



## A foxy intoxication

John M. Wilson<sup>a</sup>, Frank McGeorge<sup>b</sup>, Susan Smolinske<sup>c</sup>, Robert Meatherall<sup>d,\*</sup>

<sup>a</sup>Clinical Pathology, William Beaumont Hospital, 3601 West Thirteen Mile Road, Royal Oak, MI 48073, USA

<sup>b</sup>Department of Emergency Medicine, William Beaumont Hospital, 3601 West Thirteen Mile Road, Royal Oak, MI 48073, USA

<sup>c</sup>Childrens Hospital of Michigan Poison Center, 4160 John R St., Suite 16, Detroit, MI 48201, USA

<sup>d</sup>Laboratory Medicine, St. Boniface General Hospital, 409 Tache Avenue, Winnipeg, Manitoba, Canada R2H 2A6

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### Abstract

Foxy is the colloquial name for the hallucinogen 5-ethoxy-diisopropyltryptamine (5-MeO-DIPT). A non-fatality involving a 23-year-old Caucasian man who ingested a capsule containing 5-MeO-DIPT is described. He presented to the Emergency Department, not with visual nor auditory hallucinations but with sensory hallucinations, that of formication and paranoia. He was observed and given supportive care for 4 h, then discharged without any known sequelae. Blood and urine were collected for laboratory analyses. Foxy and its metabolites were identified in urine by gas chromatography–mass spectrometry. The concentrations of 5-MeO-DIPT in the serum and urine were 0.14 and 1.6 µg/mL, respectively. The drug undergoes oxidative deamination to form 5-methoxy-indole acetic acid. The urinary concentration of this metabolite was 0.17 µg/mL. Also, the urine contained three other related compounds. Two of them have been described in a previous case of 5-MeO-DIPT ingestion as 5-methoxy-isopropyltryptamine (5-MeO-IPT) and 5-methoxy-diisopropyltryptamine-*N'*-oxide (5-MeO-DIPT-*N'*-oxide). The third compound was substantially present in the urine and was tentatively identified as 5-hydroxy-diisopropyltryptamine (5-OH-DIPT). Only the parent drug, 5-MeO-DIPT was detected in the serum sample.

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### 1. Introduction

Foxy, 5-methoxy-diisopropyltryptamine, is a relatively new hallucinogen that is gaining popularity among recreational drug users. Most tryptamines are taken parenterally to avoid rapid metabolism by the monoamine oxygenase system. However, 5-MeO-DIPT is unique, in that it may be taken orally because it is resistant to monoamine oxygenase degradation [1].

Law enforcement agencies have reported seizures of capsules and tablets in ten states of the United States since 2001. The drug's use has been reported at clubs in Arizona, California, Florida, Delaware, Idaho, and New York. A report analyzing data from the American Association of Poison Control Centers TESS database contained 41 reports of 5-MeO-DIPT exposures to poison centers for the 15 month

period from April 2002 to the end of June 2003. The outcome of these exposures was major in 2 cases, moderate in 26, minor in 8 and no effect in 1. Clinical effects commonly involved agitation (59%), hallucinations (39%), tachycardia (37%), hypertension (17%), and confusion (15%). Tremors and seizures were rare. The geographic area of TESS cases was noted to expand during this time frame from three states in April 2002 to July 2002, to seven by the end of October, then 12 by December 2002, and finally 17 states by June 2003. Cases were primarily clustered in the West, Midwest Great Lakes area, and East coast [2]. Identification of Foxy in these cases was based on patient history alone. Confirmation by drug analysis, if performed, was not stated in the report.

### 2. Case history

A 23-year-old Caucasian male presented to the Emergency Department, 3 h after taking a capsule from a friend

\* Corresponding author. Tel.: +1 204 237 2259.

E-mail address: [rmeather@sbgh.mb.ca](mailto:rmeather@sbgh.mb.ca) (R. Meatherall).

that was reported to be “acid to get high on”. The capsule appeared to be homemade; he was not told of its contents. The exact source of the capsule beyond that of his friend was unknown and it was given, not sold, to him. Prior to ingesting the capsule, he said he had ingested four beers. Half an hour prior to presentation (2.5 h after ingesting the capsule), he became nauseous and vomited four times, each with clear emesis. He experienced a diffuse sense of formication (tactile hallucinations) and paranoia and specifically denied any auditory hallucinations, visual hallucinations or any focal neurologic complaints. Besides the capsule and the alcohol, he denied any other ingestions. He had a history of asthma but was not actively using his prescribed albuterol inhaler. He denied any known drug allergies and was otherwise healthy.

