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REVIEW

Pharmacology of Methylphenidate, Amphetamine Enantiomers and Pemoline in Attention-Deficit Hyperactivity Disorder

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Racemic methylphenidate remains the drug of choice for attention-deficit hyperactivity disorder (ADHD). Methylphenidate appears to produce psychostimulation by inhibiting the presynaptic uptake of impulse-released dopamine. The absolute bioavailability of methylphenidate in humans is quite low and variable; mean 23 per cent for the therapeutic (+)-isomer and 5 per cent for the (−)-isomer. The primary site of presystemic metabolism may be the gut and/or intestinal wall. Brain concentrations of methylphenidate average eight times that of blood. A T_{max} of 1·5–2·5 h, a C_{max} of 6–15 ng/ml and a $T_{1/2}$ of 2–3·5 h are typical. The area under the plasma concentration–time curves for immediate-release versus sustained-release formulations are nearly identical, but the relative efficacy is unresolved. Dextroamphetamine has generally been found to compare favourably with methylphenidate in ADHD; it acts through release of newly synthesized dopamine. Levoamphetamine is present as a minor component in a combination product (Adderall®), but the rationale for inclusion of the levo isomer remains unclear. Pemoline appears to both release and block the uptake of dopamine. Though rarely exhibiting sympathomimetic side-effects, potential hepatotoxicity relegates pemoline to a second-line status. © 1997 John Wiley & Sons, Ltd.

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INTRODUCTION

The present review focuses on the psychostimulants used to treat attention-deficit hyperactivity disorder (ADHD); their pharmacodynamics, pharmacokinetics, and clinical utilization. ADHD as defined by the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV, American Psychiatric Association, 1994), or hyperkinetic disorder as defined by the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10, World Health Organization, 1992), is a complex, heterogeneous and pervasive psychiatric illness. Symptoms frequently include varying degrees of inattention, hyperactivity, and impulsivity. The ultimate manifestations of ADHD can range from mild to severe decrements in academic, social, and occupational performance. This disorder occurs in approximately 3–5 per cent of school-aged children (Szatmari *et al.*, 1989), is diagnosed 4–9 times more frequently in boys than in girls, and presents as the most common mental disorder in childhood (Sandberg, 1996). Indeed, ADHD has been reported to account for up to 50 per cent of the child psychiatric population seen in the clinic (Cantwell, 1996).

The biological basis of ADHD remains elusive. A genetic predisposition is frequently in evidence (Castellanos and Rapoport, 1992) and in some

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instances pre-/perinatal or environmental factors (Milberger *et al.*, 1997), including lead toxicity (Needleman *et al.*, 1979), may be pertinent; or a combination of factors thereof (Cantwell, 1996; Spencer *et al.*, 1996b). Children affected with ADHD are at an increased risk for the development of other psychiatric conditions in childhood, adolescence, and adulthood. These include antisocial behaviour, substance abuse, mood disorders, and anxiety disorders (McArdle *et al.*, 1995; Spencer *et al.*, 1996a). Persistence of ADHD symptoms into adulthood has been estimated to be in the range of 10–60 per cent (Fargason and Ford, 1994; Spencer *et al.*, 1996b).

Psychostimulants constitute the primary pharmacotherapy for children diagnosed with ADHD and these drugs have been reported to significantly improve 70–80 per cent of such patients (Greenhill, 1992; Committee on Children with Disabilities, 1996). The foremost of the stimulants is methylphenidate, accounting for 70–>90 per cent of the ADHD drug therapy (Safer and Krager, 1988; Swanson *et al.*, 1995; Greenhill *et al.*, 1996). Dextroamphetamine and pemoline are generally regarded as second-line pharmacotherapies. Due to the frequency of comorbid disorders, as well as the complexity of ADHD, multiple-modality therapeutic approaches combining stimulants with psychosocial interventions are recommended (Cantwell, 1996; Damico and Armstrong, 1996; Greenhill *et al.*, 1996).

Controversy has arisen over whether psychostimulants for ADHD are overprescribed in the United States (Wilens and Biederman, 1992; Diller, 1996). British practitioners are much less likely to prescribe psychostimulants for this condition (Greenhill, 1992; Sandberg, 1996; Bonn, 1996). This disparity in prescribing practices has been attributed to both the narrower ICD-10 criteria for diagnosing hyperkinetic disorder and the underdiagnosis of the disorder in the United Kingdom (Bonn, 1996).

