Behavior and Motor Activity Response in Hyperactive Children and Plasma Amphetamine Levels Following a Sustained Release Preparation

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Abstract. Amphetamine has been clearly documented to be an efficacious treatment for hyperactive children. Recently, pharmacokinetics of elixir, tablet, and sustained-release preparations have been studied in hyperactive children. Sustained release has been thought to provide a prolonged clinical response. In this study, nine hyperactive children, selected by specific exclusion-inclusion criteria, were administered single oral doses of sustained-release d-amphetamine and placebo; plasma levels, behavioral response, and motor activity were observed in double-blind design. The results, as with the earlier studies, indicate that significant clinical response is not observed beyond 4 hours and that responses occur only during the absorption phase and are not correlated with specific plasma levels of d-amphetamine.

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Amphetamines have been used for over 40 years (Bradley, 1937) to treat children with aggressive, impulsive behavioral disturbances. Double-blind placebo-controlled studies of the effects of d-amphetamine on hyperactive children (HAC) have confirmed its efficacy (Greenberg et al., 1972; Arnold et al., 1972; Conners et al.,

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1972; Huestis et al., 1975) and its use as a standard for comparison in pharmacotherapeutic trials. In normal prepubertal boys, Rapoport et al. (1978) have described cognitive and behavioral responses to d-amphetamine similar to those observed in HAC. Recent studies have reported some of the pharmacokinetic characteristics of d-amphetamine in HAC; e.g., apparent elimination half-life, $\bar{X} \pm$ SEM, 6.8 ± 0.5 h (Brown et al., 1977, 1978, 1979a, 1979b). Sustained-release d-amphetamine has been shown to be released at a slower rate than tablets and to have a similar half-life in adults and animals (Beckett and Tucker, 1966; Rosen et al., 1967; Brown et al., 1979b); this characteristic has been thought to be relevant to attaining a prolonged clinical response in HAC (Wender, 1971; Gross and Wilson, 1974; Safer and Allen, 1976; Ross and Ross, 1976; Cantwell and Carlson, 1978). This study was undertaken to review pharmacokinetic differences between tablets and sustained-release d-amphetamine following single-dose administration. Clinical responses from tablets and elixir by similar methodology also are compared to these results.

Methods

Male children, ages 60 to 144 months, were evaluated at the National Institute of Mental Health (NIH Clinical Center, Bethesda, Maryland) for impulsive, maladaptive social behavior, hyperactivity and learning disability. We obtained the community teachers' behavior ratings off-medication by using the 39-item Conners' Teacher Rating Scale (CTRS) (1969). Children and families were assessed in a preadmission screening. All research methods and procedures were approved by the NIMH Institutional Review Board (IRB) and the NIH Medical Board.

Exclusion criteria were: (1) "hard" neurological findings, i.e., clinical seizure disorder or any other medical disorder (we scored all children for neurological "soft signs" using PANESS) (Guy, 1976); (2) borderline psychosis—as determined by Creak (1961) and the proposed DSM-III criteria (1978); and (3) IQ < 80 on WISC-R. Inclusion criteria for the study group were two standard deviations (SD) or more, above published (Werry et al., 1975) norms for similarly aged boys on Factor I (conduct problem) or Factor IV (hyperactivity) of the CTRS by community teachers' ratings; children were also rated by the NIH teacher. Eight of nine children had Factor I scores > 2 SD; two of nine had Factor IV scores > 1 SD < 2 SD—one of these had a Factor II (attention)

score > 2 SD and the other > 1 SD < 2 SD. Thus, though Factor I behavior is prominent in these children, there were no children who showed only this behavior. Each child further received a complete medical and psychiatric examination to confirm hyperactivity and rule out other conditions during a 5-day inpatient assessment before research procedures were initiated. This study group (N = 9) may be described ($\bar{X} \pm$ SD) as follows: age, 97 ± 25 mos.; weight, 28.0 ± 11.8 kg; WISC-R IQ (full scale), 97 ± 7; and family income, $17,278 ± $10,814.

