Sustained Release Methylphenidate: Pharmacokinetic Studies in ADDH Males

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Abstract. Methylphenidate is widely used in the treatment of school-age children with attention deficit disorder with hyperactivity (ADDH). It is available in a short-acting (MPH) and a long-acting (MPH-SR) preparation. Nine males with ADDH participated in a 1-day pharmacokinetic study following a single morning dose of 20 mg. MPH-SR. Data are presented on MPH-SR's half-life (T 1/2), peak concentrations achieved (C_{max}) and the time to the peak plasma concentrations (T_{max}). Similar data were gathered from a second group of eight ADDH males treated with a higher, single morning dose of standard, short-acting MPH. After adjusting for dose differences, comparisons of the two sets of plasma concentration curves suggest that MPH-SR has a longer T_{max}, but that it does not reach the same C_{max} as an identical dose of standard MPH. *J. Am. Acad. Child Adolesc. Psychiatry*, 1989, 28, 5:768–772. **Key Words:** attention deficit disorder, methylphenidate, methylphenidate-SR, psychopharmacology.

Attention deficit disorder with hyperactivity (ADDH) has a very high response to stimulant medication; controlled studies (Gittelman-Klein, 1975, 1987; Barkley, 1982) show up to 70% response rate to methylphenidate (MPH). Stimulants act by decreasing motor hyperactivity and increasing on-task attention (Werry et al., 1987; Douglas et al., 1988). Yet MPH administration has been troubled because its brief half-life of 3.3 hours (Gualtieri et al., 1981, 1982, 1984) necessitates twice per day dosing, once after breakfast and once during the school day. Children are often reluctant to take the medication in school, which results in poor compliance (Brown et al., 1985; Firestone, 1982). A slow release formulation (sustained-release Ritalin®) (MPH-SR) has been made available for a once per day morning dose (The Medical Letter, 1984, 1988).

Controlled studies of MPH-SR (Whitehouse et al., 1980; Pelham et al., 1987; Greenhill et al., 1987) have shown short-term efficacy for the drug. Whitehouse et al. (1980) reported that MPH and MPH-SR were equally effective. Thirty children diagnosed as having "minimal brain dysfunction" were treated in a double-blind study that compared a single morning dose of MPH-SR with two doses of MPH-SA 10 mg. This study lacked dose-ranging and had no placebo group. Pelham et al. (1987), using a double-blind, placebo controlled design to study 13 boys in a summer program, reported that both drugs showed equal efficacy on the Abbreviated Conners Rating Scale but that MPH-SR had onset of action 1 hour later than MPH. They also found that the effects of MPH-SR were still evident 8 hours after ingestion, and its peak of action measured by a continuous performance task was 1 hour later than that seen with MPH. A panel of 11 experts reviewed "blinded" clinical records and found that MPH was a more effective treatment agent than was MPH-SR.

One longer-term study has questioned the efficacy of single morning administration of MPH-SR over time. Fried et al. (1987) administered MPH-SR to 40 ADDH boys, aged 7 to 12 years and followed them for 6 months. Forty-five percent of the boys dropped out of the study, and those who remained in required an increase in MPH-SR dose or required additional doses of standard MPH. The reason for this lack of efficacy is not clear, because MPH-SR employs the same active methyphenidate that has been found to be clinically effective at the 20 mg. per day dose in over 22 controlled studies (Barkley, 1982). Possible explanations of MPH-SR's relative inefficacy include problems in absorption in the gastrointestinal track from its wax-matrix resin vehicle, delayed absorption, pharmacokinetic differences or differences at the brain receptor level (pharmacodynamic differences) or tachyphylaxis (Jackson, pers. commun.). Only one report discussed the excretion of urinary ritalinic acid, MPH's major metabolite, after administration of MPH-SR to children (FDA, 1982). MPH-SR was found to be absorbed more slowly but as completely as standard MPH. Ritalinic acid's time to peak concentration (T_{max}) was slower than the standard preparation, and is listed at 4.7 hrs (1.3 to 8.2 hours). Ritalinic acid does not cross the blood-brain barrier and is not psychoactive. Its concentration, either in blood or urine, does not correlate well with concentrations of the active parent compound, MPH. No studies have yet reported MPH-SR plasma concentrations following oral administration to human subjects.

