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SPECIAL ISSUE - CORRESPONDENCE CASE REPORT

WILEY

Is heptaminol a (major) metabolite of octodrine?

1 | CASE VIGNETTE

In 2018, two adverse analytical findings (AAFs) were reported concerning the specified stimulant heptaminol in the context of routine doping controls by a World Anti-Doping Agency (WADA)-accredited laboratory. In the course of inquests into these cases, both affected athletes declared the use of nutritional supplements, advertised as fat-burner and pre-workout products. These supplements did not list heptaminol as an ingredient on the respective product labels, and chromatographic-mass spectrometric analyses confirmed the absence of heptaminol. However, both supplements declared the ingredient 2-aminoisoheptane, a frequently observed (whilst incorrect) synonym for octodrine. Further analyses confirmed the presence of octodrine in both products. In one of the products the roughly estimated concentration of octodrine was ca. 30 mg/g. The manufacturer-recommended dose of this supplement was one scoop (6 g) dissolved in 250 mL of water 30 min before training, corresponding to an octodrine consumption of 180 mg.

2 | BACKGROUND AND STUDY RATIONALE

Octodrine (also referred to as e.g. 1,5-dimethylhexaneamine/DMHA; 2-amino-6-methylheptane) is a psychoactive central nervous system stimulant.[1] It is not listed explicitly on the WADA 2019 Prohibited List, but it can be categorized as a specified stimulant because of its structural similarity to methylhexaneamine.[2] Originally developed as a aerosol for the treatment of bronchitis or laryngitis in the 1940s, octodrine has recently been re-introduced on the nutritional supplement market as a "pre-workout" and "fat-burner" product.[3]

Because of the structural similarity between octodrine and heptaminol (Figure 1), it is expected that metabolic conversion of octodrine results in the formation of heptaminol, i.e. the finding of heptaminol in a doping control sample may not only originate from an administration of heptaminol but also from the ingestion of octodrine. Therefore, the aim of this pilot study was to investigate if and to what extent octodrine is metabolized to heptaminol in humans.

3 | EXPERIMENTAL

Following written informed consent, one healthy male volunteer (62 years, 170 cm, 80 kg) conducted an excretion study with a single oral dose of ca. 1 g of the tested dietary supplement containing approximately ca. 30 mg of octodrine. Urine samples were collected up to 95 h following administration and were analyzed by means of established test methods employing gas chromatography–mass spectrometry (GC–MS). Sample preparation and analysis were performed as described elsewhere.[4,5] In brief, 5 mL of urine was fortified with 15 µg of *N*,*N*-diisopropyldodecan-1-amine as internal standard (ISTD, in-house synthesis). The urine was basified using 0.5 mL of 5 M aqueous potassium hydroxide. After the addition of 1.5 mL methyl *tert*-butyl ether and approx. 3 g of sodium sulfate, the sample was shaken for 20 min and subsequently centrifuged for 5 min at 1800 × g. In addition to the excretion study samples, reference standards were prepared using blank urine fortified with 1 µg/mL and 0.1 µg/mL of octodrine (purchased from Sigma-Aldrich, Germany) and heptaminol (purchased from LGC, UK), respectively. The organic layer was then transferred to a GC vial for GC–MS analysis. Here, an Agilent 6890/5973 GC–MS system (Waldbronn, Germany) was used, equipped with an Agilent HP5MS GC column (inner diameter 0.25 mm, film thickness 0.25 µm). A volume of 5 µL was injected in split mode with a ratio of 1:3. The GC was operated with helium as the carrier gas at constant pressure of 1.24 bar. A temperature gradient was used starting at 80°C for 0.4 min increasing to 335°C with 30°C/min with the final temperature being maintained for 3.4 min. The mass spectrometer was operated with an electron ionization source (70 eV) and data were acquired in full scan analysis (m/z 40–400, 2 scans/s). The concentrations of both heptaminol and octodrine in the excretion study samples were determined by comparing peak

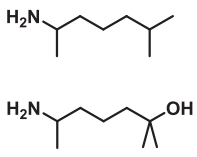

FIGURE 1 Structures of octodrine (top, 6-methylheptan-2-amine) and heptaminol (bottom, 6-amino-2-methylheptan-2-ol)

area ratios of extracted ion chromatograms of the respective sample with the reference standards. Extracted ion chromatograms used to determine peak areas (exemplary) are shown in Figure 2.

4 | RESULTS AND DISCUSSION

The obtained data are presented in Figures 2, 3 and Table 1. Extracted ion chromatograms of a blank sample, one post-administration sample collected at 14.5 h after dietary supplement intake, a reference standard prepared at a concentration of 1 µg/mL, and all relevant mass spectra are shown in Figure 3. In the post-administration samples, both octodrine and heptaminol were detected. Octodrine was detected for 25 h with a maximum concentration of ca. 4 µg/mL at 7 h post-ingestion. Heptaminol was detected for 50 h with a maximum concentration of approximately 24 µg/mL also 7 h after octodrine dosing. The acquired data demonstrate the presumed metabolic conversion of octodrine to heptaminol. Of note, in this pilot study heptaminol was detected for twice for as long as the ingested octodrine, which needs to be taken into consideration when result-