A low monoamine, low xanthine, normal salt diet was maintained. The controlled diet was necessary: (1) for urinary metabolite studies not reported in this paper; (2) for minimizing variations in urinary pH for pharmacokinetic studies of amphetamine; and (3) for a standard state of hydration (Beckett et al., 1969; Rowland, 1969; Axelrod, 1970). Instructions for this diet were given to parents for weekends and those nights when the child was at home. Urinary pH was monitored by Ames Dipstix on days when blood samples were obtained for d-amphetamine analyses. The mean (± SEM) urinary pH was 6.3 ± 0.4 from an average of 2.7 determinations/patient (range 5.0-7.0). To minimize the number of venipunctures, a heparin-lock and armband were utilized to collect serial blood samples. Usually a single venipuncture sufficed for eight h, though occasionally more than one venipuncture was necessary either for initiating and/or continuing the procedure. Lunch was at a fixed time in relation to blood sampling. A standard breakfast (9 g protein, 26 g carbohydrate, 15 g lipid), usually 75% consumed, was provided between 8:30 and 9:00 A.M. prior to baseline blood at 9:00-9:30 A.M. Placebo and amphetamine were given in varying order with at least three intervening drug-free days. Unlike an earlier study (Brown et al., 1979a), plasma samples for norepinephrine (NE) and dopamine-β-hydroxylase were drawn at h 1-3 with small sham drawings at h 4-6, thus allowing a similar placebo day in which plasma samples were being obtained. We attempted to keep the dose of d-amphetamine as near as possible to 0.5 mg/kg, using 5 mg sustained-release capsules (0.48 ± .01 mg/kg). Environmental variables during the 6 h following single-dose administration included dissimilar school material and different numbers of children on the unit. Scheduled activities were similar, i.e., 1 h for initiating the study, 2 h in the classroom followed by three intervals, each for 1 h, for lunch, occupational therapy, and art therapy, respectively.

Double-blind behavioral ratings by the same research assistant

using the 10-item abbreviated CTRS (ABCTRS) (Conners, 1973) were done on all blood sampling days between 15-30 min following the hourly blood drawing. Likewise, on all study days motor activity was automatically and continuously recorded with a newly developed acceleration-sensitive device (Colburn et al., 1976a, 1976b). Unlike the initial tablet study (Brown et al., 1979a) with 1 h activity summations, but similar to the elixir study (Brown et al., 1977), the motor activity summations in the current study were 15 min at baseline and following each hourly blood sampling. Motor activity counts for consecutive 7.5 min intervals were stored in a memory cell for periods up to 32 h and read out from a PDP-11 minicomputer. The interval length and sensitivity of this device may be adjusted in order to adapt it to the level and kind of movement disorder being studied or to a specific protocol design. An impulse generated by a movement is amplified, routed, and stored in a time-sequence memory location. The entire apparatus is 4 × 6 × 1 cm and weighs 75 g. Activity monitors can be calibrated with each other. The ambulatory motor activity monitor was worn in a vest pocket over the thoracic dorsal area (special vests fitted to each child). Motor activity data intervals were taken consistently during each hour.

Levels of d-amphetamine in plasma were determined by a radioimmunoassay (RIA). The assay relies on competitive binding between amphetamine (in the plasma of the subject) and radiolabeled amphetamine to an antibody raised to a methamphetamine-bovine serum complex. The assay was adapted by Ebert et al. (1976) from a technique of Cheng et al. (1973). The antibody to methamphetamine does not distinguish amphetamine and methamphetamine. Neither does it cross-react significantly with the major metabolites formed from amphetamine in man (benzoic acid, hippuric acid, parahydroxyamphetamine, norephedrine, or parahydroxyephedrine). The midpoint of the standard curve was 1.6 ng, and the minimal detectable dose was 100 pg. Assays were performed directly, in duplicate, with 0.1 cc of plasma. The intra-assay coefficient of variation is 6.9% and the interassay coefficient of variation is 12.3%. In the same laboratory, both RIA and gas chromatography-mass spectrometry (GC-MS) were used to measure amphetamine plasma levels; a highly significant multiple correlation coefficient was found ($R = 0.98223$). RIA samples were run in duplicate, while GC-MS samples were run singly. Since more error is inherent in RIA values, RIA was regressed on

GC-MS. Although GC-MS was 1.9 times more sensitive than RIA, for most purposes, the convenience of the RIA method outweighs the technical superiority of the GC-MS (Powers and Ebert, 1979).

Results

The results of the CTRS behavior ratings performed by the children's community teachers, for whom the scale was intended, are shown in table 1. The community teachers' ratings on Factors I, II, and IV were generally higher than the NIH teachers' ratings. HAC group ratings by community teachers were significantly different from norms on Factors I, II, and IV ($p < .001$); but ratings by the NIH teachers were significantly different only for Factor IV ($p < .01$) (two-tailed t-tests). Factor II has been shown to have a smaller z score (2.16) than Factors I and IV (2.54 and 3.22, respectively) (Werry et al., 1975) in HAC vs. normals and might thus be thought to be less sensitive in differentiating HAC from normal children. As a further evaluation of the exclusion-inclusion criteria used for this study and other studies in this research program, we obtained a Spearman rank-order correlation relating community and NIH teachers' ratings from 42 children screened for several studies. Correlation for both Factors I and IV are significant (Factor I, $r_s = 0.43$, $p < .01$; Factor II, $r_s = -0.04$, ns; Factor IV, $r_s =$

