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SHORT COMMUNICATION

Bad trip due to 25I-NBOMe: a case report from the EU project SPICE II plus

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ABSTRACT

Objective: The potent hallucinogenic drug 25I-NBOMe has recently emerged on the drug market. We present a case with analytically confirmed 25I-NBOMe intoxication from the prospective study "SPICE II Plus".

Case report: Because of a severe headache a 42-year-old man took one sip of a pediatric analgesic syrup, which had been refilled with a self-made solution of 25I-NBOMe in ethanol. Thirty minutes later restlessness occurred. On arrival in the emergency department mydriasis, strong sweating, disorientation, and agitation were noticed. Within short time the patient developed severe agitation, coenesthesia, and complex hallucinations. In blood serum samples obtained at admission revealed the presence of 25I-NBOMe (34 ng/mL), 2C-I (12 ng/mL) and 25I-NBOH (<1 ng/mL) (LC-ESI-MS/MS). The presumed analgesic syrup contained 25I-NBOMe (2800 μg/mL), and besides ethanol no other compounds were detected. After six hours, the symptoms resolved without further complications.

Conclusions: This is a unique case of an analytically confirmed, accidental ingestion of 25I-NBOMe in a drug naïve adult. The finding of 2C-I in the serum sample 50 minutes after intake indicates a fast metabolic breakdown of 25I-NBOMe due to first-pass metabolism.

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Introduction

The N-(2-methoxybenzyl) derivatives of substituted phenethylamines of the "2C series" (Alexander Shulgin, PiHKAL), also called "NBOMes", have recently emerged on the drug market. Among this group, 25I-NBOMe, the *N*-(2-methoxybenzyl) derivative of 2C-I, has previously been implicated in clinical intoxications and fatalities [1]. 25I-NBOMe is a highly potent, high-affinity agonist of the 5-HT_{2A} receptor, originally synthesized for research [2]. It is thought that the hallucinogenic effect of 25I-NBOMe is mediated by activation of the 5-HT_{2A} receptor. We present a case with an analytically confirmed 25I-NBOMe intoxication from a prospective study conducted within the EU project SPICE II Plus.

Case report

Because of a severe headache a 42-year-old hitherto healthy man took a sip of a pediatric analgesic syrup stored in the family's refrigerator. Thirty minutes later, he complained about restlessness. On arrival at hospital (50 min p.i.), vital signs were unremarkable (blood pressure 120/80 mmHg, heart rate 96/min). The examination revealed excessively dilated pupils, strong sweating, disorientation to time and to person, and agitation. At that time the patient's son reported that he had replaced the analgesic syrup with a self-made ethanolic solution of 25I-NBOMe (supposed concentration: 320 μg/mL).

Twenty minutes later, the patient developed severe agitation, screaming, coenaesthesia, auditory and somatic hallucinations, and complex visual hallucinations (particularly serious traffic accidents). Blood pressure was at maximum 127/97 mmHg, and heart rate 100/min. Laboratory results (including creatine kinase, glucose, blood count) and clinical findings, especially body temperature and electrocardiogram were unremarkable during the in-patient stay.

After six hours, the symptoms resolved. Discharge was on the next day. Therapy consisted of supportive care, administration of intravenous fluids and benzodiazepines (in total 20 mg diazepam). Urine and serum samples as well as the analgesic syrup were collected and analyzed with LC-MS/MS.

Methods

Urine and serum samples underwent solid-phase extraction (Aspec GX-274, Chromabond® Drug cartridges). The extracts were dried under a stream of nitrogen (40 °C) and reconstituted in mobile phase. The presumed analgesic liquid was diluted with ethanol prior to analysis.

Analysis of all samples was performed applying a Shimadzu HPLC system coupled to a Sciex QTrap® 4000 mass spectrometer. The authentic samples were analyzed in positive multiple reaction monitoring (MRM) mode. 25I-NBOMe, 2C-I and 25I-NBOH were included as analytes. Other

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metabolites like the hydroxylated metabolites of 25I-NBOMe were not included due to non-availability of reference standards.

Toxicological analyses

Serum and urine concentrations of 25I-NBOMe, 2C-I and 25I-NBOH are shown in Table 1. The presumed analgesic syrup was also analyzed. It contained an unexpected high concentration of 2800 μg/mL 25I-NBOMe, probably due to a dilution error of the patient's son. Other substances beside ethanol were not detected, in particular neither 2C-I nor 25I-NBOH.

Discussion

This is a unique case of an analytically confirmed, accidental ingestion of 25I-NBOMe in a drug naïve adult. Two metabolites of 25I-NBOMe were quantified in serum and urine specimens, namely 2C-I and 25I-NBOH. The observed clinical effects are largely comparable to former reports, but there are also differences. The pronounced symptoms (severe agitation, coenesthesia, complex hallucinations) resolved within six hours like reported before by Stellpflug et al. [3]. In contrast, the clinical course was half a day or longer in the majority of the published 25I-NBOMe cases. Furthermore, pronounced tachycardia, hypertension, and complications such as seizures, hyperpyrexia, and rhabdomyolysis were reported [4,5]. The differences observed may be explained by a variance in dose, with the ingested dose of 25I-NBOMe being probably smaller in the here presented case than in many previously published reports. There may be a great variability in psychotropic effects of hallucinogenic agents, and a "bad trip" is especially plausible after unintentional intake.

