CLINICAL TRIALS

Acute tolerance to methylphenidate in the treatment of attention deficit hyperactivity disorder in children

Objectives: **To evaluate the efficacy of several drug delivery patterns of methylphenidate and to determine whether acute tolerance develops to this widely used stimulant medication in the treatment of children with attention deficit hyperactivity disorder.**
Methods: **Double-blind trials were conducted in a laboratory school setting in which multiple measures of efficacy were obtained frequently in the morning and afternoon across the school day. In study I, relative efficacy was determined for three dosing patterns of methylphenidate: a standard twice-daily profile, a flat profile, and an ascending profile. In study II, tolerance was assessed by comparison of three-times-a-day regimens in which the time of the middle dose varied.**
Results: **In study I, the efficacy of the ascending treatment increased across the day, and in the afternoon it was equal to the efficacy of the twice-daily treatment, indicating that an initial bolus was not required for efficacy. The efficacy of the flat treatment declined across the day, and in the afternoon it was significantly less than in the twice-daily treatment, suggesting that tolerance may be developing. In study II, acute improvements in efficacy were reduced to the second of two closely spaced but not to two widely spaced bolus doses, suggesting that shortly after exposure to high concentrations, efficacy is reduced to given concentrations of methylphenidate. In a concentration–effect model, a tolerance term was needed to account for counterclockwise hysteresis.**
Conclusions: **Acute tolerance to methylphenidate appears to exist. This should be considered in the design of an optimal dosing regimen for the treatment of children with attention deficit hyperactivity disorder. (Clin Pharmacol Ther 1999;66:295-305.)**

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Stimulant medications have been used for about 50 years[1] to treat children with attention deficit hyperactivity disorder (ADHD).[2] Standard clinical practice has remained essentially unchanged since amphetamine (INN, amfetamine)[3] was replaced by methylphenidate[4-6] about 25 years ago as the primary stimulant prescribed to treat ADHD. Methylphenidate use has increased dramatically,[7] and now more than 10 million prescriptions are written for methylphenidate each year in the United States.[8]

Methylphenidate releases and inhibits uptake of catecholamines (primarily dopamine),[9-10] and the resulting increase in these neurotransmitters is considered to be the basis for its clinical efficacy. Within 1 to 2 hours after oral administration of a clinical dose of methylphenidate, peak serum concentration is achieved and maximum clinical effects are manifested (ie, decreases in the symptoms of ADHD: hyperactivity, inattention, and impulsivity).[11-15] Methylphenidate has a short pharmacokinetic half-life and an equally short

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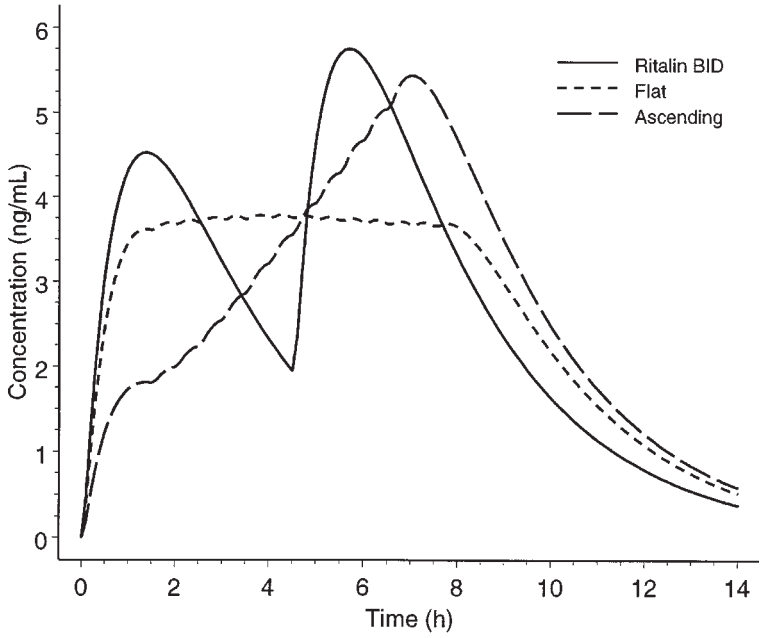

