Methylphenidate and ritalinic acid determination in serum and saliva from patients with attention deficit hyperactivity disorder

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Objective

In the therapy of attention deficit hyperactivity disorder (ADHD) methylphenidate (MPH) nowadays represents first line treatment in combination with psychotherapy. It is one of the best-studied pediatric psychopharmacological drugs with a vast amount of clinical experience. Since methylphenidate has addiction potential and shows varying metabolic characteristics in children, pharmacokinetic drug monitoring is advised [1]. Similar variations in metabolic properties can be found in patients with hepatic or renal insufficiency. All these patient groups would also benefit from a less invasive and less painful sampling. However, in pediatric drug therapy there are only few reliable studies, in particular randomised and controlled trials being rare. To avoid pain in children through invasive blood collection, the use of oral fluid would be the diagnostic material of choice. Additionally, it is a noninvasive, simple and cost-effective alternative as part of an optimized pharmacotherapy. In this study we quantified methylphenidate and its metabolite ritalinic acid (RA) from saliva by mass spectrometry.

Methods

From 19 ADHD patients (9 children, 1 adolescent and 9 adults) taking methylphenidate, serum and saliva were obtained for the validation of the Chromsystems Masla® TDM Parameter Set Antidepressants 2/Psychostimulants, which includes methylphenidate and its main metabolite ritalinic acid as parameters for LC-MS/MS measurements. The study participants took predominantly long-acting sustained release formulations like Medikinet retard® or Ritalin LR®. The daily intake ranged between 5 and 60 mg MPH, corresponding to a dosage of 0.1 to 1.4 mg/kg/day of body weight. The blood and saliva samples were taken two to three hours after drug intake, when highest concentrations can be expected in both, serum and oral fluid [2]. After a brief interim storage at -80°C, serum and saliva samples were processed using the Chromsystems kit Antidepressants 2/Psychostimulants for LC-MS/MS analysis following the manufacturer’s instructions. Calibrators and controls for the determination of MPH in serum or plasma were also from Chromsystems. A series of MPH standards in saliva was produced by spiking with MPH hydrochloride.

Results

The measured serum concentrations for methylphenidate correspond with the usual and published data [3]. This allows a substantially simplified form of drug monitoring in pediatric pharmacotherapy.

Serum and oral fluid chromatograms of a patient taking methylphenidate

Serum concentration MPH (ng/ml), mean ± SD, (min., max.)

<table>
<thead>
<tr>
<th>Patients</th>
<th>Dose rate/kg BW (mg/kg BW), mean ± SD, (min., max.)</th>
<th>Dose rate per day (mg), mean ± SD, (min., max.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kids (8–12 years)</td>
<td>9</td>
<td>26.3 ± 11.8 [5, 60]</td>
</tr>
<tr>
<td>Adolescents (13–18 years)</td>
<td>1</td>
<td>0.6 ± 0.4 [0.1, 1.4]</td>
</tr>
<tr>
<td>Adults (≥18 years)</td>
<td>9</td>
<td>9.3 ± 9.6 [0.1, 35.3]</td>
</tr>
<tr>
<td>Age (years) mean ± SD (min., max.)</td>
<td>19.4 ± 13 (8.48)</td>
<td>43.4 ± 51.9 (0.1, 211)</td>
</tr>
</tbody>
</table>

Chemical structures

Conclusion

> The Masla® TDM Parameter Set Antidepressants 2/Psychostimulants from Chromsystems is methodologically and analytically suitable for the determination of MPH and its main metabolite RA in serum/plasma as well as saliva by LC-MS/MS.

> This allows a substantially simplified form of drug monitoring in pediatric pharmacotherapy.

> The measured serum concentrations for methylphenidate correspond with the usual and published data [3].

> Correlations between serum and oral fluid concentrations described by Marchei et al. (2010) range between r = 0.22 (fast-release formulation) and r = 0.79 (extended-release formulation) for MPH, and r = 0.4 (fast-release formulation) and r = 0.79 (extended-release formulation) for RA. Our results with r = 0.51 for MPH and r = 0.64 are precisely in between. Probably the fast-releasing pharmaceutical form causes buccal contamination and falsifies the saliva concentration [4].

References


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