On examination, he was alert, though anxious and very scared. Review of his vital signs was normal with no hyperautonomic activity or hyperpyrexia identified. His temperature was 37 °C, pulse 76 bpm, respirations 18 per min, and blood pressure 135/70 mmHg. His pupils were midpoint and reactive. Neurologically, he was non-focal with normal central nervous system, normal cerebellar function with no tremor or ataxia. His motor function and deep tendon reflexes were normal. He had no unusual sensations other than the subjective formication. The heart, lung and abdominal examination were unremarkable.

Given the unknown nature of his ingestion, activated charcoal was administered and the patient was provided intravenous fluids at 75 cc/h. Blood and urine were collected approximately 4 h after ingesting the capsule for routine hematology, chemistry and toxicology testing. He received supportive care for an additional 3 h, at which time his condition had improved and he was discharged with no complaints. Attempts at further follow-up were unsuccessful; he has not re-presented to our hospital system within the last 6 months.

### 3. Methods

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

Amphetamines (1000 ng/mL cut-off), barbiturates (200 ng/mL cut-off), cannabinoids (50 ng/mL cut-off), benzoyllecgonine (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, Canada). Also, benzodiazepines (100 µg/mL cut-off) were screened by CEDIA (Microgenics, Fremont, CA), using a Hitachi 717 analyzer (Roche Diagnostics, Laval, QC). LSD (500 pg/mL cut-off) was screened in a separate procedure by ELISA (Immunoanalysis Corp., Pomona, CA). A positive cannabinoid screening test was confirmed by GC-MS analysis of 11-nor- $\Delta^9$ -tetrahydrocannabinol-9-carboxylic acid

in the urine using a method modified from that described by Wimbish and Johnson [3].

A urine drug screen was initially performed using thin layer chromatography (Toxi-Lab, Irving, CA). Following the discovery of unidentified spots, the urine was further investigated by GC-MS. In this procedure, 2 mL of urine, 500 ng of internal standard, SKF-525A (Proadifen, Smith-Kline-French), 0.5 mL of 1N sodium hydroxide and 5 mL of dichloromethane were added to a 12 mL screw top extraction tube. The tube was rotated for 5 min to mix the contents and then it was centrifuged for 5 min to separate the phases. The aqueous layer was removed by aspiration and the organic layer was transferred to a 10 mL glass centrifuge tube which was placed in a 45 °C water bath under a stream of air to evaporate the solvent. The residue was reconstituted with 25 µL of ethyl acetate and 1 µL was injected splitless into the GC-MS. A Hewlett-Packard 5972B Mass Selective Detector (Agilent Technologies, Wilmington, DE) equipped with a split-splitless injector and a DB-5MS column, 30 m × 0.25 mm, 0.25 µm film (J&W Scientific, Folsom, CA) was used for drug identification. The oven was programmed from 120 °C, with a 3 min hold to 225 °C at 10 °C/min. Following another 5 min hold, the oven temperature was raised to 300 °C at 15 °C/min where it was maintained for 3 min.

Analyses of 5-MeO-DIPT and its metabolites 5-MeO-IAA and 5-OH-IAA in the urine sample were performed by GC-MS methods as previously described by Meatherall and Sharma [4]. Quantitation of 5-MeO-DIPT in the serum sample employed the same method as used for the urine sample except that the serum-based calibrators were at 10-fold lower concentrations; 0.4, 0.2, 0.1, 0.05, and 0 µg/mL. Standard curves for 5-MeO-DIPT in urine and serum were linear with correlation coefficients ( $r^2$ ) of 0.992 and 0.962, respectively. Extensive method validations were not undertaken as is customary for case reports involving novel drugs. The reported drug concentrations must be viewed accordingly.