Table 1. Concentrations of 25I-NBOMe, 2C-I and 25I-NBOH in serum and in urine.

		Concentration (ng/mL)		
Time after ingestion	Specimen	25I-NBOMe	25I-NBOH	2C-I
50 min	Serum	34	<1	12
13 hours	Serum	4.2	n.d.	2.1
43.5 hours	Serum	n.d.	n.d.	<1.0
16.5 hours	Urine	n.d.	n.d.	8.2
43.5 hours	Urine	n.d.	1.2	3.5

n.d.: not detected. Ethanol was not detected in the blood.

The 25I-NBOMe serum levels in our case were in the same range as, or higher than reported in cases of fatal intoxication [6–8]. Although standard toxicological analyses were performed in all reported cases, further intoxicants could not be ruled out completely. In addition, post-mortem redistribution of the lipophilic drug may have led to lower 25I-NBOMe concentrations. On the other hand, a severe poisoning associated with much lower serum levels (0.76 ng/mL) was reported [5]. When comparing concentrations, it has to be considered that measurement uncertainty might be relatively high in infrequently analyzed drugs like 25I-NBOMe.

In user fora, sublingual or buccal administration of low doses of 25I-NBOMe (750 μg–1 mg) dominates [1]. Ethanolic solutions of 25I-NBOMe are often applied for intranasal insufflation of the drug. However, the presumed analgesic syrup was swallowed in our case, which could lead to differences in toxicokinetics.

Several articles were published recently on the metabolism of 25I-NBOMe using various experimental approaches [9–12]. Demethylated, hydroxylated and *N*-demethoxybenzylated compounds were identified among the main phase I metabolites. Glucuronidation and sulfation occurred as phase II reactions. Caspar et al. demonstrated that CYP2C9 and CYP2C19 among the CYP-isoenzymes were mainly involved in *O*-demethylation, CYP1A2 and CYP3A4 in hydroxylation and CYP3A4 in *N*-demethoxybenzylation forming 2C-I [9], although Nielsen et al. found slightly differing results [12] (see also Figure 1). Although in these studies authentic urine samples were included, it has to be mentioned that next to genetic or phenotyp-dependent differences, the route of application might be relevant for predicting the spectrum of main metabolites.

In the literature further 25I-NBOMe intoxications are described, but only few report the identification of 2C-I in urine specimens, and none in serum samples [3–5,13]. The rapid breakdown of 25I-NBOMe to 2C-I within 50 minutes in our case could be explained by an extensive first pass metabolism. Another possible site of 2C-I formation is intestinal CYP3A4: It is known from other substrates of CYP3A4, that intestinal CYP3A4 plays an important role in first pass metabolism [14,15]. Therefore, the involvement of CYP3A4 in the

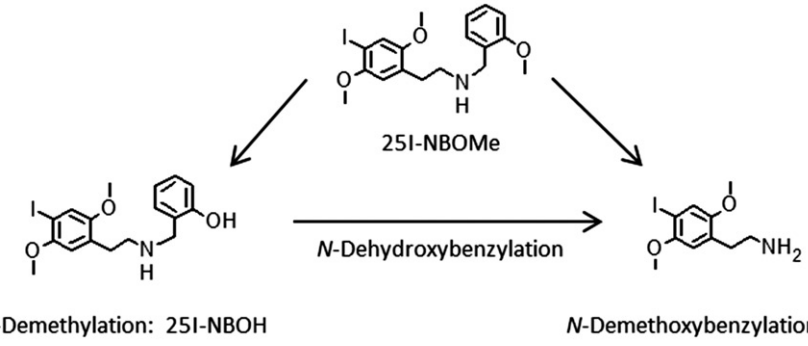

Figure 1. Main metabolic pathways of metabolism of 25I-NBOMe: CYP2C9 and CYP2C19 were mainly involved in *O*-demethylation, CYP1A2 and CYP3A4 in hydroxylation, and CYP3A4 in *N*-demethoxybenzylation forming 2C-I [9]. In addition, 2C-I may also be formed by *N*-dehydroxybenzylation [12].

small intestine could explain the high first pass effect in our case.

The metabolites 2C-I and 25I-NBOH are phenethylamines with hallucinogenic activity mediated by the 5-HT_{2A} receptor. Both are sold as designer-hallucinogens themselves. Out of these, only 2C-I reached serum levels possibly eliciting clinical effects in our case. 25I-NBOMe is a very potent 5-HT_{2A} receptor agonist ($EC_{50} = 0.25\ \mu M$) with high 5-HT_{2A} receptor affinity ($K_i = 0.0006\ \mu M$). The 5-HT_{2A} receptor activation potency of 2C-I is approximately fourfold higher ($EC_{50} = 0.06\ \mu M$), but the 5-HT_{2A} receptor affinity is much lower ($K_i = 0.0035\ \mu M$) [16]. In our case the serum concentration of 25I-NBOMe was about four times higher than that the serum concentration of 2C-I, and therefore, a high relevance of the metabolite 2C-I to the clinical findings seems rather unlikely.

Conclusions

The concentration of 2C-I in the serum sample taken shortly after drug intake indicates a fast metabolic breakdown of 25I-NBOMe, most probably due to first-pass metabolism after oral ingestion. Toxicokinetics of other NBOMe derivatives of phenethylamines are likely to be similar.

Acknowledgements

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Disclosure statement

No potential conflict of interest was reported by the authors.

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