Table 1

Behavioral Rating Characteristics
Connors's Teacher Rating Scale Factor Scores ($\bar{X} \pm SD$)

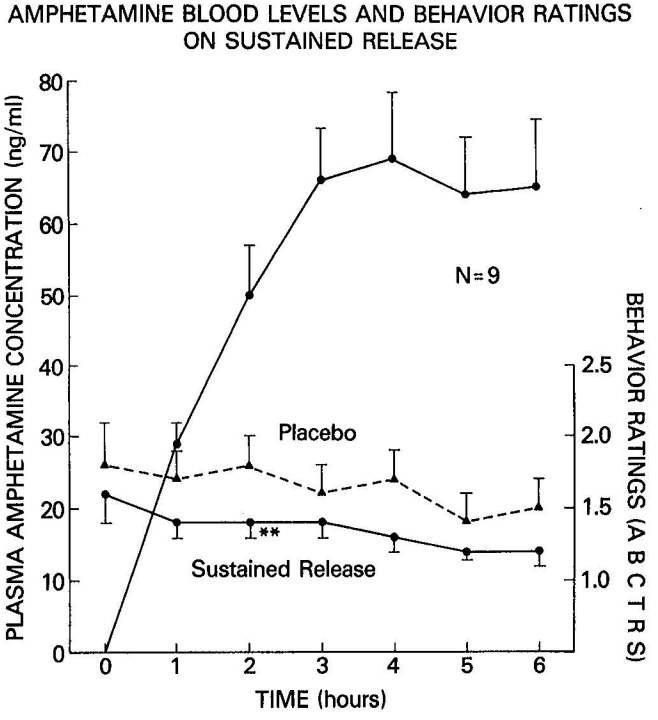
	Factor I	Factor II	Factor IV	N
Norms[a]	1.21 (.39)	1.60 (.58)	1.56 (.65)	143
Study Group[b]				9
Community Teacher	2.53 (.51)[f]	2.85 (.65)[f]	3.48 (.60)[f]	
NIH Teacher	1.34 (.48)	1.54 (.48)	2.20 (.65)[e]	
Community Teacher versus NIH Teacher (r_s)[c]	0.43[e]	−0.04	0.37[d]	43

[a] Werry et al. (1975).
[b] Study Group versus Norms, two-tailed t-test.
[c] Spearman rank-order correlation coefficients.
[d] $p < .05$.
[e] $p < .01$.
[f] $p < .001$.

0.39, $p < .01$). The data reported here are consistent with the z scores cited above.

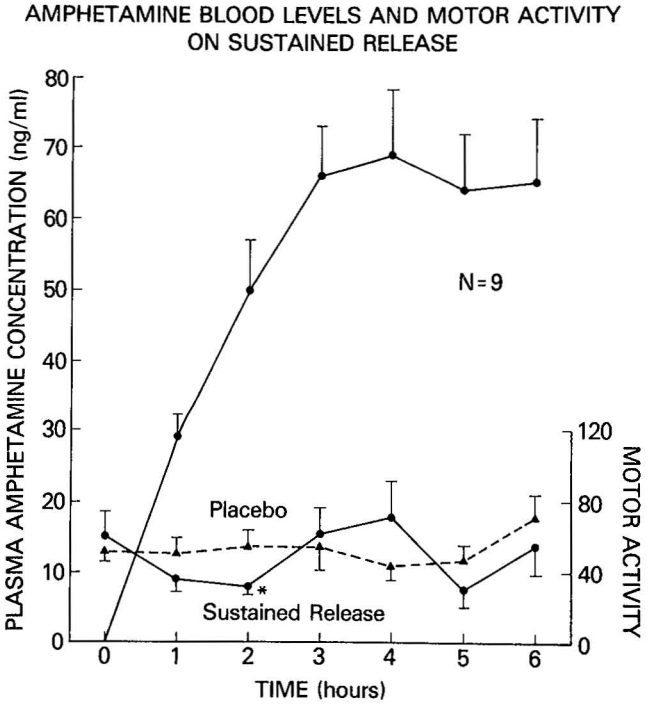
Peak plasma levels occurred between 3-8 h ($\bar{X} \pm SEM = 65.7 \pm 7.1$, 70.2 ± 7.9, 65.8 ± 7.8, 64.8 ± 8.8, 68.6 ± 7.6, and 64.1 ± 9.5 ng/ml, respectively). Plasma levels of d-amphetamine in individual children differed threefold at 1 h, fivefold at 2 h, threefold at h 3 and 4, and two and one-halffold thereafter. The coefficients of variation ($CV = SD/\bar{X}$ expressed as a percent) of d-amphetamine plasma levels during the absorption phase at h 1-8 are 38, 42, 32, 34, 36, 38, 31, and 39%, respectively.