For the 5-MeO-DIPT analysis, urine and serum were extracted from 1 mL of alkalinized fluid into a mixed solvent consisting of 4 mL of methyl-*t*-butyl ether and 2 mL of dichloromethane. The internal standard was *p*-chlorodisopyramide (Aventis, Laval, Quebec). The two phases were separated by centrifugation and the top organic phase was transferred to a conical tube containing 100 µL of 0.1N HCl. This organic portion was dried at 45 °C under a stream of nitrogen. After the addition of 50 µL of acetonitrile to the remaining 100 µL of HCl, the mixture was washed with 250 µL of hexane by vortex mixing for 1 min. The hexane was aspirated to waste, 100 µL of 1 M NaHCO<sub>3</sub>, pH 9, and 2 mL of dichloromethane were added and the tube contents vortex mixed for 2 min. After centrifugation to separate the phases, the upper aqueous portion was aspirated to waste. The remaining dichloromethane was dried by adding 100 mg of anhydrous sodium sulfate then transferred to another conical tube. 100 µL of acetonitrile was added as a keeper solvent before the dichloromethane was evaporated

with nitrogen. The acetonitrile was further reduced to 30  $\mu\text{L}$  then taken to the GC-MS for analysis. Using a temperature programmable injector, 1  $\mu\text{L}$  was injected at 85  $^{\circ}\text{C}$ , followed by heating at 13  $^{\circ}\text{C}/\text{min}$  to a final temperature of 290  $^{\circ}\text{C}$ . Spectra were collected in the electron impact mode at 1 scan/s using an ITS40 ion trap (Thermoquest Finnigan, San Jose, CA). The capillary column was a DB-1, 15 m  $\times$  25 mm  $\times$  0.25  $\mu\text{m}$  film (J & W Scientific, Folsom, CA). The initial oven temperature was held at 80  $^{\circ}\text{C}$  for 1 min, then raised at 10  $^{\circ}\text{C}/\text{min}$  to 290  $^{\circ}\text{C}$  where it was again held for 5 min. Quantitation ions for 5-MeO-DIPT and the internal standard, *p*-chlorodisopyramide were  $m/z = 114$  and 229, respectively.

#### 4. Results

Hematology analysis, consisting of complete blood count and differential, was normal, as was a chemistry panel that included serum electrolytes, glucose, urea, and creatinine. Serum ethanol, salicylates, and acetaminophen were all negative. The serum and urine creatinine were 0.9 and 1220 mg/dL, respectively. Urinalysis was also normal. The immunoassay screening tests were all negative except for cannabinoids, which were greater than 100 ng/mL. Subsequent GC-MS confirmation testing resulted in 11-nor- $\Delta^9$ -tetrahydrocannabinol-9-carboxylic acid concentration of 88 ng/mL.

Screening by thin layer chromatography resulted in the following findings: Toxigram-A showed 3 spots with Rf's of 2.4, 4.6, and 6.1. At stage I in development, all spots were blanch. At stage II, spots at 2.4 and 6.1 faded while the spot at 4.6 turned tan in color. All spots absorbed at stage III and all turned brown at stage IV. Follow-up urine screening by GC-MS showed a large peak and two much smaller peaks which had the same mass spectra and expected retention times as 5-MeO-DIPT, and the tentatively identified metabolites 5-methoxy-isopropyltryptamine (5-MeO-IPT) and 5-methoxy-diisopropyltryptamine-*N'*-oxide (5-MeO-DIPT-

*N'*-oxide), respectively [4]. In addition, the chromatogram had one other prominent unidentified peak, which appeared at a slightly longer retention time than 5-MeO-DIPT. The urine and serum were stored frozen for 1 month pending quantitative analysis.

The 5-MeO-DIPT, concentrations in urine and serum, were 1.6 and 0.14  $\mu\text{g}/\text{mL}$ , respectively. A portion of the chromatogram from the urine extract is shown in Fig. 1. The 5-MeO-DIPT is the prominent peak with retention time of 800 s. The small Peak A at 705 s has the same retention time and mass spectrum as the previously reported 5-MeO-IPT metabolite. The 5-MeO-DIPT-*N'*-oxide metabolite, with an expected retention time (Peak B) of 880 s, is missing, although a small amount was present one month earlier during the initial GC-MS screening. This suggests that 5-MeO-DIPT-*N'*-oxide is unstable in frozen urine samples. The mass spectrum of the large Peak C eluting at 835 s is shown in Fig. 2. It is tentatively identified as 5-hydroxy-diisopropyltryptamine (5-OH-DIPT). A fragmentation pattern analogous to 5-MeO-DIPT would give a base peak having  $m/z = 114$  from the  $\text{CH}_2\text{-N}[\text{CH}(\text{CH}_3)_2]^+$  ion and a  $M + 1$  ion with  $m/z = 261$ . A 1  $\mu\text{L}$  portion of the same extract was re-injected with mass spectra acquired under chemical ionization conditions using 5% ammonia in methane as the reagent gas. The  $m/z = 261$  ion increase to 32% abundance. No higher mass ions were present.

