Foxy, a Designer Tryptamine Hallucinogen*

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Abstract

Foxy is slang for 5-methoxy-N,N-diisopropyltryptamine. It has hallucinogenic properties, similar to other tryptamine compounds, and is mildly euphoric. This case report describes a 21-year-old Caucasian man who ingested a pill called Foxy containing an unknown amount of drug. He was observed in hospital for 2 h, during which time he had mild hallucinations and could not move his limbs. A urine sample was collected approximately 4 h after drug ingestion. The patient was then discharged with no follow up assessment. The 5-methoxy-N,N-diisopropyltryptamine was identified in the urine by gas chromatography–mass spectrometry. Standards prepared from the pure material were used in the identification. Quantitative analysis using the same analytical technique resulted in a urinary concentration of 1.7 µg/mL. Through oxidative deamination, the metabolite, 5-methoxy-indole acetic acid, was formed. It was identified in the urine, and the concentration was determined to be 1.3 µg/mL using gas chromatography–mass spectrometry. Two other compounds were discovered in the urine sample as a result of a routine drug screen. From their mass spectra, they were tentatively identified as 5-methoxy-N-isopropyltryptamine and 5-methoxy-N,N-diisopropyltryptamine-N’-oxide.

Introduction

Foxy, 5-methoxy-N,N-diisopropyltryptamine (5-MeO-DIPT), is an uncommon designer hallucinogen. The structure is shown in Figure 1. It is the diisopropyl analogue of the more familiar hallucinogen 5-methoxy-dimethyltryptamine. The U.S. Drug Enforcement Administration identified (1–6) capsules containing 5-MeO-DIPT obtained in California, Arizona, New York, Washington state, Texas, and Virginia. Further analysis of one of the capsules showed it to contain a 4-mg dose (1). In Canada, Health Protection Branch, Winnipeg was the first to report the seizure of capsules in two separate instances.

Clinically, the drug promotes emotional expression, a talkative uninhibited state (7), and visual and auditory sensory distortions (8). No other clinical studies appear in the medical literature. There are no reported pharmacological studies in humans. Some of the drug’s physiological properties are also common to the recreational drug methylenedioxymethylamphetamine (Ecstasy). Not surprisingly, 5-MeO-DIPT is a club drug (2) and has been substituted for Ecstasy on the street (3).

Case History

A 21-year-old Caucasian man presented to the emergency department about 1.5 h after consuming a pill to get high. He was told the pill was called Foxy; it was sold to him on the street for $10. Within an hour of ingestion, he said he felt “weird”. He started seeing unfamiliar symbols on the wall and could not move his limbs. No nausea, pain, or visual deficit were apparent. He denied using any other recreational drugs or alcohol.

On examination, he was alert and oriented. His pulse was 106 with a blood pressure of 122/56 mm Hg and a respiration rate of 20. His pupils were 8 mm, equal, and reactive. Extra ocular movements were intact, and there was no motor sensory deficit. His cardiorespiratory examination was unremarkable. He received only supportive care throughout his hospital stay. The effects wore off 3.5 h after ingestion. He stopped seeing the symbols and could move his limbs normally. A urine sample was collected at 4 h postingestion for a drug screen just before he was discharged from hospital. Blood was not collected because no other laboratory work up was required. There was no investigative follow up.

The patient did not have a documented drug-abuse problem.

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Methods

Authentic 5-MeO-DIPT powder was obtained from Health Protection Branch (Health Canada, Winnipeg, MB, Canada); 5-methoxyindoleacetic acid (5-MeO-IAA) and 5-hydroxyindoleacetic acid (5-HIAA) were obtained from Aldrich (Oakville, ON, Canada).

Amphetamines (1000 ng/mL cut-off), barbiturates (200 ng/mL cut-off), cannabinoids (50 ng/mL cut-off), benzoylcegonine (150 ng/mL cut-off), opiates (300 ng/mL cut-off), and phencyclidine (25 ng/mL cut-off) were screened by EMIT II Plus (Dade Behring, Mississauga, ON, Canada). Also, benzodiazepines (100 ng/mL cut-off) were screened by CEDIA (Microgenics, Freemont, CA) using a Hitachi 717 analyzer (Roche Diagnostics, Laval, QC, Canada). LSD (500 pg/mL cut-off) was screened in a separate procedure by ELISA (Immunalysis Corp., Pomona, CA).

Basic and neutral drugs were screened by gas chromatography–mass spectrometry (GC–MS) using a modified method of Foerster et al. (9); acidic and neutral drugs were screened by a method developed for barbiturate analysis (10). Alcohols were screened by GC on a 1.83-m Carbopack B column coated with 5% Carbowax 20M (11) supplied by Supelco (Oakville, ON, Canada). Direct injection (12) was used for sample introduction.