Fig 1. Study I: Simulated plasma methylphenidate concentrations for a 20-mg total daily dose delivered by twice-daily (bid), flat, and ascending dosing regimens.

duration of efficacy of about 2 to 3 hours,[11-15] so twice-daily (bid) or three-times-a-day (tid) dosing is typical. Because the clinically effective dose varies among children (from 5 to 20 mg per administration), individual titration is required. Years of clinical practice[16-19] confirm that bid or tid dosing regimens provide effective and safe treatment. Even though some observations of tolerance have been noted (eg, to side effects and in certain high dosing regimens),[20] in most cases clinical effectiveness is maintained over years of treatment without increasing dose.[21] It therefore appears that children with ADHD do not develop long-term tolerance to treatment with typical clinical doses of methylphenidate.

The short duration of efficacy of methylphenidate creates serious practical problems for effectiveness (because of waxing and waning of effects), for compliance (because of frequent missed doses with multiple daily administrations), for privacy (because of the need to administer medication at school or in other public settings), and for protection against diversion of this controlled drug (because of the difficulty in controlling access by others when it is stored outside the home).

To address these problems, sustained-release preparations intended for once-a-day administration of methylphenidate[22-26] (and amphetamine)[26-28] have been developed, but they are not considered to be as effective as multiple doses of immediate-release preparations and are not widely accepted for clinical use.[8,24] The reasons for reduced efficacy of sustained-release preparations are unknown. Two characteristics of sustained-release patterns of drug delivery may contribute to reduced efficacy. First, a reduced or delayed bolus of drug (compared with the immediate-release pattern) may not result in sufficient increase in brain catecholamines to produce standard clinical effects.[9,10,22,27,28] Second, the continuous rate of drug delivery may produce acute tolerance (tachyphylaxis).[29]

Two studies were conducted to test whether these characteristics of drug delivery contribute to reduced efficacy of methylphenidate on measures of behavior and attention. Study I investigated the time course of efficacy produced by two experimental patterns of drug delivery established by frequent dosing (a large bolus followed by small constant doses that generates a flat profile and a small bolus followed by small increasing doses that generates an ascending profile), compared with the standard pattern of drug delivery in clinical treatment (two large bolus doses that generate the bid profile of peaks and troughs) and a placebo control condition. Study II established two experimental tid dosing regimens in which the timing of the second bolus dose was varied to establish patterns of peaks and troughs appropriate for the evaluation of acute tolerance and for pharmacodynamic modeling of the rela-

tionship between simulated methylphenidate concentration and effect.

METHODS

Study I. Three methylphenidate delivery profiles (bid, flat, and ascending) and placebo were compared in a four-period, double-blind, randomized crossover study. Behavior, attention, and cognitive performance measures were taken frequently in a laboratory school setting in which children diagnosed with ADHD experience repeated classroom sessions across each day.[31-32]

The bid regimen (twice-daily dosing with immediate-release methylphenidate) was expected to produce peaks and troughs (Fig 1) in drug concentration during the typical school day.[9,12-15] The flat regimen was designed to provide an initial peak and then a constant methylphenidate concentration throughout the day. The ascending regimen was designed to produce an increasing methylphenidate level from a low drug concentration (ie, the bid trough level) established early in the morning to a high drug concentration (ie, the bid peak level) by the end of the day. All treatments were administered in identical capsules given precisely at 30-minute intervals throughout the day (an initial capsule at 7:30 AM followed by capsules at 8:30, 9, 9:30, 10, 10:30, 11, 11:30 AM and at 12, 12:30, 1, 1:30, 2, 2:30, and 3 PM). The timing of actual drug administration differed across regimens to create the desired drug delivery pattern and expected concentration profiles. For example, only two of the capsules administered in the bid regimen contained methylphenidate, whereas all capsules administered in the flat and ascending regimens contained methylphenidate, but in differing amounts.