MPH-SR concentrations in plasma following administration to ADDH children could clarify the bioavailability issue. The authors measured plasma levels of MPH-SR in ADDH

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males. The study focused on whether MPH-SR (given once daily) produces very low methylphenidate plasma concentrations or shows delayed absorption and a delayed peak when compared to data previously collected on plasma levels of standard MPH (Greenhill et al., 1983).

Method

Thirteen males, aged 8 to 14, were selected for the pharmacokinetic study. They met *DSM-III* (APA, 1980) criteria for the diagnosis of ADDH and scored at least 1.8 out of a possible 3 points on Factor IV (hyperactivity factor) of the Conners teacher questionnaire (Goyette et al., 1978; Connors, 1985). All boys had been responders to standard MPH, which was defined as a 25% drop in the Factor IV CTQ score; eight had been treated previously with MPH-SR. Consents were obtained from both parent and child concerned, and an Institutional-Review-Board-approved volunteer's fee was paid to the family, after the day-long study was fully completed.

All the children were drug-free and refrained from eating or drinking caffeinated beverages 12 hours before the study. A vein catheter was placed in the non-dominant arm, and a slow infusion of 5% Dextrose in water was maintained. In three children, the arm vein catheter did not work and had to be removed in order to prevent infiltration. Another child's data was not used because the saliva data indicated that he had chewed up the MPH-SR tablet, and it acted quickly, like standard methylphenidate. This left nine children, whose mean age was 11.398 ± 1.85 years (range 8.08 to 13.4 years), and who had a mean Hollingshead (1957) socioeconomic status of 4.11 ± 1.27.

The children received 20 mg of MPH-SR (0.44 ± 0.20 mg/kg, range 0.2 to 0.83 mg/kg) in a single morning dose at 8:30 AM. Standard, short-acting methylphenidate was not used in this study. Therefore, both plasma and saliva MPH levels were collected at hourly intervals for 8 hours. The children were given hourly tests of motor steadiness (Gardner steadiness test, see Gardner et al., 1979), hand-eye coordination (Purdue form board), and activity levels (measured using an actometer).

Plasma and saliva MPH levels were assayed using standard methods described elsewhere (Danhof and Breimer, 1978; Mucklow et al., 1978, 1982; Hungund et al., 1979; Greenhill et al., 1987). The coefficient of variation for this method is 8% for interassay and 5% for intra-assay. The mean plasma concentration of MPH at each collection time, the 1-hour measure most often associated with the peak, the slope of the absorption phase, and area under-the-curve were included in the pharmacokinetic analysis. The raw data were subjected to iterative exponential stripping procedure (Bergner et al., 1973). The parameters derived from above were used as starting values for estimation of pharmacokinetic parameters using nonlin analysis (NONLIN, 1984) with assumption of a one-compartment open model. Although the pharmacokinetics of MPH have been adequately described in the rat in a two-compartment open model (Gal et al., 1977), the use of a one-compartment equation for human data has been shown to introduce negligible (1% to 3%) errors in drug clearance calculations (Hungund et al., 1979). Test with an *F*-test (Boxenbaum et al, 1974) showed essentially no difference between pharmacokinetic parameters derived by either model. Parsimony dictates using the model with the least number of compartments. Other data were analyzed using BMDP (Dixon, 1985).

Scores of the Purdue peg board, activity monitor, and steadiness test were correlated with plasma and saliva levels.

The data from this study suggest that methylphenidate plasma levels can be collected from ADDH boys with little difficulty. Cooperation with the procedure may have been greatly enhanced for some children by the volunteer's fee. However, two other children declined the study because of fear of needles, despite any possible monetary inducement.

An earlier report (Greenhill et al., 1983) described a methylphenidate pharmacokinetic study of standard MPH using identical plasma collection techniques and pharmacokinetic modeling. The six ADDH males were younger (mean age 8.59 ± 1.3 years, range 6.58 to 10.38 years), and they had been given a higher single morning dose of standard MPH (mean loading dose, 0.89 ± 0.14 mg/kg, range 0.64 to 1.01 mg/kg). After adjusting for dose, these data may be cautiously used for contrast purposes.