Figure 1 shows the behavioral response to a single dose of sustained-release d-amphetamine compared with placebo. There was a significant difference between drug and placebo ABCTRS ratings at h 2 (paired t-tests: $t = 3.00$, $p < .01$). In HAC, the



behavioral (ABCTRS) response to a single oral dose of sustained-release d-amphetamine is inversely related to rising plasma d-amphetamine levels, though there is no significant correlation between individual behavioral response ratings and individual plasma amphetamine levels when all data points are considered.

Figure 2 shows the motor activity response to a single dose of sustained-release d-amphetamine compared with placebo. There was a significant difference in motor activity counts at h 2 (paired $t = 2.55$, $p < .03$). In HAC, the motor activity response to a single oral dose of d-amphetamine is also inversely related to rising plasma d-amphetamine values; but again there is no significant correlation between individual motor activity response and individual plasma amphetamine levels when all data points are considered.



All t-tests were one-tailed because a large majority of HAC have a positive response to amphetamine (Millichap, 1973) or no response. The very few children who have a negative response are often considered borderline psychotic (excluded from this study) prior to medication (Wender, 1971).

Discussion

The mean (± SEM) apparent half-lives for tablet d-amphetamine and for sustained-release d-amphetamine (identical doses) obtained from an earlier group of seven children studied on two separate occasions were not significantly different (6.6 ± .05 and 8.4 ± 1.2 h, respectively) (fig. 3, Brown et al., 1979b). In both, apparent half-lives were calculated from a least squares linear regression analysis done on the plasma disappearance curve of each patient over a 30-h interval. For tablet, peak values occurred between h 3 and 4 (63.6 ± 5.3 and 63.3 ± 6.1 ng/ml, respectively); and for the sustained release, peak values occurred between h 3-6 (60.7 ± 7.8, 62.2 ± 6.2, 61.7 ± 2.2 ng/ml at h 3, 4, and 6, respectively). Sustained release thus gave a somewhat more plateaulike blood level during this peak level period. Plasma levels of d-amphetamine in individual children differed fourfold at h 1, two and one-halffold at h 2, twofold at h 3, and less than twofold at h 4 after tablet and threefold at h 1, and about twofold at h 2-4 after sustained release. Thus, the early absorption of tablets was somewhat more variable than that of sustained-release capsules; whereas the variability in plasma levels following both was somewhat less during h 6-30 (elimination) as compared to h 1-6 (absorption). The CV of d-amphetamine plasma levels during the absorption phase at h 1-4 were 66, 31, 22, and 24%, respectively, for tablet, and 47, 30, 34, and 25%, respectively, for sustained release. When plasma values obtained from tablets and from sustained release were compared for similarity in these seven children, the intraclass correlation coefficients (ICC) of serial plasma d-amphetamine levels on the two study days were significant in five of the seven individuals (ICC range, .52 − .98, $p < .01$); however, a chi-square test indicated that the seven ICC's did not differ significantly from one another. The pooled ICC was .83. The interchangeability of sets of plasma amphetamine values is quite high for a given child, whether he receives tablet or sustained release; the interchangeability of these sets of values is only modestly less than those reported when

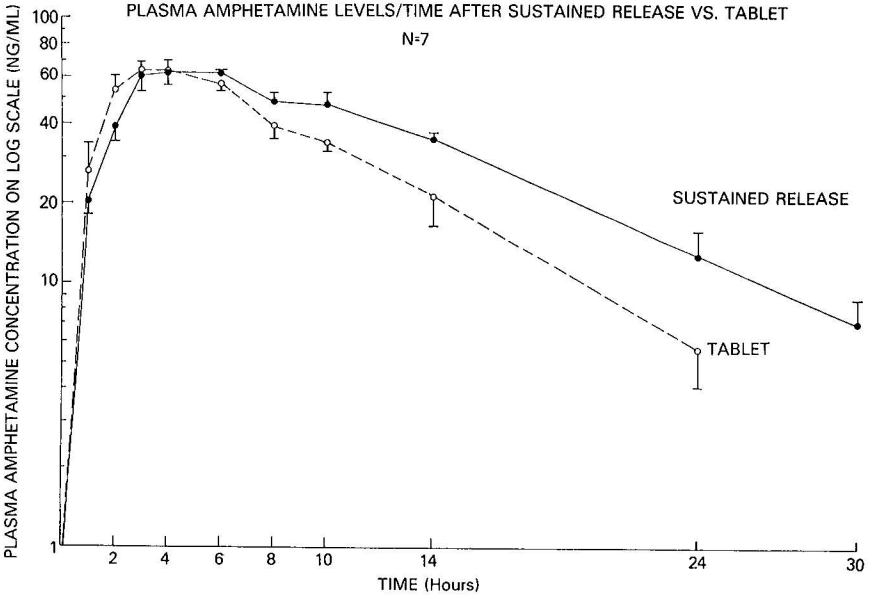
individual children are given tablets on two separate occasions (Brown et al., 1979a, 1979b). Thus, to the degree that differing plasma pharmacokinetics from these two preparations could be expected to effect differing clinical responses, one would predict only modest differences, if any, in clinical response. The plasma data from this study group are similar to the earlier HAC group given sustained-release d-amphetamine. The standard breakfast given to the sustained-release study group here reported (and not to the earlier group) appears to have little effect on the CV.

