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Dexmethylphenidate Extended Release in Attention-Deficit Hyperactivity Disorder

A Viewpoint by Kennerly S. Patrick

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Methylphenidate (MPH) remains the front-line agent in the treatment of ADHD. The beneficial behavioural effects of this drug appear to be based on transporter reuptake inhibition of impulse-released dopamine. The molecular structure of methylphenidate contains two chiral centres giving rise to four stereoisomers, *d*-threo, *l*-threo-, *d*-erythro and *l*-erythro, of which only the *d*-threo isomer possesses therapeutic activity. All four isomers were present in a forerunner product Centedrin, circa 1950. Subsequently, two-isomer (racemic threo) products of *d*,*l*-methylphenidate emerged to offer lower cardiovascular toxicity.

In 2002, enantiopure *d*-methylphenidate (dexmethylphenidate) became available. Any finite clinical advantage of administering a MPH product devoid of the non-therapeutic *l*-threo isomer remains to be established. Preclinical and clinical evaluations of *l*-methylphenidate have found little or no activity, toxic or otherwise. Curiously, some efficacy studies have reported that *d*-methylphenidate elicits a longer pharmacodynamic half-life than *d*,*l*-methylphenidate administered at twice the total dose.

Chiral/racemic switch products, such as dexmethylphenidate, inherently decrease total metabolic burden and reduce the probability of drug-drug interactions. The pharmacokinetics of *l*-methylphenidate are being actively investigated in this context. Virtually all of the *l*-isomer content of oral *d*,*l*-methylphenidate is metabolised presystemically. However, a poor metaboliser phenotype has recently been reported. In this individual, plasma *l*-methylphenidate concentrations approximated that of *d*-methylphenidate. If such a phenotype occurs with the frequency to constitute a distinct polymorph, a compelling advantage for dexmethylphenidate over its racemate may exist.

Sustained-release MPH formulations gradually release the drug to overcome the short half-life of MPH, while permitting single daily dose administration. However, the reduced absorption rate of MPH from sustained-release products has correlated with reduced efficacy relative to immediate release (IR) regimens. Accordingly, modified-release MPH products (dexmethylphenidate XR) were developed to provide biphasic 'pulsed' drug release profiles simulating the rapid release of two daily doses of MPH IR. In so doing, issues of compliance, peer ridicule and drug diversion associated with lunchtime dose administration of MPH IR are also overcome.

The pharmaceutically more complex nature of modified-release formulations generally results in greater variability in drug plasma concentrations when compared to IR dose administration. These precedents not withstanding, the prescribing information for dexmethylphenidate XR reports not more, but less, fluctuation in plasma concentrations when compared to dexmethylphenidate IR, although supporting statistical data were not supplied. Definitive conclusions regarding any advantage dexmethylphenidate XR offers over other treatment options for ADHD await more comprehensive pharmacokinetic characterisation and head-to-head efficacy comparisons. ▲