Results

All subjects tolerated the MPH-SR medication without reported side effects. Peak plasma levels of the parent compound, MPH, ranged between 4.08 and 17.49 ng/ml, with a mean maximum plasma concentration (C_{max}) of 8.54 ± 2.84 ng/ml. Correlations between the peak plasma level and the dose-by-weight ($r = 0.8765$, $p < 0.01$) were significant. Time of peak plasma level (T_{max}) ranged between 1.85 and 4.90 hours, with a mean time to peak of 3.36 ± 1.08 hours. Plasma half-life (T 1/2 B) ranged between 2.20 and 6.26 hours, with a mean of 4.12 ± 1.52 hours. Plasma levels were easily detectable at 7 hours after the single dose of 20 mg and averaged 7.22 ± 3.82 ng/ml in plasma.

The area-under-the-curve (AUC) for the nine boys on MPH-SR (73.81 ± 36.63) correlated with the dose-by-weight of the medication taken, $r = 0.8040$, $p < 0.01$. Measurements of half-life and AUC for MPH-SR are shown in Table 1.

Beta or metabolic phase demonstrated by the curves in these eight subjects closely matches the monoexponential decay curve that might be predicted from a standard single-release tablet. This can be shown most clearly for a single

TABLE 1. *Pharmacokinetic Data on MPH-SR Plasma Levels*

Patient No.	Dose (mg/kg)	$T_{1/2_B}$ (hr)	C_{MAX} (ng/ml)	T_{MAX} (hr)	AUC_{1-f} ng/ml/hr
7	0.32	4.90	8.03	2.19	74.50
21	0.38	4.10	5.87	3.54	46.27
27	0.83	3.09	17.49	4.23	163.40
33	0.35	4.72	6.85	4.06	56.53
42	0.36	2.69	8.55	3.54	72.80
43	0.55	6.26	8.53	1.85	84.70
63	0.62	2.20	10.70	4.90	68.10
73	0.31	2.87	4.08	3.87	37.47
74	0.20	6.26	6.77	2.04	60.54
Mean	0.44	4.12	8.54	3.36	73.81
SD	0.20	1.52	3.48	1.08	36.63

subject, which is demonstrated in Figure 1. The figure is a computer-generated graph using NONLIN to curve-fit the data from Subject 7. The smoothness of the slope of the decay phase seen here does not support the general notion of a multiple-release vehicle, which should continue to show a curve made up of many peaks. In addition, the bioavailability during the eight hours of testing was lower for the MPH-SR than for the standard MPH.

MPH saliva levels after ingestion of the standard-release MPH tablet followed a course similar to that of the plasma levels. One child chewed the SR tablet slightly, giving a falsely high saliva level (3485.30 ng), so his saliva and plasma data had to be excluded. This subject's plasma levels were the highest levels reached (19.6 ng/ml). This subject's peak was reached at 2.87 hours, suggesting that more MPH may have been released earlier with the other subjects. One must be careful about subject's chewing their medications in studies like this one, and thus saliva level measurements have proven helpful (Roose and Licamele, 1984). The remaining 9 males reached MPH peak concentrations in saliva that ranged between 10 ng/ml to 78.80 ng/ml. The plasma and saliva MPH level measures did not correlate ($r = 0.22$, $p < 0.44$). Although one cannot predict plasma levels from saliva MPH measurement, the saliva method has promise as a compliance check.

The drop in motor steadiness error rates (time out of 180 seconds making errors on the Gardner Steadiness Test) and change in gross motor activity levels measured by the actometer (ACTDIF) showed the greatest changes within the first 3 hours after taking MPH-SR. Maximum change in activity levels over the first 3 hours (baseline mean count = 2690.88 ± 2013.48; 3-hour mean count = 2840.11 ± 2105.11) correlated with change in MPH plasma concentrations during the same period ($r = 0.6841$, $p < 0.01$). Baseline steadiness errors (touch-time) for the MPH-SR group averaged 29.78 ± 9.72, and fell to 20.33 ± 11.77 by 180 minutes; the correlation between the drop in error rate and rise in plasma levels during absorption was significant ($r = 0.414$, $p < 0.44$). The Purdue Form board showed no significant correlation with MPH-SR levels.

