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Methylphenidate Transdermal System In Attention-Deficit Hyperactivity Disorder in Children

A Viewpoint by Raul R. Silva

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Stimulants have been the mainstay of pharmacological treatment for attention-deficit hyperactivity disorder (ADHD) since the late 1930s.[1] Methylphenidate (MPH) preparations are the most frequently used psychostimulants.[2] The majority of MPH products are racemic mixtures of the *d*- and *l*-isomers of threo-methylphenidate.

For many years, the available products had a truncated duration of action necessitating multiple administrations over the course of the day. During the past few years a number of oral methylphenidate preparations (Concerta®, Metadate CD®, Ritalin LA®, and Focalin XR®)[1] have been introduced into the market employing technologies that permit the extended release of this otherwise short-acting agent. Capitalising on the differences between these products, in terms of their delivery systems and the proportions of the doses that are released over the day, may help clinicians tailor treatment decisions to patients' individual needs.

The US FDA recently approved the use of the methylphenidate patch in paediatric age groups who suffer from ADHD. The water-resistant methylphenidate patch uses a novel technology to deliver this product. It is referred to as a DOT Matrix™ technology, with a silicone layer that serves to adhere the patch to the skin, and an acrylic component that holds the active substance (MPH) for release. This new version of the patch seems to have lower rates of skin irritation than those reported with earlier patch technologies. A study that examined the skin sensitivity issue compared the DOT Matrix™ MPH patch to a placebo transdermal system (PTS) patch and revealed lower rates of irritation than the control condition (1.3% for MPH patch vs 2.5% for PTS patch), implying skin sensitivity may be due to the patch itself and not the medication it contains.[3]

The patches are available in 12.5–37.5 cm^2 sizes, and deliver dosages ranging from 12.3 to 31.3 mg/day, which are intended to be released over ≈9 hours. With the patch being applied for this amount of time, maximal plasma concentrations are achieved in about 8 hours (median); 31% lower plasma concentrations have been reported when the patch is applied to areas such as scapula rather than the patch's recommended application site, the hip.[4]

An interesting difference between this product and orally administered racemic mixtures seems to exist in their pharmacokinetic profiles.[5] With the patch, *d*- to *l*- isomer plasma level ratios are in the order of ≈2 **:** 1 for parameters such as peak plasma concentration and area under the plasma concentration-time curve. This is in contrast to the 10-fold differences evident with oral administration of MPH.[6] One would have to question the potential role of the plasma isomeric discrepancy on the higher adverse event rates associated with the patch when compared with one of the long-acting oral MPH preparations (Concerta®).[7] In that study, relatively higher daily doses of the oral product yielded lower rates of adverse effects. Unfortunately, in that report statistical comparisons were not provided, but based on those results one would have to question the statistical significance of those differences in larger study samples, especially for certain sequelae such as decreased appetite, insomnia, nausea and tics. Experience and clinical use of the product will help further clarify this issue.

In terms of efficacy, the product has demonstrated consistent superiority to placebo[7,8] and similar degrees of effectiveness when compared with another long-acting oral MPH preparation.[7,9] In one study, significant superiority was noted from hours 2 through 12 following dosing, when compared with placebo.[8] The patch may clearly be most beneficial for those patients who require extended coverage and also have difficulty swallowing, although some of the other extended-release preparations (Metadate CD®, Ritalin LA®, and Focalin XR®) have demonstrated that their unencapsulated contents can be sprinkled over cold substances with few discernible effects on their pharmacokinetics profiles. Special considerations for healthcare professionals pre-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

scribing this agent may be required for those patients who do not return home directly after school and forget to remove the patch after 9 hours. Also, when the patch is placed in a region that is accessible to a child, they may remove the patch prematurely and produce shorter duration of effects than may be desired.

Given the pharmacodynamic and kinetic features of this product, one would have to believe the next step would be to study this agent at higher doses and with longer periods of patch exposure in adult populations, who often require longer-acting effects than are experienced with the currently available oral extended-release MPH preparations. Ultimately, this is another welcome addition to the pharmacological armamentarium clinicians have to help treat children with ADHD. ▲

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