METHYLPHENIDATE

Methylphenidate (Ritalin®, α-phenyl-2-piperidine-acetic acid methyl ester, Figure 1) has been the mainstay in ADHD pharmacotherapy for over 20 years, largely supplanting dextroamphetamine for reasons such as a lower incidence of side-effects (Greenhill, 1992) and a duration of action perhaps better corresponding to school hours. Methylphenidate is increasingly being prescribed to treat ADHD (Swanson *et al.*, 1995) and pharmaceutical production of methylphenidate has increased over five-fold between 1990 and 1995. This recent rise in methylphenidate utilization may reflect revisions in clinical diagnostic guidelines and a greater recognition of the drug's efficacy, among other possible factors (Diller, 1996). However, this rise has met with considerable consternation within elements of the lay public, particularly in view

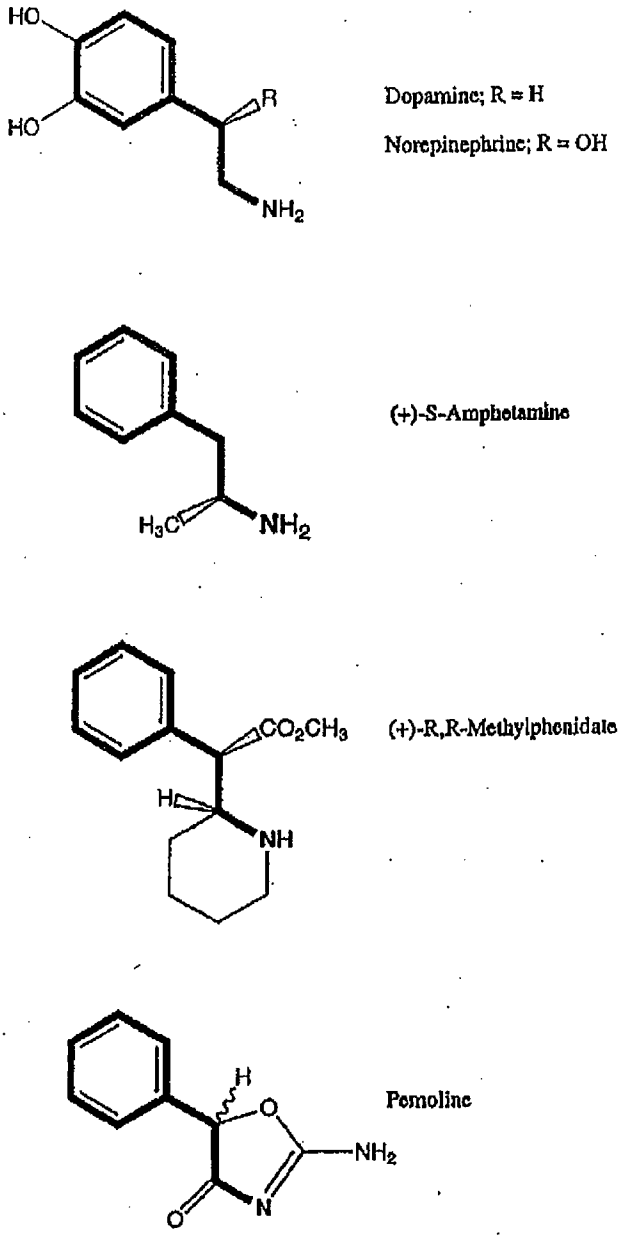

Figure 1. Structure of catecholamines (top) and the catecholaminergic agents used to treat ADHD. The common molecular features are depicted in bold

of numerous media reports regarding methylphenidate recreational abuse.

Chemistry

The drug is formulated as the freely soluble hydrochloride salt. The basicity of methylphenidate, pKa 8·5 (Maxwell *et al.*, 1970) or 8·8 (Siegal *et al.*, 1959), is more than one pK unit lower than amphetamine. Thus, at physiologic pH approximately 3 per cent is calculated to be found as the lipid diffusible free base versus > 1 per cent for amphetamine. This may have implications for the rate and extent of tissue accumulation (Patrick *et al.*, 1984). Though the presence of the methyl ester is essential for the pharmacodynamic actions (Patrick *et al.*, 1987a), this functional group renders the drug subject to hydrolytic degradation in biological samples, with implications for pharmacokinetic sample collection/storage protocols. At pH 7·4 and 37°C methylphenidate hydrolyses with a $T_{1/2}$ of approximately 9 h; in plasma at room temperature the $T_{1/2}$ is 43 h (Wargin *et al.*, 1983). The non-enzymatic mechanism of hydrolysis primarily involves base catalysis as is consistent with an acid pH of 2·86 offering the drug the greatest aqueous stability (Siegal *et al.*, 1959).