Positive screening tests were obtained for cannabinoids and opiates. The major urinary metabolite, Δ⁹-carboxy-tetrahydrocannabinol, was confirmed by GC–MS using a modification of the method described by Wimbish and Johnson (13). The opiates were confirmed and quantitated by GC–MS (14). Acetaminophen was detected in both the basic and acidic drug screen and subsequently quantitated by HPLC (15).

Analysis of 5-MeO-DIPT

The urine quantitation of 5-MeO-DIPT was performed by GC–MS. A stock standard was prepared in methanol at 1000 μg/mL and was used to spike urine at 4, 2, 1, 0.5, and 0 μg/mL. One-milliliter aliquots of the standards and case sample were pipetted into 12-mL screw-capped extraction tubes. One microgram of the internal standard, p-chlorodisopyramide (Searle, Mississauga, ON, Canada), was added to each tube. After the addition of 0.8 mL of 1M NaHCO₃ (pH 9), 4 mL of methyl-t-butyl-ether, and 2 mL of methylene chloride, the tubes were capped and mixed on a rotating wheel for 15 min. The two phases were separated by centrifugation, and the top solvent layer was transferred to a 5-mL conical tube containing 100 μL of 0.1N HCl. The solvent was dried in a 45°C sand bath under a gentle stream of nitrogen. Acetonitrile (50 μL) was added to the remaining 100 μL of HCl and washed with 250 μL of hexane to remove lipids. The hexane was aspirated to waste. After the addition of 100 μL of 1M NaHCO₃ and 2 mL of methylene chloride, the contents were mixed by vortex mixing for 2 min, then centrifuged to separate the phases. The upper aqueous layer was aspirated to waste. The remaining organic solvent was dried with 100 mg of anhydrous sodium sulfate then transferred to a clean 5-mL conical tube. Acetonitrile (100 μL) was added as a keeper solvent before the methylene chloride was evaporated with nitrogen. The acetonitrile was further reduced to 30 μL, of which 1 μL was injected into the GC–MS. The GC–MS was an ITS40 ion trap running Magnum software (Thermoquest Finnigan, San Jose, CA). Separation was performed with a DB-1 (15-m x 0.25-mm, 0.25-μm film thickness) methyl silicone capillary column. A 1-m x 0.52-mm retention gap deactivated with 5% phenyl methyl silicone connected the analytical column to the temperature programmable injector. Helium carrier gas flowed at 45 cm/s. The oven was initially held at 80°C for 1 min, then programmed at 10°C/min to a final temperature of 290°C, where it was held for 5 min. The temperature programmable injector was ramped from 85°C to 290°C at 13°C/min. Electron impact mass spectra were collected in full scan from 44 to 650 amu at 1 scan/s. Mass spectral fit to 5-MeO-DIPT in the case sample was 990 of a possible 1000; the retention time agreed within 3 s. The quantitation ions for 5-MeO-DIPT and the internal standard p-chlorodisopyramide were the base peak ions, 114 and 229 amu, respectively. Linear regression of the 6 calibration standards between 0 and 4 μg/mL was handled by the Magnum software. The standard curve was linear with a correlation coefficient (r²) of 0.94. By interpolation, the 5-MeO-DIPT concentration was determined to be 1.7 μg/mL. Four months later, repeat analysis of a frozen urine aliquot using freshly prepared urine calibrators resulted in a 5-MeO-DIPT concentration of 1.8 μg/mL.

Analysis of 5-MeO-IAA and 5-HIAA

Methanolic stock standards of each were prepared at a concentration of 1000 μg/mL. Combined dilutions were prepared in drug-free urine at 4, 1, 0.5, 0.1, and 0 μg/mL. The standards and patient sample were assayed using a modification of a method routinely used to quantitate barbiturates (10). Phosphate buffer (pH 6.8) was replaced by 1N HCl in the solvent extraction part of the procedure to enhance the recovery of these two compounds. The extract was dried and ethylated to form derivatives suitable for GC–MS analysis. The retention times of derivatized 5-MeO-IAA, 5-HIAA, and the internal standard tolybarb were 698, 728, and 654 s, respectively. The quantitation ions were the base peak ions 160, 174, and 274 amu. Linear regressions of the calibration standards were used to calculate the patient values. In addition, 10 drug-free urine samples from healthy volunteers were analyzed to establish normal baseline values.