The apparent elimination half-life of plasma levels of d-amphetamine for a goup of 16 HAC (6.8 ± 0.5 h) who received tablets (Brown et al., 1979a, 1979b) was considerably less than that reported for eight depressed adults (19.4 ± 4.6 h) (Ebert et al., 1976; van Kammen and Murphy, 1975). Both groups attained peak levels at the same time; and both showed the maximal behavioral response at the same time, h 1-4). The findings of Ebert et al. (1976) are consistent with other adult studies when urinary pH is considered (Davis et al., 1971; Kreuz and Axelrod, 1974). More recent work (Gershon et al., 1979; Nurnberger et al., 1979) indicates that normal adult twins show an elimination half-life of 10.5 h when the diet is controlled and the urinary pH is more similar to that of the HAC here reported. Though urinary pH differences could account for some of the half-life differences between the depressed adults and the HAC, it is very unlikely to account for the differences between the HAC and the normal adults. If HAC do eliminate d-amphetamine more rapidly than normal adults, no explanation is clear currently. The half-life of methylphenidate in HAC is 2.6 h, SD ± 0.16 (Hungund et al., 1979) as compared to normal adults (approximately 2 h) (Faraj et al., 1974). The metabolism of amphetamine is more dependent upon liver enzymes than that of methylphenidate. Children and adults apparently absorb d-amphetamine and respond behaviorally in a similar fashion with regard to time, but adults may eliminate the drug more slowly.

The earlier study of the response of HAC to a single dose of d-amphetamine (0.45 ± .02 mg/kg) also showed that significant behavioral and motor activity responses occurred during the absorption phase (h 1-4) and did not correlate with plasma amphetamine levels (Brown et al., 1979a). A later replication study of the response of a different group of 14 HAC to a single dose of d-amphetamine elixir (0.5 mg/kg) with armboard, heparin-lock,

and placebo blood study days (as in this study) showed results similar to the tablet study as well as reliable results within the same group of children (similar drug study conditions on two separate occasions) (Brown et al., 1977). ABCTRS ratings are somewhat dependent upon interactions between children; though the ratings themselves were done consistently on both amphetamine and placebo study days, interactions between children were not consistent across all intervals on a given study day. Lack of behavioral effects postpeak amphetamine levels (h 5 and 6) could possibly be due to the decreased behavioral rating on placebo days at those time intervals, whereas the return of disruptive behavior on amphetamine days is less than baseline for the postpeak intervals; but the likelihood of a type II error in this small N sample is reduced by our having used one-tailed t-tests. The preferable statistical analysis to employ in such a study would be an analysis of variance to assess drug effect, time effect, and their possible interaction, as well as the avoidance of a possible occasional significant difference by paired t-test from chance alone. However, difficulties in obtaining complete serial sets of data for all children studied (particularly behavior) determined the choice of paired t-tests.

When the earlier absorption-elimination study of tablet and sustained-release amphetamine is compared to the current study (see figs. 1, 2, and 3), it is clear that the peak plasma level occurs later and lasts longer with sustained-release (up to h 8), though this later occurrence and more plateaulike peak plasma level is not accompanied by a longer period of significant response to the medication (in fact, the significant response appears to be shorter). Additionally, the earlier and more significant responses to tablet, and particularly to elixir, may further indicate that clinical response is related to absorption. The pharmacogenetic studies of Gershon et al. (1979) in normal adult twins indicate that the period of maximal behavioral change occurs within h 1 after intravenous d-amphetamine despite a mean elimination half-life of greater than 10 h. Behavioral response thus appears unlikely to be a secondary response to plasma amphetamine level. These authors suggest that genetic variation in the amount of releasable catecholamines, susceptibility of cellular and vesicular membranes to amphetamine, or sensitivity of postsynaptic receptor sites may, in part, explain this profile of response. Pharmacokinetic data for methylphenidate in HAC may or may not be consistent with that of d-amphetamine. Hungund et al. (1979) suggest that the low



