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Dexmethylphenidate Extended Release in Attention-Deficit Hyperactivity Disorder

A Viewpoint by Gabriele Masi and Alessandro Zuddas

IRCCS Stella Maris, Scientific Institute of Child Neurology and Psychiatry, Calambrone, Pisa, Italy, and Child Neurology and Psychiatry, Department of Neuroscience, University of Cagliari, Cagliari, Italy

The classical formulation of methylphenidate (MPH) is a mixture of 50% *d*-threo-MPH (*d*-MPH) and 50% *l*-threo-MPH (*l*-MPH). Preclinical and clinical studies indicate that *d*-MPH and *l*-MPH have different binding specificities in the brain.[1] *d*-MPH is as, or more, effective than *d*,*l*-MPH and both are more active than *l*-MPH.

After oral administration of the racemic mixture, plasma levels of *d*-MPH were >5-fold higher than *l*-MPH levels, and the percentage excretion of *l*-MPH metabolites (i.e. *l*-ritalinic acid) during the first 3–4 hours was ≈2-fold that of the *d*-enantiomer,[2] suggesting a stereoselective metabolism. In the baboon and the rat, positron emission tomographic (PET) studies have shown that after oral administration of [^{11}C]*d*- or *l*-MPH, the global brain [^{11}C] uptake was higher with [^{11}C]*l*-MPH than with [^{11}C]*d*-MPH; however, [^{11}C] labelling after *d*-MPH was mainly as an unchanged tracer, whereas that after *l*-MPH was mainly as a labelled metabolite.[3] In baboons and humans, the ratio of basal ganglia to cerebellar distribution volumes of [^{11}C] *d*-MPH (DVBG/DVCB) at steady-state was 2- to 3-fold higher than that of [^{11}C]*l*-MPH. Pretreatment with unlabelled MPH markedly reduced the striatal but not the cerebellar uptake of [^{11}C]*d*-MPH, whereas there was no effect on DVBG/DVCB for [^{11}C]*l*-MPH, suggesting no specific dopamine transporter binding for *l*-MPH. Finally, in rats, *d*-MPH increased extracellular dopamine concentration by 650% whereas *l*-MPH did not affect dopamine levels.[1]

The duration of efficacy of *d*-MPH is ≈5–6 hours, with a slightly longer duration of action than *d*,*l*-MPH. *d*-MPH has been marketed for the treatment of ADHD in patients aged ≥6 years, at a dose half that of the racemic dose, without a significant effect of food intake on the bioavailability of the medication. Even though a single dose of *d*-MPH has proven effective in controlling ADHD symptoms for 6–7 hours, dexmethylphenidate XR was developed to overcome the short-term action of the immediate-release medication, and to allow once-daily administration. An adequate technology (Spheroidal Oral Drug Absorption System, SODAS), with a biphasic drug delivery of 50% immediate release and a 50% modified release, leading to a second plasma drug pulse 4 hours after intake, limits the acute tolerance concerns associated with the first-generation of extended-release MPH.

Available evidence from controlled studies with dexmethylphenidate XR strongly suggests that it is safe and effective in the treatment of paediatric and adult ADHD, with a duration of action up to 12 hours. Long-term studies are needed to further support the efficacy and safety of this medication, compared with other once-daily preparations, such as OROS (Osmotic, controlled-Release Oral System) MPH, extended-release mixed amphetamine salts and the nonstimulant atomoxetine. Questions related to the maintainence of clinical effect during the 12 hours following intake, limited dose-administration options and difficulty in swallowing capsules have been raised with OROS-MPH. The possibility of a longer duration of action of dexmethylphenidate XR, and the ease of administering the medication with foods in younger children who cannot swallow pills, make it an interesting preparation. However, more specifically designed, active-control studies published in peer-reviewed journals are needed to fully evaluate the role of dexmethylphenidate XR in ADHD. ▲

References

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