<sup>1,8</sup>

### Methods for Enhancing Compliance

#### **Patient/Family Education**

When asked to name the primary determinant of compliance in children, most health care providers would respond with the taste or cost of the medication. In fact, the key factor for successful treatment is education. The patient and family must understand both the need for treatment and the method for administering it properly. A thorough discussion of the medication regimen, tailored to the age and

maturity of the patient, and scheduled follow-up are the best methods to gain patient/family compliance. Barriers to complying with recommended treatments must also be identified.<sup>1-5,12,13,18</sup>

In adolescents, the use of contracts or written agreements may bolster compliance. Weinstein<sup>12</sup> has published a representative case of a child with asthma in which contracts were part of a successful intervention program.

Patients also benefit from written instructions. Increasingly, the availability of written patient medication information is being viewed as an important factor in enhancing compliance. The FDA has set a goal that by the year 2000, 75% of patients will receive written information on how to take their medication and possible adverse effects.<sup>20</sup>

#### **Choice of Regimen**

In the treatment of acute illness, *duration of therapy* plays a large role in determining compliance. In cases of infectious diseases, the use of antibiotics has been found to decline rapidly after symptomatic improvement is seen. While compliance may be at 50% early in therapy, one study in children with pharyngitis has shown a decline to less than 20% at day 9 of a 10 day antibiotic course.<sup>1,2</sup>

It has been well established that short-course therapy leads to improved compliance. A single dose therapy which can be administered by a health care provider during a clinic or emergency room visit may be viewed as the optimal method to ensure drug delivery. This option has been used successfully in the management of sexually-transmitted diseases for several years. Treatment with a single dose of ceftriaxone has been suggested as an option for the treatment of otitis media in children, but raises questions of cost benefit and therapeutic efficacy.<sup>21</sup>

In treating both acute and chronic conditions, the *frequency of dose administration* should be considered. Several studies have demonstrated the impact of reducing dosing frequency in improving patient compliance.<sup>1,2,7</sup> Once or twice daily regimens have been associated with compliance rates of 70 to 80%, while compliance with regimens requiring three or four daily doses drops to 40 to 50%.<sup>2</sup>

Reducing frequency of dosing is a goal of new drug development. Pharmaceutical manufacturers continue to seek methods to prolong drug effect, such as extended release

products and the development of agents with longer durations of effect. Pediatric health care providers, however, should be aware of the limitations of extended or sustained release dosage forms which are designed for use in adults.

The *timing of dose administration* should also be tailored to enhance compliance. The administration of doses may be timed in relation to typical family activities, such as meals, homework, or television shows to serve as a reminder.<sup>12</sup> Avoiding dosing during school hours is advisable, to prevent medication from being lost and to decrease the stigmatization of illness in older children.

Although of lesser significance, *palatability* should be considered when choosing a treatment regimen. In cases where therapeutic alternatives exist, the best tasting or most easily swallowed product should be chosen. It should be noted, however, that taste preferences differ considerably between adults and children. In 1996, El-Chaar and colleagues<sup>19</sup> demonstrated that unlike adults with distinct preferences, children were compliant with most medications regardless of whether "better-tasting" brand or generic formulations were used.

In cases where no alternatives are available, flavorings or placement of a drug into a gelatin capsule may be necessary to ensure compliance. Health care providers may find it beneficial to identify local pharmacies that are capable of tailoring medications for children.

The *cost of therapy* and the *ease in obtaining the medication* should not be overlooked. Although studies have shown that compliance is generally not correlated to socioeconomic status or prescription cost,<sup>1,4,6,13,15</sup> these issues may be a significant concern for some patients.

A knowledge of resources available to those patients unable to afford treatment may help avoid unnecessary treatment failures. There may be several alternative medication sources for these patients, such as free clinics and pharmaceutical manufacturer-supported free medication programs. The University of Virginia Department of Pharmacy Services can assist qualified patients in obtaining medications through manufacturers. For more information, call 2-1986.

