To the Editor:
The prescription of medicines like methylphenidate for Attention Deficit Hyperactivity Disorder (ADHD) has increased ten-fold since 2004 in Denmark, and now amounts to approximately 12 million defined daily doses per year. Testing the patients for drug abuse is highly relevant, because the link between ADHD and drug abuse continues to be an area of interest in both adolescent and child psychiatry. Non-medical use of the drug methylphenidate has also increased, e.g., injection of crushed tablets. The compound is now included in routine drug-of-abuse testing at our department.

The analytical method for methylphenidate, applying liquid chromatography and electrospray ionisation tandem mass spectrometry after injection of urine diluted with isotope-labelled internal standards, is highly specific and sensitive. Multiple reaction monitoring (MRM) detects three different ion transitions for both methylphenidate and its major metabolite, ritalinic acid, with proper acceptance criteria for relative ion abundance ratios. The method is valued for diagnostic verification of drug abuse and for non-compliance in prescribed users, primarily in patients with ADHD.

However, we have become aware of a widespread and solid myth among health care professionals that methylphenidate, sharing some pharmacological properties with amphetamine, cross reacts in immunoassays for amphetamine and that laboratory tests do not discriminate between amphetamine and methylphenidate. Thus, according to this hypothesis, results from urine tests for amphetamine class compounds are neglected and misinterpreted. Testing might even be abandoned because it is assumed that methylphenidate and amphetamine cannot be distinguished.

In our laboratory, cross reactivity of methylphenidate has never caused false-positive results in hundreds of authentic, routine urine samples from patients treated with methylphenidate that were screened for amphetamines by enzyme multiplied immunoassay technique (EMIT, Siemens Healthcare Diagnostics). Siemens found no cross reactivity for methylphenidate (at 1,000 ng/mL), as stated in the EMIT II Plus amphetamine assay instructions for use.

There is, to our knowledge, only a single report by Manzi et al. describing cross reactivity of methylphenidate in amphetamine assays (1). This case has been widely cited and methylphenidate has found its way into lists of “agents contributing to positive results by immunoassays,” specifically in assays for amphetamines (2). Even worse, it is equally stated (unreferredenced) in the Summary of Product Characteristics (SPC) of both Ritalin tablets (Novartis Pharmaceuticals) and Concerta prolonged release tablets (Janssen-Cilag), that “this product contains methylphenidate which may induce a false positive laboratory test for amphetamines, particularly with immunoassay screen test” (3, 4). We question both the validity of this information and the in vitro experiments by Manzi et al., spiking urine samples with crushed tablets instead of pure reference standards (1). Our view is also supported by Mach et al. in a comparison study of immunoassay screening and gas chromatography with mass spectrometry (GC–MS) as reference method (5). In this work, a surprisingly high rate of unconfirmed amphetamine positive samples (44%) was reported from a Triage 8 screening device range. However, none of the compounds previously reported to cause false-positive amphetamine results (including methylphenidate) were detected by GC–MS.

Recently, we learned that court decisions in Denmark are influenced by the erroneous views that methylphenidate and amphetamine class substances are not reported correctly by the biochemical laboratories, supporting the claims of the accused individuals that the subscribed doses of methylphenidate were not supplemented with illegal amphetamine drugs. Such misinformation could have serious implications when used as an argument in the decision-making process.

We find it strange that systematic cross reactivity of methylphenidate and related metabolites, in case it does occur, has not been reported widely in the scientific literature, because it would lead to numerous false-positive samples and render the amphetamine screening procedure useless. For this reason, we found it unnecessary to conduct any studies, because there are no suspicious cases indicating cross reactivity.

However, we do not want to claim non-cross reactivity between methylphenidate and amphetamine in the many amphetamine testing products on the market for the following reasons: (i) immunoassay screening should never be reported as a final result; on the contrary, it should always be verified (confirmed) by chromatography with mass spectrometry, as stated in guidelines for drug testing (6); (ii) Consequently, any important clinical or court decisions that are solely based on drugs-of-abuse testing by immunoassays can be regarded as intrinsically biased, ethically troublesome, misleading and not very helpful, e.g., when used for on-site poisoning testing in an emergency setting (5). If a cross reactivity or analytical interference is suspected in a commercially available product, it must be evaluated and documented by the manufacturer. It cannot automatically be assumed that such a cross reactivity or interference exists for any batch or clone of antibodies.

When methylphenidate is described as an “amphetamine-like” drug, it should only be with regards to the pharmacological, dopamine-releasing properties. We conclude that when laboratory screening procedures are followed by confirmation of potential positives by gas or liquid chromatography with mass spectrometric detection, methylphenidate will not be mistaken for amphetamine class compounds or vice versa, nor will the presence of methylphenidate in a urine sample mask abuse of amphetamines when proper analytical methods are used.

References
patients with suspected poisoning presenting at an emergency department. Therapeutic Drug Monitoring, 29, 27–39.

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