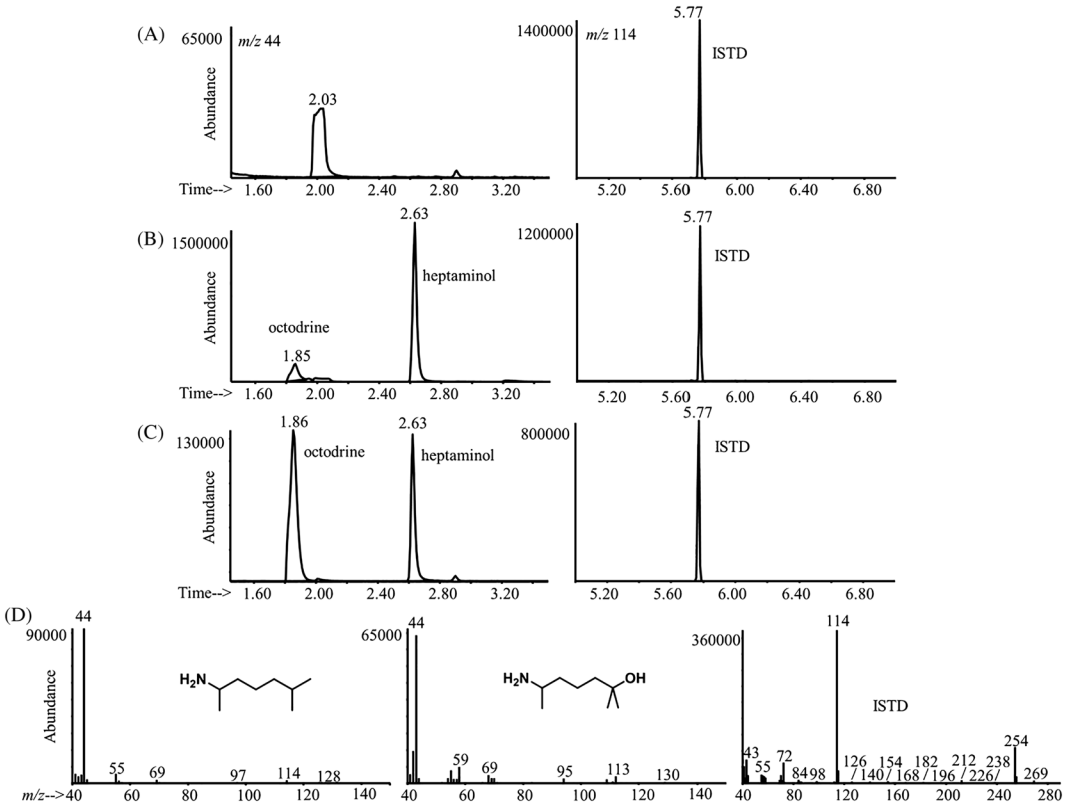

FIGURE 2 Extracted ion chromatograms of A, a blank sample (m/z 44, left) with respective ISTD (m/z 114, right), B, an elimination study urine sample collected 14.5 h post-administration (m/z 44, left) and respective ISTD (m/z 114, right), C, a reference standard with a concentration of 1 µg/mL (m/z 44, left) and respective ISTD (m/z 114, right); D, mass spectra of octodrine (left), heptaminol (center) and the ISTD (right)

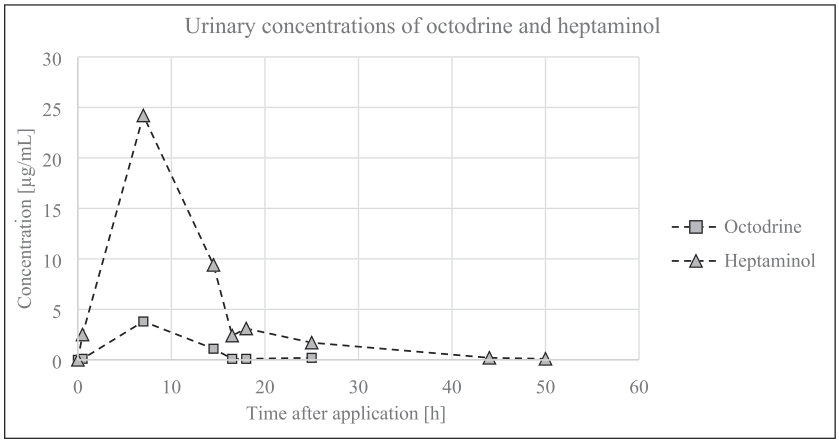

FIGURE 3 Urinary concentrations of octodrine and heptaminol after oral administration of ca. 30 mg of octodrine

TABLE 1 Approximate urinary concentrations of octodrine and heptaminol following an oral administration of 30 mg of octodrine (n.d., not detected)

Time after application (h)	c (Octodrine) (µg/mL)	c (Heptaminol) (µg/mL)
0	0	0
0.5	0.1	3
7	4	24
14.5	1	9
16.5	0.1	2
18	0.1	3
25	0.2	2
44	n.d.	0.2
50	n.d.	0.1
68	n.d.	n.d.
74	n.d.	n.d.
95	n.d.	n.d.

managing authorities (RMAs) handle adverse analytical findings concerning heptaminol. The presence of heptaminol in a doping control sample may not only originate from an administration of heptaminol but also from the ingestion of octodrine.

5 | CONCLUSIONS

In this pilot study, it was demonstrated that the oral administration of octodrine can result in the urinary elimination of significant amounts of heptaminol. Both substances are prohibited in sport and, furthermore, the WADA prohibited list 2020 will include octodrine by name as a specified stimulant (S6b). Nevertheless, future laboratory statistics might need to outline the fact that heptaminol-related adverse analytical findings could also be the result of octodrine use for more accurate reporting and interpretation of statistics concerning drug prevalence and (mis)use.

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