

Mebeverine and a false positive ecstasy instant drug test

Introduction

Mebeverine (Duspatal®) is a antispasmodic drug which is indicated *for the symptomatic treatment irritable bowel syndrome*. It is a musculotropic drug which acts directly at the smooth muscle of the gastrointestinal tract without affecting normal gut motility. Since this action is not mediated by the autonomic nervous system, administration of mebeverine does not result in the usual anticholinergic side effects. Mebeverine was granted marketing authorization in the Netherlands in 1979. [1]

Drug testing is regularly used in healthcare and criminal situations. But also in other areas drug tests can be performed, like in workplace drug testing, during sports activities and even in home situations where parents want to test their children. Drug screening can be performed using samples of urine, saliva, sweat, blood, hair or nails. Urine samples are a preferred test substance, because the collecting is easy and it usually contains high concentrations of drugs and their metabolites [2]. The most common used screening methods are immuno-assay screening, gas chromatography/mass spectrometry (GC/MS) or liquid chromatography/mass spectrometry (LC/MS) [2,3]. Home-testing kits or instant drug tests usually use immunoassay screening [2]. These tests are available as single or multi tests and can detect various drugs, like barbiturates, benzodiazepines, amphetamines and ecstasy. Various companies offer instant drug tests which can be bought at drugstores, pharmacies and web shops.

Reports

Netherlands Pharmacovigilance Centre Lareb

In March 2016 the Netherlands Pharmacovigilance Centre Lareb received a non-serious report from a nurse of a false positive ecstasy urine instant drug test associated with the use of mebeverine (NL-LRB-214657) [4]. This report concerns a male aged 41-50 years who used mebeverine for gastrointestinal discomfort with an unknown dosage. The test was performed after unspecified weeks after start of mebeverine. Concomitant medication was not reported. The used test was a Nal von Minden - Drug Screen® instant test. An additional laboratory urine test (name unknown) showed a negative result for XTC. The same urine sample was used for both tests. The reporter mentioned that a colleague who used mebeverine as well had the same results.

Eudravigilance & WHO Vigilyze

The Eudravigilance and WHO Vigilyze database contain one other case-report similar to the report received by Lareb [5,6]. This case-report from a consumer from the United Kingdom (U.K.) concerns a male of an unknown age with amphetamines positive following administration of mebeverine with an unknown latency. This case was classified as serious other.

Other sources of information

SmPC

The Dutch SmPCs of mebeverine do not mention that mebeverine can produce false positive reactions in amphetamine or ecstasy urine tests [1,7]. In the U.K. SmPC of mebeverine oral suspension it is mentioned that mebeverine does not produce false positive reactions in standard diagnostic urine tests, but it is not mentioned if this is also applicable to ecstasy or amphetamine drug tests [8].

Literature

Kraemer et al. describe that a single intake of 405mg mebeverine can result in a positive fluorescence polarization immunoassay (FPIA) for amphetamine. They mention that in their study they found relative low concentrations of amphetamine in the urine samples due to the single dose. Patients that undergo long-term treatment with mebeverine will reach higher results after reaching steady-state [9]. Elliott et al. found that mebeverine can result in a positive result of a cloned enzyme donor immunoassay (CEDIA) amphetamine assay [10]. Kerssemakers et al. describe in their book a case of a positive amphetamine test associated with the use of mebeverine. This patient with a cocaine problem tested positive for amphetamine which almost resulted in dismissal from the clinic. But the

patients fierce denial led to further investigation were started and it turned out that a remedy against intestinal cramps, mebeverine (Duspatal®), was responsible [11].

On the cross reactivity list of 'nal von minden Drug-Screen® rapid tests urine' mebeverine (Duspatalin) is mentioned as substance that could cause a positive result with the ecstasy (MDMA) test [12]. The website of the hospital pharmacy Midden-Brabant (ZAMB) and Dasgupta et al. mention mebeverine as drug that can interfere with amphetamine immunoassays [13,14].

Prescription data

Table 1. Number of patients using mebeverine in the Netherlands between 2010 and 2014 [15]

| Drug | 2010 | 2011 | 2012 | 2013 | 2014 |
|------------|---------|---------|---------|---------|---------|
| Mebeverine | 131,120 | 129,750 | 126,060 | 117,000 | 113,660 |

