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MEBEVERINE METABOLISM

1.0 Introduction

WADA wishes to draw the attention of the Laboratories to the following observations and instructions on the analysis and reporting of ***para*-hydroxy-amphetamine (*p*-OH-A)**.

The metabolism of **Mebeverine**, a non-prohibited, antispasmodic substance used for the treatment of irritable bowel disease (IBD), indicates that it can metabolize into *p*-OH-A, which also constitutes a *Metabolite* of other *Prohibited Substances*, including but not limited to **Amphetamine**, **Selegiline** and **Famprofazone**.

In addition to *p*-OH-A, it has been shown that mebeverine can also metabolize into the specific *Metabolites* i) **Mebeverine Alcohol**, ii) **Mebeverine Acid** and iii) **Desmethyl Mebeverine Acid** (Figure 1) [1,2].

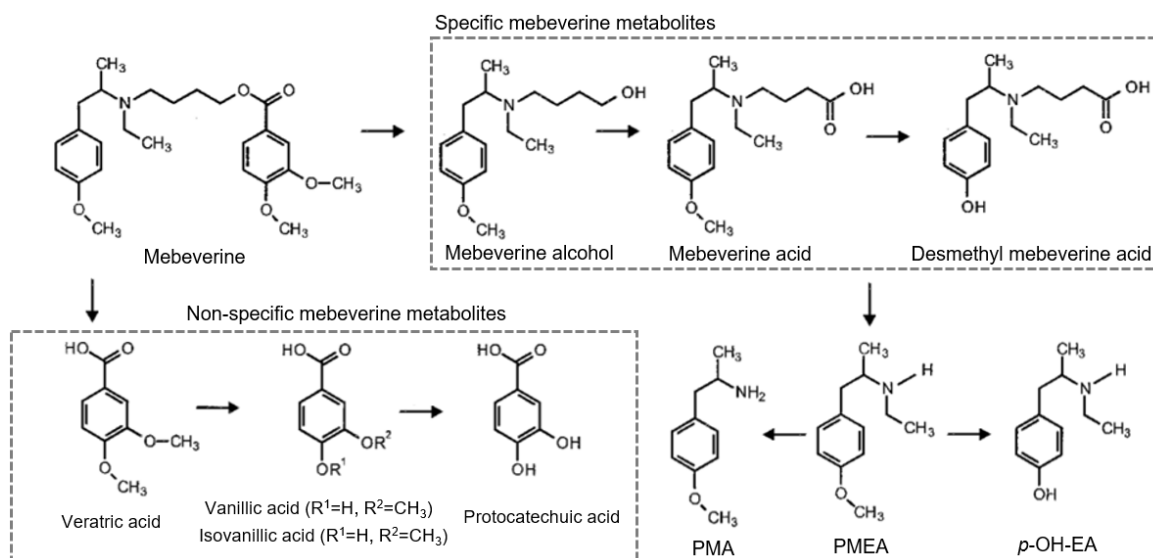


Figure 1. Metabolism of Mebeverine (adapted from Kraemer, Bickeboeller-Friedrich and Maurer, [1] Moskaleva et al., [3] and Kristinsson, Snorraddóttir, and Jóhannsson [4]).

2.0 Reporting Requirements

Before reporting an *Adverse Analytical Finding (AAF)* based on the detection of *p*-OH-A, the Laboratory shall confirm the absence of additional mebeverine specific *Metabolites* (Mebeverine acid and desmethyl mebeverine acid) to exclude mebeverine as the primary source of *p*-OH-A).

[Comment: The mebeverine parent compound is not detected in urine, and its acidic *Metabolites* (veratric acid, vanillic acid, isovanillic acid and protocatechuic acid) are not specific because they can be originated from the ingestion of certain food [1].]

WADA Technical Letter – TL02

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3.0 References

- [1] Kraemer T., Bickeboeller-Friedrich J., and Maurer H.H. On the metabolism of the amphetamine-derived antispasmodic drug mebeverine: gas chromatography-mass spectrometry studies on rat liver microsomes and on human urine. *Drug Metab Dispos.* **28**(3): 339-347, 2000.
- [2] Zaitseva K., *et al.* Determination of a newly encountered designer drug “p-methoxyethylamphetamine” and its metabolites in human urine and blood. *Forensic Sci Int.* **177**(1): 77-84, 2008.
- [3] Moskalova, N.E., *et al.* HPLC–MS/MS method for the simultaneous quantification of desmethylmebeverine acid, mebeverine acid and mebeverine alcohol in human plasma along with its application to a pharmacokinetics study. *J. Pharm. Biomed.* **138**: 118-125, 2017.
- [4] Kristinsson, J., Snorraddottir, I. and Johannsson, M. The metabolism of mebeverine in man: Identification of urinary metabolites by gas chromatography/mass spectrometry. *Pharmacol Toxicol.* **74**(3): 174-180, 1994.