Thirty-eight children (33 boys and five girls; age range, 7 to 12 years; mean age, 9.2 years), with clinical diagnoses of ADHD and receiving current treatment with methylphenidate doses of 5 to 15 mg administered two or three times per day, were recruited for this trial. Parents signed consent forms and children signed assent forms to enter a protocol approved by the University of California Irvine Institutional Review Board. A structured interview (Diagnostic Interview Schedule for Children)[30] was used to confirm the diagnosis of ADHD based on DSM-IV criteria, including onset by 7 years of age, presence of at least six of the nine symptoms in the Inattention or the Hyperactive-Impulsive domains, and significant impairment in at least two settings (eg, home and school).

Each of two cohorts of children was evaluated in the laboratory school setting from 7 AM until 6 PM on five consecutive Saturdays. On the first Saturday, a cohort was first divided by age into two groups. These groups were then introduced to the staff and became familiar with the setting of the classroom (staffed with one teacher and one classroom aide) and the playground (staffed with four recess aides). On subsequent Saturdays, each child received (in random order) one of the following treatments: (1) bid: two doses of immediate-release methylphenidate (Ritalin hydrochloride) administered 4½ hours apart as the total daily dose; (2) flat: an initial loading dose of immediate-release methylphenidate equal to 80% of the morning dose of the bid condition, with the remaining amount of the total daily dose administered (starting 1½ hours later) in small equal doses at 30-minute intervals over 6 hours; (3) ascending: an initial loading dose of immediate-release methylphenidate equal to 40% of the morning dose of the bid condition, with the remaining amount of the daily dose administered (starting 1½ hours later) in small increasing doses administered at 30-minute intervals over 5 hours; (4) placebo: lactose administered in all capsules.

On study days, the teacher evaluated each child after four 30-minute group classroom sessions, and each child was tested on a computer in a 30-minute individual laboratory session immediately before or after each of these classroom sessions. These laboratory school[31] evaluations were scheduled at 1 and 3½ hours after the bid dosing times to coincide with expected peaks and troughs in methylphenidate plasma concentration in the bid regimen. Each classroom session had similar written seat work (eg, solving math problems) and group activities (eg, listening to and discussing a presentation to the class). Classroom rules that defined appropriate and inappropriate behavior were established and, after each classroom session, teachers completed the CLAM and the SKAMP rating scales[32-34] to provide subjective but systematic evaluations of several dimensions of behavior.[35] The CLAM scale has 16 symptom-related items that are rated on a four-point scale (not at all, just a little, pretty much, and very much). It provides three established index scores based on averaging ratings from subsets of items (10 items for the Conners hyperactivity index, five items for the inattention/overactivity index, and five items for the aggression/defiance index). The SKAMP scale has 10 items describing problem behaviors in the classroom setting that are rated on a seven-point impairment scale (none, slight, mild, moderate, severe, very severe, or maximal). It provides two established index scores based on averaging ratings from subsets of items (six items for the attention index and four items for the deportment index). In each laboratory session, children were tested on a display-memory scanning task to provide objective measures (reaction time and accuracy) of cognitive