protein-binding results in a high percentage of free drug made available for metabolism to pharmacologically inactive metabolites could explain methylphenidate's brief course of therapeutic action in HAC; however, amphetamine also shows low protein-binding, but has an approximately threefold longer half-life, while similarly having a relatively brief duration of therapeutic action in HAC. Swanson et al. (1978, 1979) have reported time-response (cognitive behavior) patterns after single doses of methylphenidate. The maximal behavior effect, favorable or adverse, was observed at h 2-4, though favorable responders appeared to attain maximal effect earlier than adverse responders. The "behavioral half-life" (time taken for a 50% decline from the maximum effect)" was 4 h. This "behavioral half-life" more closely approximates the plasma rate of disappearance (half-life) for both methylphenidate and ritalinic acid (its major metabolite) than it does that of d-amphetamine. One might hypothesize that behavioral effect is correlated with methylphenidate and not with d-amphetamine; or alternatively, maximal clinical effect from both stimulants is related to the absorption phase (oral methylphenidate reaches its peak plasma level at about 2 h and d-amphetamine at 3-4 h), while the

"behavioral" and pharmacological half-life of methylphenidate is coincidental. Whether the differences in behavioral parameters being measured contribute to an understanding of the mechanism of response for methylphenidate and d-amphetamine is unclear (Sprague and Sleator, 1977).

Studies in rats of the effect of methamphetamine on NE metabolism and behavior demonstrate that methamphetamine (5.0 mg/kg) inhibits reuptake and increases normetanephrine levels in the first several hours postdrug administration. In these experiments, increases in normetanephrine, a metabolite that reflects extraneuronal metabolism of NE, correlate highly with the behavioral response to methamphetamine (Cook and Schanberg, 1970). When rhesus monkeys were assessed behaviorally after single oral doses of d-amphetamine (0.32 and 1.0 mg/kg), maximal behavioral effects were seen prior to the peak plasma level of amphetamine at times when the plasma level was twofold lower than that which was subsequently attained (Downs and Braude, 1977). The mechanism of the decreased response to later similar levels of d-amphetamine (from a single dose) in plasma may be related to depletion of catecholamine stores, to replacement by a "false neurotransmitter" metabolite of amphetamine (Kopin, 1968a, 1968b), or to alteration in receptor sensitivity (Bunney and Murphy, 1975).

The most important clinical question relates to whether sustained-release d-amphetamine actually does lead to a prolonged clinical response. Despite the literature that raises this prolongation as a possibility, these data would not support such a conclusion, nor would the pharmacokinetic-clinical response data in previous studies. Gross and Wilson (1974) suggest that variable absorption —"delayed and incomplete"—may account for some of the variation in clinical response; however, our data suggest modest variation within the group during the absorption phase. Earlier data suggest less variation during the early absorption phase for sustained release than for tablet, as well as more plateaulike plasma levels during the peak level period; both preparations show somewhat less variability during h 6-30, as compared to the early hours during the absorption phase. Thus, the variability in absorption and elimination between sustained release and tablet appear to be either unrelated to the observed clinical response in this study, or the slower rate of absorption for the sustained release may relate to a later onset and less significant clinical response vs. the response observed after tablet. Safer and Allen (1976) found that at least

10% of HAC who take 15 mg sustained-release spansules as a beginning dose will experience insomnia. Our study did not provide for systematically observing differences between tablet and spansule response in the evening hours. Insomnia has sometimes been a clinical complaint on the evening of the several single-dose studies; such appears to have been dose-related, but not preparation-related. The period during which absorption and elimination are in equilibrium (peak plasma level) clearly does last longer for the spansules than for the tablets at the same dose. Thus, for some children, this prolonged peak plasma level might relate to insomnia, though one could also hypothesize less of a "rebound effect"—an effect that is sometimes felt to be observable clinically, but which has not been documented in a controlled study. Should the clinical response be related to a necessary rate of absorption and be unrelated to the peak plasma level per se and its duration, then the earlier studies would not lead one to predict a prolonged response. These data would not suggest that there is any general advantage in single-dose sustained-release capsule vs. a tablet at 8:00 A.M. and 12:00 P.M., since there is no evidence that any pharmacologically induced therapeutic effect can be obtained beyond 4 hours from the oral administration of a single dose (0.5 mg/kg) of d-amphetamine to HAC.

In conclusion, this study of sustained-release d-amphetamine, like earlier single-dose amphetamine studies in hyperactive children, shows significant behavior and motor activity responses to the medication only during the absorption phase, and these responses are not correlated with specific plasma levels of d-amphetamine. Furthermore, despite pharmacokinetic differences between elixir, tablet, and sustained release, all at the same dose, there is no evidence that a prolonged clinical response results from the use of the sustained-release preparation.

References

Arnold, L. E., Wender, P. H., McCloskey, K., & Snyder, S. H. (1972), Levoamphetamine and dextroamphetamine. *Arch. Gen. Psychiat.*, 27:816–822.