The other group on standard MPH showed higher plasma levels, probably caused by the difference in dosage (see Fig. 2). As a result, the standard short-acting MPH's peak plasma levels (C_{max}) were significantly higher than those reported here

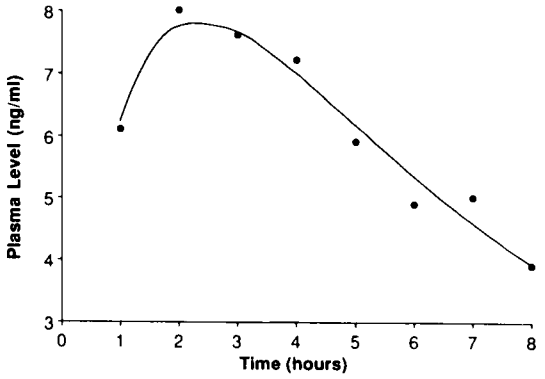

FIG. 1. Plasma level methylphenidate: Patient 7 nonlin fit.

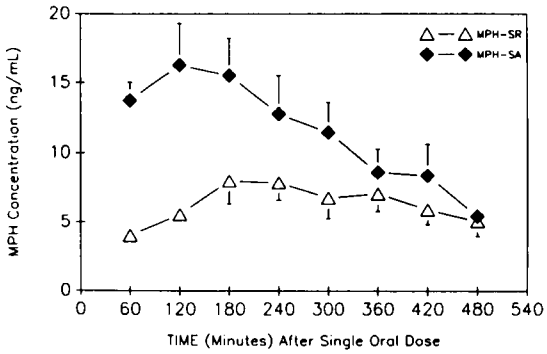

FIG. 2. Plasma MPH concentrations after either 20 mg MPH-SR ($N = 9$) or 25 mg MPH-SA ($N = 6$).

for MPH-SR (24.1 ng versus 8.8 ng, pooled t test = 4.04, $p < 0.0014$). The C_{max} correlates with dose across these two samples ($r = 0.8280$, $p < 0.005$), indicating that differences in peak concentration are related more to the large differences in dose than to type of preparation. The time to peak, T_{max}, was significantly longer for MPH-SR (3.36 ± 1.08 hours) than that for the standard, short-acting preparation (1.625 ± 0.77 hours, $t = 3.43$, $p < 0.0045$). Half-life, on the other hand, showed little difference between the two MPH preparations (standard MPH, 3.33 ± 0.65 hours; MPH-SR, 4.12 ± 1.52 hours; pooled $t = 1.2$, $p < 0.2514$).

As with the current MPH-SR sample, the standard MPH group also demonstrated a significant negative correlation between plasma levels and drop in Gardner Steadiness Test error rate ($r = 0.91$, $p < 0.0001$) during the absorption phase. MPH peaked significantly sooner in the standard MPH-treated group (1.7 hours versus 2.6 hours, pooled t test = 3.6, $p < 0.0026$).

Dosage effects on comparisons between these two groups were adjusted for by calculating the area under the curve per milligram (AUC/mg/kg). Using this approach, the group on standard MPH (mean AUC/dose = 128.51 ± 43.19) showed a lower dose-adjusted AUC from the mean of the group on MPH-SR (AUC/dose = 177.87 ± 62.91). These differences did not reach significance, however, when tested by either t test (Pooled $t = 1.67$, $p < 0.1197$) or nonparametric statistics (Kruskal-Wallis = 2.72, $p < 0.0990$; Mann Whitney = 13, $p < 0.0990$).

Discussion

This study is a preliminary descriptive report on a fixed-dose pharmacokinetic study of MPH-SR in boys with ADDH. A single, acute loading dose was given and plasma concentrations were followed for 8 hours. Observations were limited to tests of motor steadiness and Purdue Peg board performance, and motor counts using simple summation-type mechanical activity counters. The results suggest that MPH-SR is indeed slow in release, reaching a peak in twice the period of time reported in several other studies (Gualtieri et al., 1982; Greenhill et al., 1983; Pelham et al., 1987) of ADDH boys given a single, oral dose of standard MPH.

There are many limitations inherent in this study. Ideally, the boys in this study should have been their own controls.

Instead of a contrast group, with different ages and on different doses, the same boys would have been the best group to also be given identical doses of standard MPH. The standard MPH could have been given in the normal twice-per-day dosing pattern, morning and noon, rather than one large loading dose, as with the contrast group. Also, no control periods or groups are available to help interpret the performance measures. The ADDH males were not followed over time on MPH-SR, so these data cannot truly be used to study the decrease in efficacy of MPH-SR over time reported by Fried et al. (1987). The authors also had no measure of gastric emptying time, which could greatly affect absorption. The correlations between the peak MPH-SR plasma levels and maximum change on the Gardner Steadiness Test were found only for the first 3 hours. The lack of correlation between activity measures and plasma levels may have been due to the very high variability in these measures for a very small sample of subjects.