Results

No alcohols were present in the urine, consistent with the history upon arrival at the hospital. Of the immunoassay screening tests, cannabinoids (89 ng/mL) and opiates (26,380 ng/mL) were positive; all others were negative at the cut-offs previously specified. Subsequent GC–MS confirmation testing resulted in Δ⁹-carboxy-tetrahydrocannabinol of 44 ng/mL, codeine of 28,122 ng/mL, and morphine of 48 ng/mL. Acetaminophen and caffeine were present in the acid-neutral drug screen. Acetaminophen, determined by HPLC, was 77 μg/mL. The urine was concentrated; creatinine was 1945 mg/L (17.2 mmol/L).

The GC–MS basic drug screen revealed a large 5-MeO-DIPT peak, codeine, nicotine, cotinine, acetaminophen, caffeine, and...
two other peaks that were assumed to be 5-MeO-DIPT metabolites. The 5-MeO-DIPT, having a retention time of 803 s, was subsequently quantified by GC–MS, and found to be 1.7 µg/mL. A portion of the chromatogram is shown in Figure 2. The two peaks A and B, presumed to be metabolites, eluted at 703 s and 881 s, respectively. Mass spectra of 5-MeO-DIPT, peaks A and B are shown in Figure 3. The mass spectrum of 5-MeO-DIPT is a simple one, having a base peak m/z 114 amu, probably from the fragment CH₂-N-[CH(CH₃)₂]₂⁺ ion. Such fragmentation is typical of N terminal aliphatic amines. The [M+H]+ ion with mass 275 amu is observed with 10% relative abundance. Peak A was presumptively identified as a metabolite 5-methoxy-N-desisopropyltryptamine (5-MeO-IPT). The mass spectrum has as base peak of 161 amu with strong ions at 72, 160 and 233 amu. The 72 amu ion is attributed to the fragment CH₂-NH(CH₃)₂ ion. The [M+H]+ ion with mass 233 amu is relatively strong, having a 75% relative abundance. Peak B was presumptively identified as the metabolite 5-methoxy-N,N-diisopropyltryptamine-N'-oxide metabolite (5-MeO-DIPToN-oxide). The base peak is 114 amu, and like the parent drug, is attributed to the CH₂-N-[CH(CH₃)₂]₂⁺ fragment ion. A weak, 2% abundance ion was observed at m/z 291 amu which was assigned as the [M+H]+ ion. A second 1-µL aliquot of the urine extract was injected, and chemical ionization spectra were acquired using 5% ammonia in methane as the reagent gas. The [M+H]+ ions for 5-MeO-DIPT, peak A, and peak B were raised to 60%, 100%, and 20% relative abundance, respectively. There were no significant higher mass ions than the [M+H]+ ions in the respective CI mass spectra. The same extract was also analyzed with an HP5973 MSD (Agilent Technologies, Montréal, QC, Canada) in the EI mode. The mass spectra were identical except that weak M+ ions replaced the [M+H]+ ions. The tendency to sometimes form [M+H]+ in ion traps, whereas M+ are formed in quadrupole instruments is characteristic of the two types of MS.

A method developed for the confirmation of urinary amphetamines (16) was applied to an aliquot of the urine. In this method, the amphetamines are extracted into an organic solvent; the primary and secondary amines groups are derivatized with propyl chloroformate, and the tertiary amines are left unreacted. The resultant chromatogram showed the disappearance of peak A and the appearance of a new peak at 945 s. The mass spectrum and proposed structure are shown in Figure 4. The peak A metabolite, being a secondary amine, formed the expected propylchloroformate derivative.

It is reasonable to predict N-desisopropylation to be a contending metabolic pathway leading to the production of 5-MeO-IPT and hence anticipate its appearance in the urine. By analogy, Sitaram et al. (17) have shown the N-desmethyl metabolite, 5-methoxy-N-methyltryptamine to be a minor urinary metabolite following administered 5-methoxy-N,N-
dimethyltryptamine to rats. Also, Barker et al. (18) have described the N-demethylation of deuterated N,N-dimethyltryptamine in rat brain.

The assignment of peak B as the N'-oxide metabolite is proposed on the basis of 5-methoxy-N,N-dimethyltryptamine administration to rats and the recovery of formed 5-methoxy-N,N-dimethyltryptamine-N'-oxide from their urine (17,19,20) and other tissues (17). It is also possible that peak B is 6-hydroxy-5-methoxy-N,N-diisopropyltryptamine. Although hydroxylation of indole derivatives at the 6 position has been proposed (21), there is no supporting evidence in the literature to show that this pathway plays a major role in animals or humans. In addition, Agurell et al. (19) claim that there is negligible in-vivo 6-hydroxylation of 5-methoxy-N,N-dimethyltryptamine in the rat. The identity of both peaks A and B will remain speculative until such time as authentic 5-MeO-DIPT metabolites become available.