Mechanism

Kraemer et al studied the metabolism of mebeverine resulting in the metabolic pathway shown in figure 1. Mebeverine (MB; I) is metabolized via ester hydrolysis to mebeverine-alcohol (MB-OH; II) and veratric acid (VA; III). Veratric acid can form three other metabolites: O-demethyl VA (vanillic and/or isovanillic acid; IV,V), O-bisdemethyl VA (protocatechuic acid; VI). Mebeverine-alcohol forms eight metabolites including some amphetamine-like compounds. Via O-demethylation and ring hydroxylation hydroxy MB-OH (VII), O-demethyl MB-OH (VIII), O-demethyl-hydroxy MB-OH (IX) are formed. The metabolites N-desethyl MB-OH (X) and N-desethyl-O-demethyl MB-OH (XI) are formed by N-deethylation and O-demethylation. N-dehydroxybutylation of MB-OH leads to methoxyethylamphetamine (MO-EA; XII) and after O-demethylation to hydroxyethylamphetamine (HO-EH; XIII). N-bisdealkylation of MO-EA leads to p-methoxyamphetamine (PMA; XIV). MO-EA and PMA are also known as designer drugs. [9,16]

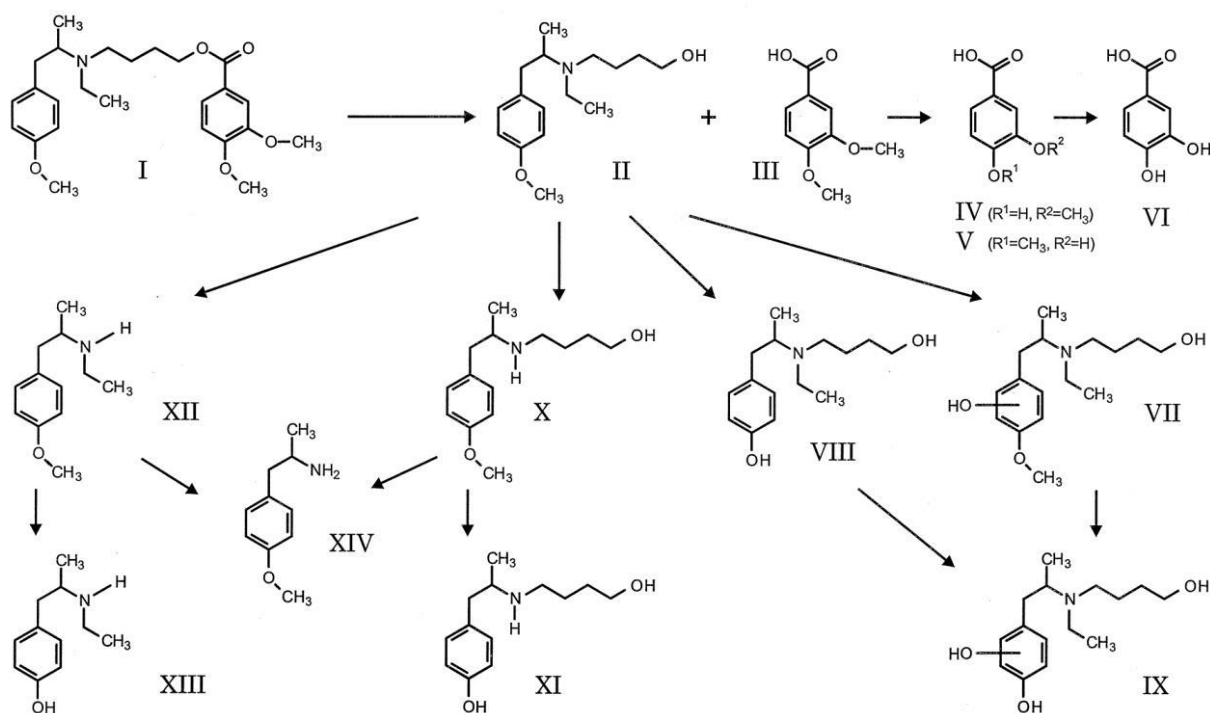
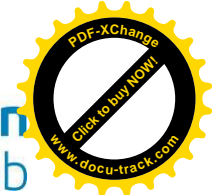


Figure 1: Schematic overview of mebeverine metabolism and breakdown

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received one report that mentioned two cases of a false positive ecstasy instant drug test associated with the use of mebeverine. In Eudravigilance and the WHO database one other report could be found of a similar association. In literature it is described



that mebeverine can result in positive results of amphetamine immunoassays. A nal von minden representative confirmed that their Drug-Screen® Drug Rapid Tests Urine are based on immunoassays [17] and that they can cross react with mebeverine. This makes a causal relation between the positive ecstasy instant test and mebeverine plausible.

The reporter mentioned that the pharmacist and psychiatrist of the psychiatric institute were unaware that mebeverine could interfere with the ecstasy instant test. Also at her educational institute for 'verpleegkundig specialist' they never heard of this before. Since false positive drug tests can have serious consequences, such as exclusions from a sporting event, risk of dismissal from clinics or inappropriate medical treatment in emergencies, Lareb wants to inform the Dutch Medicines Evaluation Board about these findings. Patients and healthcare professionals should be warned for the possibility that mebeverine can cause a positive ecstasy or amphetamine instant drug test. Additional data from the Marketing authorization Holder could strengthen this signal.

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