Axelrod, J. (1970), Amphetamine. In: *Amphetamine and Related Compounds*, ed. E. Costa & S. Garattini. New York: Raven Press, pp. 207–216.

Beckett, A. H., Salmon, J. A., & Mitchord, M. (1969), The relations between blood levels and urinary excretion of amphetamine under controlled acidic and under fluctuating urinary pH values using (^{14}C) amphetamine. *J. Pharm. Pharmacol.*, 21:251–259.

——— & TUCKER, G. T. (1966), A method for the evaluation of some oral prolonged-release forms of dexamphetamine in man, using urinary excretion data. *J. Pharm. Pharmacol.*, 18 (Suppl): 72S–75S.

BRADLEY, C. (1937), The behavior of children receiving benzedrine. *Amer. J. Psychiat.*, 94:577–585.

BROWN, G. L., EBERT, M. H., & HUNT, R. D. (1978), Plasma d-amphetamine absorption and elimination in hyperactive children. *Psychopharm. Bull.*, 14:33–35.

——— ——— MIKKELSEN, E. J., BUNNEY, W. E., JR., & KOPIN, I. J. (1979a), Plasma levels of d-amphetamine in hyperactive children. *Psychopharmacology*, 62:133–140.

——— ——— ——— & HUNT, R. D. (1979b), Clinical pharmacology of d-amphetamine in hyperactive children. In: *Pharmacokinetics of Psychoactive Drugs*, ed. L. A. Gottschalk. New York: Spectrum, pp. 137–153.

——— ——— ——— KOPIN, I. J., & BUNNEY, W. E., JR. (1977), Reliability of behavior and activity responses in hyperactive children following single doses of d-amphetamine. Read at the American Psychiatric Association Annual Meeting, Toronto.

BUNNEY, W. E., JR. & MURPHY, D. L. (1975), Strategies for the systematic study of neurotransmitter receptor function in man. In: *Pre- and Post-Synaptic Receptors*, ed. E. Usdin & W. E. Bunney, Jr. New York: Marcel Dekker, pp. 283–311.

CANTWELL, D. P. & CARLSON, G. A. (1978), Stimulants. In: *Pediatric Psychopharmacology*, ed. J. S. Werry. New York: Brunner/Mazel, pp. 171–207.

CHENG, L. T., KIM, S. Y., CHUNG, A., & CASTRO, A. (1973), Amphetamine. *FEBS Lett.*, 36:339–342.

COLBURN, T. R., SMITH, B. A., & GUARINI, J. J. (1976a), An ambulating activity monitor with solid state memory. *Biomed. Sci. Instruments*, 12:117–122.

——— ——— ——— & SIMMONS, N. N. (1976b), An ambulatory activity monitor with solid state memory. *ISA Trans.*, 15:149–154.

CONNERS, C. K. (1969), A teacher rating scale for use in drug studies with children. *Amer. J. Psychiat.*, 126:152–156.

——— (1973), Rating scales for use in drug studies with children. *Psychopharm. Bull.* (Special Issue—Pharmacotherapy of Children):24–29.

——— TAYLOR, E., MEO, G., KURTZ, M. A., & FOURNIER, M. (1972), Magnesium pemoline and dextroamphetamine. *Psychopharmacologia* (Berl.), 26:321–336.

COOK, J. D. & SCHANBERG, S. M. (1970), The effects of methamphetamine on behavior and on the uptake, release, and metabolism of norepinephrine. *Biochem. Pharmacol.*, 19:1165–1179.

CREAK, M. [Chairman, Progress Report of a Working Party] (1961), Schizophrenic syndrome in childhood. *Brit. Med. J.*, 2:889–890.

DAVIS, J. M., KOPIN, I. J., LEMBERGER, L., & AXELROD, J. (1971), Effects of urinary pH on amphetamine metabolism. *Ann. N.Y. Acad. Sci.*, 179:493–501.

DOWNS, D. A. & BRAUDE, M. C. (1977), Time-action and behavioral effects of amphetamine, ethanol, and acetylmethadol. *Pharmacol. Biochem. Behav.*, 6:671–676.

EBERT, M. H., VAN KAMMEN, D. P., & MURPHY, D. L. (1976), Plasma levels of amphetamine and behavioral response. In: *Pharmacokinetics of Psychoactive Drugs*, ed. L. A. Gottschalk & S. Merlis. New York: Spectrum Publications, pp. 157–169.

FARAJ, B. A., ISRAILI, Z. H., PEREL, J. M., JENKINS, M. L., HOLTZMAN, S. G., CUCINELL, S. A., & DAYTON, P. G. (1974), Metabolism and studies in man and animals. *J. Pharm. Exp. Ther.*, 191:535–547.