This descriptive report agrees with published work on MPH-SR (Pelham et al., 1987), which indicates that sustained-release vehicle produces a delayed plasma peak MPH concentration. This may have implications for the clinical efficacy of MPH. Earlier work suggests that stimulants exert their major attention-enhancing action during absorption (Brown et al., 1980; Greenhill et al., 1983). It is not clear, however, whether the rate of absorption or simply the peak plasma (or brain) concentrations alone accounts for MPH's efficacy in a given child. This might be interpreted as a "threshold" model (peak reached) or "ramp effect" model (rate of absorption driven kinetics) of drug action.

However, preliminary descriptive comments can be made about MPH-SR pharmacokinetics. The flattened curve of MPH plasma concentrations after MPH-SR ingestion (Fig. 2) resembles that seen with long-acting dextroamphetamine sulfate by Brown et al. (1980). This prolonged, stable level raises a question about whether MPH-SR may be more prone to tachyphylaxis, similar to that seen using a sympathomimetics with longer half-lives than standard MPH, such as the amphetamines (Nedergaard et al., 1988) or inhaled beta adrenergic agonists (Pauwels, 1988).

References

American Psychiatric Association (1980), *Diagnostic and Statistical Manual of Mental Disorders (Third Edition) DMS-III.* Available from the American Psychiatric Association, 1700 18th Street, N.W., Washington, DC 20009.

Barkley, R. A. (1982), *Hyperactive Children.* New York: Guilford Press.

Bergner, P-E. E., Berniker, K., Cooper, T., Gradijan, J. & Simpson, G. (1973), Lithium kinetics in man: effect of variation in dosage pattern. *Br. J. Pharmacol.*, 49:328–339.

Boxenbaum, H. G., Riegelman, S. & Elashoff, R. M. (1974), Statistical estimation in pharmacokinetics. *Journal of Pharmacokinetics and Biopharmaceutics,* 2(2):123–148.

Brown, G. L., Ebert, M. H., Mikkelsen, E. I. & Hunt, R. D. (1980), Behavior and motor activity response in hyperactive children and plasma amphetamine levels following a sustained release preparation. *J. Am. Acad. Child Psychiatry,* 19:225–239.

Brown, R. T., Borden, K. A. & Clingerman, S. R. (1985), Adherence to methylphenidate therapy in a pediatric population. *Psychopharmacol. Bull.* 21:28–36.

Conners, C. K. (1985), Rating scales and checklists for psychopharmacologic trials. *Psychopharmacol. Bull.* 21:809–851.

Danhof, M. & Breimer, D. D. (1978), Therapeutic drug monitoring in saliva. *Clinical Pharmacokinetics,* 3:39–57.

Dixon, W. (1985), *BMDP Statistical Software.* Los Angeles: University of California Press. pp. 413–425.

Douglas, V. I., Barr, R. G., Amin, K., O'Neill, M. E. & Britton, B. G. (1988), Dosage effects and individual responsitivity to methylphenidate in attention deficit disorder. *J. Child Psychol. Psychiatry,* 29:453–475.

Firestone, P. (1982), Factors associated with children's adherence to stimulant medication. *Am. J. Orthopsychiatry,* 52:447–457.

Food and Drug Administration (1982), New drug application 18-029. Department of Health and Human Services. Public Health Service. Rockville, Maryland 20857.

Fried, J., Greenhill, L., Torres, D., Martin, J. & Solomon, M. (1987, Oct.), *Sustained-release methylphenidate: long-term clinical efficacy in ADDH males.* Paper presented at the 35th Annual Meeting of the American Academy of Child and Adolescent Psychiatry, Washington, DC.

Gal, J., Hodshon, B. J., Pintouro, C., Flam, B. L. & Cho, A. K. (1977), Pharmacokinetics of methylphenidate in the rat using single-ion monitoring GLC-mass spectrometry. *J. Pharm. Sci.,* 66:866–869.

Gardner, R. A., Gardner, A. K., Caemmerer, A. & Broman, M. (1979), An instrument for measuring hyperactivity and other signs of MBD. *Journal of Clinical Child Psychology,* Fall:173–179.