All current methylphenidate products contain the drug in the racemic form, a 50 : 50 mixture of the *threo-R,R*(+)- and *threo-S,S*(−)-isomers. The presence of two chiral centres in the structure of methylphenidate allows for four possible stereoisomers, and in fact, an early methylphenidate product contained all four which are invariably generated during industrial synthesis. However, Ciba Pharmaceutical patented a process to isomerize the therapeutically inactive but sympathomimetic (Szporny and Gorog, 1961) *erythro-SR*- and *erythro-RS*-isomers into the desired *threo* configuration (Rometsch, 1958), thereby improving the therapeutic index of the product by reducing the cardiovascular toxicity associated with these *erythro* isomers. Whether a further improvement in the margin of safety would result from the resolution of the remaining two *threo*-(+)- and *threo*-(−)-isomers, in order to allow administration of only one of the two remains equivocal.

The *threo-RR*(+)-stereoisomer appears to be almost exclusively responsible for the catecholaminergic (Patrick *et al.*, 1987a)/beneficial (Srinivas *et al.*, 1992) effects of racemic methylphenidate. Accordingly, the *threo-SS*(−)-isomer might be viewed as merely 'isomeric ballast', very expensive to remove by conventional technology but benign; or possibly the (−)-isomer poses some therapeutic liability. In any case, the pressor (Patrick *et al.*, 1987a) and anorectic (Eckerman *et al.*, 1991) side-effects of methylphenidate appear to be limited, unfortunately, to the therapeutic (+)-isomer.

Pharmacodynamics

The molecular structure of methylphenidate contains a phenethylamine moiety which superimposes on its putative neural substrates dopamine and norepinephrine (Figure 1), providing for the essential receptor interactions.

The behavioural manifestations of ADHD have been theorized to involve an interactive imbalance between dopaminergic, noradrenergic and serotonergic neurotransmitter systems (Pliszka *et al.*, 1996). However, a fundamental dopaminergic dysfunction appears to have special significance. This is evidenced by a tomography study of ADHD patients where hypoperfusion of the dopamine terminal-rich striatum has been imaged (Lou *et al.*, 1989). A high regional uptake of ^{11}C-labelled methylphenidate occurs in this structure (Ding *et al.*, 1994), whereupon the drug increases striatal blood perfusion (Lou *et al.*, 1989).

The mechanism by which methylphenidate produces psychostimulant effects appears to depend prominently upon the facilitation of catecholaminergic neurotransmission. Recognizing that methylphenidate binds with high affinity to the dopamine transporter or uptake channel (Schweri *et al.*, 1985; Gatley *et al.*, 1996), it has been advanced that this binding blocks the synaptic clearance of impulse-released dopamine, leading to prolonged postsynaptic neurochemical mediation. In a baboon study, methylphenidate has been shown to accumulate in the striatum and bind to the dopamine transporter (Ding *et al.*, 1994). Further, this binding occurs enantioselectively, favouring the therapeutic (+)-isomer (Aoyama *et al.*, 1994b). Microdialysis of striatal extracellular fluid in rats has demonstrated a methylphenidate-induced elevation of dopamine, which again occurs enantioselectively (Aoyama *et al.*, 1996). Synaptosomal studies indicate that methylphenidate inhibits dopamine uptake more potently than norepinephrine uptake, and much more so than serotonin uptake (Gatley *et al.*, 1996).

Cocaine may be viewed as a prototypic dopamine uptake inhibitor (Sonders *et al.*, 1997). It

competes with methylphenidate for accumulation in the striatum (Volkow *et al.*, 1995) and both drugs elevate extracellular dopamine concentrations (Gatley *et al.*, 1996). X-ray crystallographic structures of methylphenidate and cocaine (Froimowitz *et al.*, 1995) support the existence of a pharmacophore common to the structures of both drugs, i.e., spatially analogous methyl ester, amine and phenyl groups; features all considered essential for dopamine transporter inhibition by methylphenidate (Patrick *et al.*, 1987a) or cocaine (Carroll *et al.*, 1992).