GERSHON, E. S., NURNBERGER, J. N., SITARAM, N., & GILLIN, J. C. (1979), Pharmacogenetics and the pharmacologic challenge strategy in clinical research. In: *Progress in Neuropsychopharmacology*, ed. B. Saletu. Oxford: Pergamon Press, pp. 75–83.

GREENBERG, L. M., DEEM, M. A., & MCMAHON, S. (1972), Effects of dextroamphetamine, chlorpromazine, and hydroxyzine on behavior and performance in hyperactive children. *Amer. J. Psychiat.*, 129:532–539.

GROSS, M. B. & WILSON, W. C. (1974), *Minimal Brain Dysfunction*. New York: Brunner/Mazel.

GUY, W. (1976), Physical and neurological examination for soft signs. In: *ECDEU Assessment Manual*, 384–393. Rockville, Md.: DHEW/ADAMHA/NIMH, Psychopharmacology Research Branch.

HUESTIS, R. D., ARNOLD, L. E., & SMELTZER, D. J. (1975), Caffeine versus methylphenidate and d-amphetamine in minimal brain dysfunction. *Amer. J. Psychia.*, 132:868–870.

HUNGUND, B. L., PEREL, J. M., HURWIC, M. J., SVERD, J., & WINSBERG, B. G. (1979), Pharmacokinetics of methylphenidate in hyperactive children. Read at the annual meeting of Society of Biological Psychiatry, Chicago.

KOPIN, I. J. (1968a), False adrenergic transmitters. *Ann. Rev. Pharmacol.*, 8:377–394.

——— (1968b), The influence of false neurotransmitters on adrenergic transmission. In: *Adrenergic Neurotransmission*, ed. G. E. W. Wolstenholme & M. O'Conner. Boston: Little, Brown, pp. 95–104.

KREUZ, D. S. & AXELROD, J. (1974), Amphetamine in human plasma. *Science*, 182:420–421.

MILLICHAP, J. G. (1973), Drugs in management of minimal brain dysfunction. *Ann. N.Y. Acad. Sci.*, 205:321–334.

NURNBERGER, J. I., GERSHON, E. S., EBERT, M. H., & BUCHSBAUM, M. S. (1979), Pharmacogenetics of amphetamine in normal twins. Read at the annual meeting of Society of Biological Psychiatry, Chicago.

POWERS, K. G. & EBERT, M. H. (1979), Comparison of RIA and GC-MS assays for d-amphetamine. *Biomed. Mass. Spectrometry*, 6:187–190.

RAPOPORT, J. L., BUCHSBAUM, M. S., ZAHN, T. P., WEINGARTNER, H., LUDLOW, C., & MIKKELSEN, E. J. (1978), Dextroamphetamine. *Science*, 199:560–562.

ROSEN, E., ELLISON, T., TANNENBAUM, P., FREE, S. M., & CROSLEY, A. P., JR. (1967), Comparative study in man and dog of the absorption and excretion of dextroamphetamine-^{14}C sulfate in sustained-release and nonsustained-release dosage forms. *J. Pharm. Sci.*, 56:365–369.

ROSS, D. M. & ROSS, S. A. (1976), *Hyperactivity*. New York: John Wiley.

ROWLAND, M. (1969), Amphetamine blood and urine levels in man. *J. Pharm. Sci.*, 58:508–509.

SAFER, D. J. & ALLEN, R. P. (1976), *Hyperactive Children*. Baltimore: University Park Press.

SPRAGUE, R. L. & SLEATOR, E. K. (1977), Methylphenidate in hyperkinesis. *Science*, 198:1274–1276.

SWANSON, J. M., KINSBOURNE, M., ROBERTS, W., & ZUCKER, M. A. (1978), Time-response analysis of the effect of stimulant medication on the learning ability of children referred for hyperactivity. *Pediatrics*, 61:21–29.

——— & SELDIN, S. J. (1979), Serum levels of methylphenidate in hyperactive children: I. Half-life following oral administration; II. The therapeutic range. Workshop on the Influence of Age on the Pharmacology of Psychoactive Drugs, Washington, D.C.

Task Force on Nomenclature and Statistics of the American Psychiatric Association (1978), Early childhood psychosis. In: *DSM-III Draft*, M9-M14.

VAN KAMMEN, D. P. & MURPHY, D. L. (1975), Attenuation of the euphoriant and activating effects of d- and l-amphetamine by lithium carbonate treatment. *Psychopharmacologia* (Berl.), 44:215–224.

WENDER, P. H. (1971), *Minimal Brain Dysfunction in Children*. New York: Wiley-Interscience.

WERRY, J. S., SPRAGUE, R. L., & COHEN, M. H. (1975), Conners' teacher rating scale for use in drug studies with children. *J. Abnorm. Child Psychol.*, 3:217–229.