Gittelman-Klein, R. (1975), Review of Clinical Psychopharmacological treatment of hyperkinesis. In: *Progress in Psychiatric Drug Treatment,* ed. D. F. Klein & R. Gittelman-Klein. New York: Brunner Mazel. pp. 661–674.

—— 1987, Pharmacotherapy of Childhood Hyperactivity. In: *Psychopharmacology: The Third Generation of Progress,* ed. H. Meltzer. New York: Raven Press, pp. 1215–1224.

Greenhill, L. L., Perel, J. M., Curran, S. et al. (1983, Oct.), *Attentional measures and plasma level correlations in methylphenidate treated males.* Paper presented at the annual meeting of the American Academy of Child and Adolescent Psychiatry, San Francisco, California.

—— Cooper, T., Solomon, M., Fried, J. & Cornblatt, B. (1987), Methylphenidate salivary levels in children. *Psychopharmacol. Bull.* 23:115–119.

Goyette, C., Conners, C. K. & Ulrich, R. F. (1978), Normative data on revised Conners parent and teacher rating scales. *J. Abnorm. Child Psychol.* 6:221–236.

Gualtieri, C. T., Kanoy, R., Hawk, B., et al. (1981), Growth hormone and prolacatin secretion in adults and hyperactive children relation to methylphenidate serum levels. *Psychoneuroendocrinology,* 6:331–339.

——, Wafgin, W., Kanoy, R., et al., (1982), Clinical studies of methylphenidate serum levels in children and adults. *J. Am. Acad. Child Psychiatry,* 21:19–26.

——, Hicks, R., Patrick, K., Schroeder, S. & Breese, G. (1984), Clinical correlates of methylphenidate blood levels. *Therapeutic Drug Monitoring,* 6:379–392.

Hollingshead, A. B. (1957), *Two Factor Index of Social Position.* New Haven: Yale University.

Hungund, B. L., Hanna, M. & Winsberg, B. G. (1978), A sensitive gas chromatographic method for the determination of methylphenidate (Ritalin) and its major metabolite alpha-phenyl-2-piperidine acetic acid (ritalinic acid) in human plasma using nitrogen-phosphorus detection. *Communications in Pharmacology,* 2:203–208.

——, Perel, J. M., Hurwic, M. J., Sverd, J. & Winsberg, B. G. (1979), Pharmacokinetics of methylphenidate in hyperactive children. *Br. J. Clin. Pharmacol.*, 8:571–576.

Mucklow, J. C. (1982), The use of saliva in therapeutic drug monitoring. *Therapeutic Drug Monitoring,* 4:229–247.

—— Bending, M. R., Kahn, G. C. & Dollery, C. T. (1978), Drug concentration in saliva. *Clin. Pharmacol. Ther.* 24:563–570.

Pauwels, R. (1988), Recepteurs adrenerigiques bronchiques et asthme. La tachyphylaxie et sa prevention. *Allergie et Immunologie,* 20:261–265.

Nedergaard, S., Hopkins, C. & Greenfield, S. (1988), Do nigro-striatal

neurons possess a discrete dentritic modulatory mechanism? Electrophysiological evidence from the actions of amphetamine in brain slices. *Exp. Brain Res.*, 69:444–448.

NONLIN Statistical Program (1984), Statistical Consultants, Lexington, Kentucky.

Pelham, W. E., Sturges, J., Hoza, J., et al. (1987), The effects of sustained release 20 and 10 mg Ritalin bid on cognitive and social behavior in children with attention deficit disorder. *Pediatrics*, 80:491–501.

Roose, R., & Licamele, W. (1984), Slow-release methylphenidate: problems when children chew tablets. *J. Clin. Psychiatry*, 45:525.

The Medical Letter (1984), Sustained-release methylphenidate, 26(673):97–98.

The Medical Letter (1988), Methylphenidate: Ritalin revisited, 26:97–98.

Werry, J. S. (1988), Drug, learning and cognitive function in children. *Psychol. Psychiatry*, 29:129–141.

Whitehouse, D., Shah, U. & Palmer, F. (1980), Comparison of sustained-release and standard methylphenidate in the treatment of minimal brain dysfunction. *J. Clin. Psychiatry*, 41:282–285.