In summary, many factors influence the degree of medication compliance by pediatric patients and

their families. Education on the importance of therapy and follow-up, however, are the primary determinants of successful adherence.

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## Pharmacology Literature Review

### Caffeine Pharmacokinetics

Several studies of caffeine pharmacokinetics have been conducted using standard methodology, in which a small number of infants are given a standardized dose. This study uses a newer technique, NONMEM, to determine parameters in a large group of patients using fewer samples. As with previous studies, the authors concluded that volume of distribution and clearance were influenced by weight and postnatal age. Volume of distribution was also significantly higher in infants born at > 28 weeks gestation age. Lee TC, Charles B, Steer P et al. Population pharmacokinetics of intravenous caffeine in neonates with apnea of prematurity. **Clin Pharmacol Ther** 1997;61:628-40.

#### Group B Strep. Review

This paper provides a concise review of methods to prevent Group B *Streptococcus* infections in neonates. A brief introduction covers the epidemiology, risk factors, and clinical presentation of this infection. The rest of the paper focuses on current and future methods for disease prevention. The authors divide this section into antepartum prophylaxis, intrapartum prophylaxis, and prophylactic treatment of the newborn. A cost-benefit analysis of these options is also included. Logsdon BA, Casto DT. Prevention of Group B *Streptococcus* infection in neonates. **Ann Pharmacother** 1997;31:897-906.

#### Lamotrigine Dose-Concentration Relationships

A total of 45 patients were included in this study, both children and adults. A linear relationship between dose and serum concentrations was observed. When standardized by dose and concomitant therapy, younger children, ages three to six years, had lower serum concentrations than older children ( $0.30 \pm 0.17$  versus  $0.43 \pm 0.18$  mcg/ml). There was no relationship between serum concentrations and therapeutic response. Bartoli A, Guerrini R, Belmonte A et al. The influence of dosage, age, and comedication on steady state plasma lamotrigine concentrations in epileptic children: A prospective study with preliminary assessment of correlations with clinical response. **Ther Drug Monitor** 1997;19:252-60.

#### Vancomycin Monitoring

In the era of cost containment, many institutions have questioned the need for routine monitoring of vancomycin serum concentrations. This study, from the Children's Hospital of the King's Daughters in Norfolk, evaluated the prevalence of sub- or supra-therapeutic concentrations following initial dosing in 74 children.

Inappropriately low or high trough concentrations were found in 28 patients (38%), despite the use of standard initial dosing regimens. There were no excessive peaks. The authors concluded that monitoring vancomycin serum concentrations was necessary for most patients, but suggest that trough concentrations alone may be adequate. Miles MV, Li L, Lakkis H, et al. Special considerations for monitoring vancomycin concentrations in pediatric patients. **Ther Drug Monitor** 1997;19:265-70.

#### Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 7/25/97:

1. Cabergoline (Dostinex®) was added to the formulary for hyperprolactinemia.
2. Interferon beta-1a (Avonex®) was added for the treatment of relapsing multiple sclerosis.
3. Zileuton (Zyflo®) was added for the treatment of asthma. It produces bronchodilation by inhibition of 5-lipoxygenase, resulting in inhibition of leukotriene formation. The adult dose is one 600 mg tablet taken four times daily.
4. Piperacillin/tazobactam (Zosyn®) was added. This product combines piperacillin sodium, an extended spectrum penicillin, with tazobactam sodium, a beta-lactamase inhibitor. Although not FDA-approved for use in children, this combination has been studied in the pediatric population. Infants < 6 months of age should receive a dose of 150-300 mg/kg/day (based on the piperacillin component) in divided doses every 6 to 8 hours. Older infants and children < 12 years should receive 300-400 mg/kg/day.
5. Levofloxacin (Levaquin®) was also added to the formulary, in both oral and intravenous forms. It is a fluoroquinolone antibiotic with increased Gram positive coverage.
6. Ticarcillin/clavulanate (Timentin®) and ofloxacin (Floxin®) were removed.

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