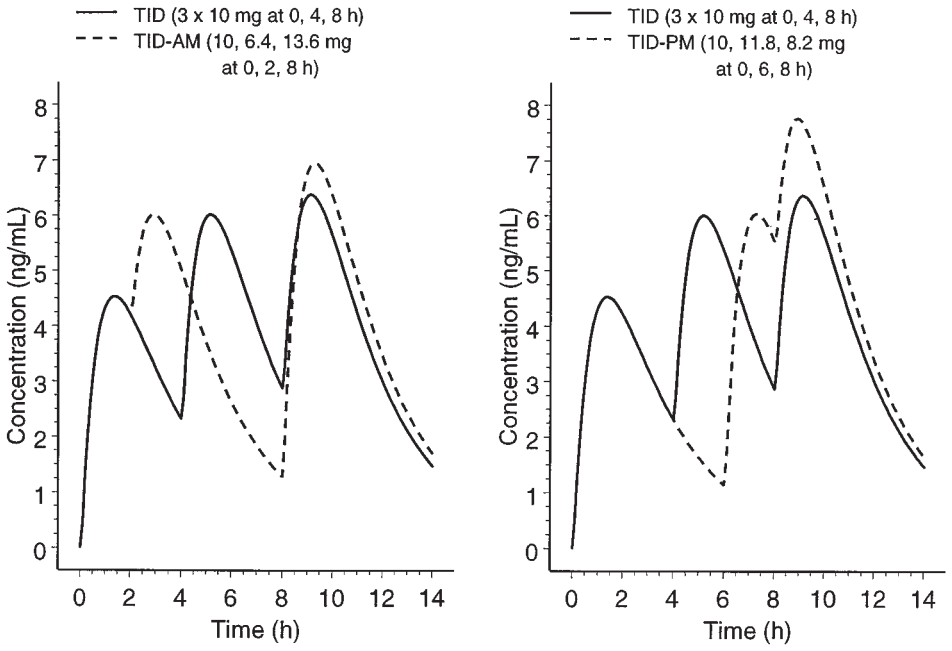

Fig 2. Study II: Simulated plasma methylphenidate concentrations for a 30-mg total daily dose delivered by the following dosing regimens: three times a day (tid), tid with the middle bolus given 2 hours after the first (tid-AM), and tid with the middle bolus given 6 hours after the first (tid-PM).

performance.[36-37] In this task, a set of either one or four digits (the memory set) is presented on a computer screen, followed by a set of four digits (the display set). The subject is asked to press one of two buttons to indicate whether or not the display set contained any one of the memory set items.

The desired methylphenidate profiles for each treatment were determined by simulation with use of published literature values[9-15] and a nominal daily dose of 20 mg. The doses required to produce the flat and ascending profiles were determined by deconvolution by use of a pharmacokinetic model with first-order absorption and one-compartment disposition. Fig 1 shows the simulated plasma methylphenidate concentration–time graphs for bid, flat, and ascending drug delivery profiles.

A mixed-effects ANOVA model was used to analyze the efficacy of the bid, flat, ascending, and placebo regimens. The ANOVA model included fixed-effect factors (regimen, session, sequence, and period) and the random-effect factors (intersubject and intrasubject effects). An overall among-regimen comparison at each time point (session) was conducted with an $\alpha = .05$ significance level. In addition, three pairwise comparisons of methylphenidate regimens within each session were estimated if the overall among-regimen difference was significant. For these comparisons, the least-squares estimate of the mean difference between the two regimens and its 95% confidence interval were calculated. No further adjustments to the significance level were made.

Study II. After a three-period, double-blind, randomized crossover trial of three treatments (tid, ascending, and placebo), a parallel design was used to evaluate two experimental tid conditions. In all drug delivery regimens, children took one capsule every ½ hour for 8 hours, starting at 7:30 AM. In the initial crossover phase, a tid regimen was used as the clinical standard (rather than the bid regimen as in study I) to extend the length of expected drug effects to 10 hours. Each subject received doses of methylphenidate at 7:30 AM, 11:30 AM, and 3:30 PM, and each dose was equal to the child's clinically titrated morning dose. In the ascending regimen, 80% of each subject's usual morning dose was administered at 7:30 AM, followed by small increasing doses administered at 30-minute intervals across the day. In the parallel phase, subjects were randomly assigned to one of two tid conditions in which the middle bolus was varied to shift the second peak to an earlier or later time. In both experimental tid regimens, the first and last bolus doses were administered at 7:30 AM and at 3:30 PM, but the time of the middle bolus was either 9:30 AM (tid-AM) or 1:30 PM (tid-PM). In both of these

conditions, the first dose was always equal to the child's usual morning dose and was ~33% of the total daily study dose. The deconvolution procedure and pharmacokinetic model that were applied in study I were used again in study II to select the second and third doses so that the magnitude of the peak after the second dose would match the magnitude of the midday peak in the standard tid condition (Fig 2). For the tid-AM condition, the second and third doses were set at ~21% and ~45%, respectively, of the total daily study dose, and for the tid-PM condition the second and third doses were set at ~39% and ~27%. The tid and ascending treatments were included for an efficacy analysis, which will be reported elsewhere; the experimental tid-AM and tid-PM regimens were used to provide data for the pharmacodynamic analysis of methylphenidate, which is the topic of this report.