A dopaminergic mechanism of action for methylphenidate based on dopamine synaptic uptake inhibition, rather than dopamine release from presynaptic stores, is supported by experiments using differential depletion of stored (vesicular) dopamine versus the newly synthesized cytoplasmic pool (Braestrup, 1977): reserpine is believed to reduce vesicular dopamine levels by disrupting vesicular membranes. Further, reserpine pretreatment attenuates the response to a methylphenidate challenge, but not significantly to dextroamphetamine (a putative releasing agent). In that the vesicular dopamine pool is released in response to a nerve impulse, it follows that reduction of vesicular dopamine should diminish an agonist response dependent upon the availability of impulse-released extraneuronal dopamine for uptake inhibition, i.e. methylphenidate. Conversely, depletion of the newly synthesized cytoplasmic pool of dopamine by tyrosine hydroxylase (the rate-limiting anabolic enzyme) inhibition using α-methyltyrosine primarily reduces the response to a dopamine-releasing type agent such as dextroamphetamine, but not by methylphenidate. (Releasing agents are believed to act on the cytoplasmic dopamine pool rather than on the 'protected' vesicular stores.)

Results using synaptosomal preparations and [^{3}H]-dopamine are also consistent with this distinction between the two indirect mechanisms of action for methylphenidate versus dextroamphetamine (Ross, 1977; Ross, 1979; Patrick *et al.*, 1987a).

Additional lines of experimental evidence support the fundamental importance of dopaminergic agonism in eliciting the response to methylphenidate. These include correlation of cerebrospinal fluid levels of the dopamine catabolite homovanillic acid with therapeutic response to methylphenidate (Castellanos *et al.*, 1996), selective chemical lesioning studies (Breese *et al.*, 1976), antagonism of methylphenidate induced behaviours by antipsychotics (Koek and Colpaert, 1993; Levy and Hobbes, 1996), and differential effects of selective monoamine uptake inhibitors (Scheel-Kruger, 1972).

Pharmacokinetics

After an oral dose of methylphenidate, very little acid-catalysed hydrolysis of the methyl ester is likely to occur in the stomach in view of the relative acid stability of the drug (Siegal *et al.*, 1959). Intestinal absorption of [^{14}C]-methylphenidate (carbonyl labelled) is nearly complete as indicated by near total recovery of radioactivity in the urine (Faraj *et al.*, 1974). However, the absolute bioavailability (F) in humans is quite low and variable. In five children, F was found to range from 11–53 per cent, with a mean of 28 per cent in the fasted state, and 31 per cent when dosing with breakfast (Chan *et al.*, 1983). Gualtieri *et al.* (1982) also found little influence of food on the relative bioavailability in children. This extensive presystemic metabolism of methylphenidate occurs enantioselectively, providing a mean F of 23 per cent for (+)-methylphenidate and only 5 per cent for the (−)-isomer (Srinivas *et al.*, 1993). Surprisingly, in dog (−)-methylphenidate exhibits greater bioavailability than its antipode (Srinivas *et al.*, 1991), pointing to the limitation of using animal models for clinical extrapolation. A low F for methylphenidate has also been reported in rat (19 per cent) and monkey (22 per cent) (Wargin *et al.*, 1983). Bioavailability studies in rats dosed with methylphenidate orally or via the portal vein indicate that the primary site of presystemic metabolism is the gut and/or intestinal wall, not the liver or lungs (Aoyama *et al.*, 1990c).

At moderate doses, methylphenidate has generally been reported to provide linear pharmacokinetics (Patrick *et al.*, 1987b). But at robust doses in humans (Aoyama *et al.*, 1993) or rat (Aoyama *et al.*, 1990b) presystemic metabolism may become saturated, allowing for increased bioavailability.

Plasma protein binding is approximately 15 per cent (Hungund *et al.*, 1979). Upon reaching the general circulation (of the rat), methylphenidate rapidly accumulates in highly perfused tissues, favouring the kidney > lung > brain > heart > liver. Brain concentrations of methylphenidate average eight times that of serum over time and attain this relationship within 1 min after intravenous administration (Patrick *et al.*, 1984).