Oxidative deamination is the major metabolic pathway for tryptamines (17,19). If 5-MeO-DIPT followed the same pathway, then 5-MeO-IAA would be formed. Further, it is possible that 5-MeO-IAA could be O-demethylated to yield 5-HIAA as it is in the rat (19). These two compounds were extracted from acidified urine. The carboxylic acid moiety of each plus the 5-hydroxy group on 5-HIAA were ethylated and analyzed by GC–MS. Extracted ion chromatograms for ethylated 5-MeO-IAA (m/z 160), ethylated 5-HIAA (m/z 174), and ethylated tolybarb (m/z 274) are displayed in Figure 5. The concentrations of 5-MeO-IAA and 5-HIAA were 1.3 μg/mL and 3.0 μg/mL, respectively. For comparison, these two compounds were determined in urine samples from 10 healthy individuals. As anticipated, no 5-MeO-IAA was detected (< 0.1 μg/mL) in any of the urine samples. However, 5-HIAA, an end product of endogenous serotonin metabolism, was present at concentrations between 1.0 and 8.9 μg/mL. Random urine concentrations are expected to be in this concentration range because the normal 24-h excretion of 5-HIAA is 1.8–6.0 mg/d (22). Because the 5-HIAA was not elevated in the patient's urine sample, it is not possible to say if demethylation of 5-MeO-IAA to 5-HIAA is an important metabolic pathway. The pathway could still be of minor importance, as has been shown in the rat (19).

**Discussion**

In 1980, Shulgin and Carter (7) described the administration of 5-MeO-DIPT to 10 human subjects. Each person received a 0.1-mg oral dose which was then increased in increments of 30 to 50% in subsequent drug administrations. Threshold subjective effects were observed with a 4-mg dose. Effective doses were between 6 and 10 mg. The peak drug effect occurred at 1 to 1.5 h after ingestion, and recovery was observed after 3 h with no residual symptoms at 6 h. Subjects reported a relaxed feeling associated with emotional enhancement. They were frequently talkative and felt their conversations to be expressive and stimulating. Shulgin and Shulgin (8) later summarized the responses from an additional 10 human subjects upon administration of 6 to 12 mg of 5-MeO-DIPT. Most subjects reported auditory and visual distortions. Two indicated aphrodisiac tendencies; one experienced gastrointestinal emptying, muscle spasms, and agitation; and one indicated a synergistic effect with marijuana. In our patient, the drug lasted 3.5 h. He said he felt "weird" (apprehensive) and saw symbols (visual hallucination) as opposed to being talkative or expressive of his emotions. Possibly there was a synergistic contribution from the cannabis, which might explain his muscle paralysis. However, it is not known when the cannabis was consumed; the patient denied other drug use at the time of his admission to hospital.

The lower alkyl substituted 5-methoxy tryptamines such as 5-methoxy-dimethyl-
n-propyl-tryptamine are nearly ineffective if taken orally because they are quickly degraded by monoamine oxygenase (23). To experience the hallucinogenic effect, these agents must be administered parenterally such as through injection, snuff, or smoking. However, 5-MeO-DIPT is different in this respect because it is effective when taken orally. The major route of 5-methoxy-N,N-dimethyltryptamine metabolism in the rat is via the oxidative deamination pathway yielding 5-MeO-IAA (19). The branched alkyl chain of the two isopropyl substituents in 5-MeO-DIPT is thought to provide enough steric hindrance to slow the oxidative deamination metabolism (7) and hence extend the drug half-life. Still, the oxidative deamination pathway administered parenterally such as through injection, snuff, or smoking. However, 5-MeO-DIPT is different in this respect because it is effective when taken orally. The major route of 5-methoxy-N,N-dimethyltryptamine metabolism in the rat is via the oxidative deamination pathway yielding 5-MeO-IAA (19). The branched alkyl chain of the two isopropyl substituents in 5-MeO-DIPT is thought to provide enough steric hindrance to slow the oxidative deamination metabolism (7) and hence extend the drug half-life. Still, the oxidative deamination pathway cannot be overlooked. In the patient’s urine sample, the concentration of 5-MeO-IAA was 1.3 μg/mL, whereas the concentration of the parent drug, 5-MeO-DIPT was 1.7 μg/mL. In addition, the N-desisopropylation, and N’-oxidation pathways are also seen to be important metabolic routes as suggested by the tentative identification of 5-MeO-IPT and 5-MeO-DIPT-N’-oxide as urinary metabolites.

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References