Thirty-two children (28 boys and four girls; age range, 7 to 12 years; mean age, 9.9 years) who had a diagnosis of ADHD and were being clinically treated with methylphenidate were recruited for this study. Their parents signed consent forms and the children assent forms approved by the University of California Irvine Institutional Review Board. The methods of study I for confirming a diagnosis of ADHD were used again in study II, and similar evaluation procedures were used for the evaluation of efficacy. The participating children were tested in the same laboratory school setting[31] for 4 study days, with at least 24 hours between each study day. The 32 children were evaluated in one cohort. On the first day, the cohort was divided into two groups of 16 children based on age, and the groups became familiar with the staff and setting of the classroom (staffed with two teachers and two aides for 16 students) and the playground (staffed by eight recess aides). On each day, hourly cycles of activities[31] were scheduled to allow for frequent classroom probes of attention and behavior across the day. The hourly cycle consisted of capsule administration (1 minute), computer math tests (9 minutes), individual classroom seat work (20 minutes), capsule administration (1 minute), library quiet time (9 minutes), and group classroom activity (20 minutes). This cycle was repeated for 10 hours (8 AM to 5 PM), with substitutions in five of the cycles (ie, those starting at 9 and 11 AM and at 1, 3, and 5 PM) to allow for recess sessions and meals during the day.

Plasma methylphenidate profiles were simulated with a nominal daily dose of 30 mg and deconvoluted with the same techniques as those used in study I. The second doses in the tid-AM and tid-PM treatments were designed to achieve earlier or later maximal plasma concentrations equivalent to the midday peak after the midday second dose in the standard tid regimen (Fig 2).

One subjective and one objective measure of efficacy were chosen for evaluations of acute tolerance. The subjective measure was the attention subscale of the SKAMP rating scale,[32-34] expressed as the average rating per item. The objective measure was a measure of activity obtained from a motion detector (Actigraph, Mini Motionlogger Actigraphs, Ambulatory Monitoring Inc, Ardsley, NY) worn on the nondominant wrist. A 5-second acquisition period was specified, and the counts were integrated over each of the precisely timed 20-minute periods of seat work activity in the classroom.

These two primary efficacy measures (SKAMP attention and Actigraph activity) were obtained during the classroom seat work activities of the laboratory school cycles.[31] For each of the 10 classroom sessions, mean values for attention and activity in the placebo condition were subtracted from the mean values for the two experimental conditions (tid-AM and tid-PM) to remove nondrug related within-day variability. To improve clarity in the visual display of the pharmacokinetic-pharmacodynamic relationship, this difference score was multiplied by –1 so that clinical improvement reflected in the pharmacodynamic measure would be positive and match the direction of change in the pharmacokinetic measure (the simulated plasma concentration of methylphenidate). These pharmacodynamic measures (placebo-adjusted efficacy scores) were plotted versus the pharmacokinetic measures (expected drug concentrations), with time coded by arrows, to evaluate whether evidence of tolerance (a counterclockwise hysteresis loop) was present in these data.

A mathematical pharmacokinetic-pharmacodynamic model of the relationship between methylphenidate concentration and efficacy measures was used to assess tolerance.[38-40] This model used methylphenidate clearance values reported in the literature as the basis for simulating individual concentration–time profiles for the various regimens. The validity of this approach was confirmed in a separate pharmacokinetic study of tid and ascending regimens administered to 21 adult volunteers (14 men and seven women): the shape of the pharmacokinetic curve in the ascending treatment (defined by the multiple small doses) matched the predicted shape based on simulation, and the within-subject pharmacokinetic variability was low (<10%).

For this study, modeling was conducted with use of the nonlinear mixed-effects approach (NONMEM)[38] and included all of the children's data to estimate the mean and individual difference parameters. An E_{max} model was fitted to the simulated methylphenidate concentrations and efficacy measures. The strengths and weaknesses of the E_{max} model have been discussed in

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