Table 1. Summary of non-enantiospecific parameters (mean) of methylphenidate*

References	Dose, route	Number of subjects	Population	$T_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/ml)
Hungund *et al.* (1979)	10–20 mg	4	Child	2·56		
Chan *et al.* (1980)	10–20 mg, i.v.	6	Child	2·02		
Shaywitz *et al.* (1982)	0·34–0·65 mg/kg	12–14	Child	2·53	1·9–2·5	11·2–20·2
Chan *et al.* (1983)	0·25–0·65 mg/kg	5	Child	2·14	1·0	34·7
Wargin *et al.* (1983)	0·3 mg/kg	5	Child	2·43	1·5	10·8
	0·3 mg/kg	10	Adult	2·14	2·1	7·8
	0·15 mg/kg	5	Adult	2·05	2·2	3·5
Birmaher *et al.* (1989)	20 mg, SR	9	Child	4·12	3·36	8·54
Patrick *et al.* (1989)	10 mg, IR, b.i.d.	18	Adult		5·33	6·4
	20 mg, SR; Ritalin®	18	Adult		3·34	4·8
	20 mg, SR; generic	18	Adult		3·25	4·6
Jarvi *et al.* (1990)	20 mg, IR; Ritalin®	24 × 2	Adult		2·1	
	20 mg, IR; generic	24 × 2	Adult		1·6	

*Abbreviations: T_{max}, time of peak concentration; C_{max}, peak concentration; $T_{1/2}$, half-life; IR, immediate-release; SR, sustained-release.

Prior to the development of enantiospecific analytical methodology for plasma methylphenidate determinations, concentrations necessarily were reported as pooled values (Patrick *et al.*, 1985), i.e., the sum of both isomers. Pharmacokinetic parameters from non-enantiospecific determinations are summarized in Table 1. Chiral derivatization of methylphenidate samples using *N*-acylated *S*-proline (Lim *et al.*, 1986; Patrick *et al.*, 1986) generates gas chromatographically resolvable diastereomers which permits separate quantitation of the active and inactive methylphenidate isomers. Results from application of enantiospecific methodology, or where only one enantiomer has been administered as an experimental 'new chemical entity', are summarized in Table 2. Generalizing from the parameters listed in these two tables, typical therapeutic doses of methylphenidate provide a T_{max} of 1·5–2·5 h, reaching a C_{max} of 6–15 ng/ml, with a $T_{1/2}$ of 2–3·5 h. The mean C_{max} and T_{max} values from the Jarvi *et al.* study (1990) fell well within this range (unpublished results, see Patrick and Jarvi (1990) for a representative concentration–time profile). The Jarvi results are significant in that the study represents the largest methylphenidate pharmacokinetic investigation of its kind. In that study, the bioavailability of the branded immediate-release (IR) formulation was compared to that of the generic product. Though a shorter T_{max} was found for the generic formulation (Table 1), the products met the FDA's criteria for bioequivalence. However, anecdotal reports of methylphenidate bioequivalence problems do exist (Weinberg, 1995).

It is noted that the Srinivas findings (Table 2) consistently indicate a longer $T_{1/2}$ for methylphenidate than most others have reported.

The considerably greater bioavailability of (+)-methylphenidate than (−)-methylphenidate is reflected in the several-fold higher concentration of the (+)-isomer in the circulation over time. The (+)-methylphenidate isomer appears to influence the pharmacokinetics of the (−)-isomers, but not conversely. No metabolic interconversion between (+)-methylphenidate and (−)-methylphenidate was observed when the separate isomers were administered to ADHD children (Srinivas *et al.*, 1992). However, unlike the well-documented metabolic isomerization of ibuprofen (Tracy *et al.*, 1993), a drug containing a single chiral centre, interconversion of (+)- and (−)-*threo*-methylphenidate would require the unprecedented inversion of both stereocentres. The remote possibility of methylphenidate metabolic epimerization, i.e., inversion of only one stereocentre to yield *erythro* configurations, still exists.

Most of a dose of methylphenidate can be accounted for in urine as the deesterified product ritalinic acid (Redalieu *et al.*, 1982; Aoyama *et al.*, 1990a). This polar metabolite attains blood concentrations 30–60 times that of methylphenidate (Wargin *et al.*, 1983; Aoyama *et al.*, 1990a), but

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