The basic extract was dried with nitrogen, reconstituted with acetonitrile and ethylated with ethyl iodide using tetramethylammonium hydroxide as catalyst [5]. Peak C at 835 s was replaced by another peak of the same size eluting slightly earlier at 825 s. The mass spectrum of this peak is shown in Fig. 3. It has a base peak of  $m/z = 114$ , like the other diisopropyl tryptamines and a smaller ion fragment with  $m/z = 289$ . This is consistent with the formation of the derivative 5-ethoxy-diisopropyltryptamine (5-EtO-DIPT). Phenolic groups are acidic in nature such that they readily ethylate by this derivatizing procedure. Likewise, the serum extract, used to quantify 5-MeO-DIPT was subjected to the same ethylation procedure. No peak appeared at 825 s,

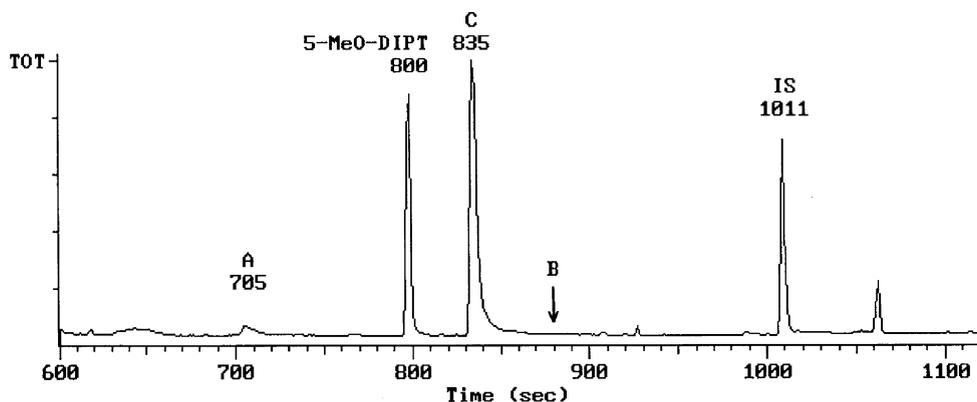


Fig. 1. Portion of GC-MS total ion chromatogram of the case urine extract: peak A-presumptively identified as 5-MeO-IPT, peak C-presumptively identified as 5-OH-DIPT, B-expected retention time of 5-MeO-DIPT-*N'*-oxide.

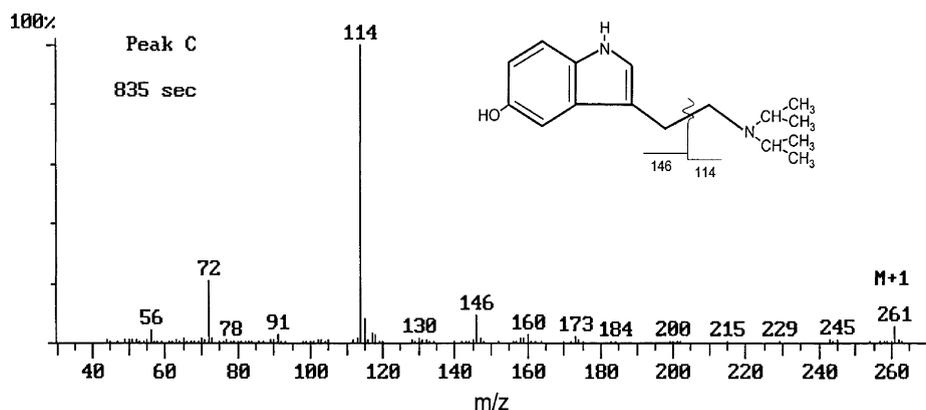


Fig. 2. Ion trap mass spectrum of Peak C, presumptively identified as 5-OH-DIPT.

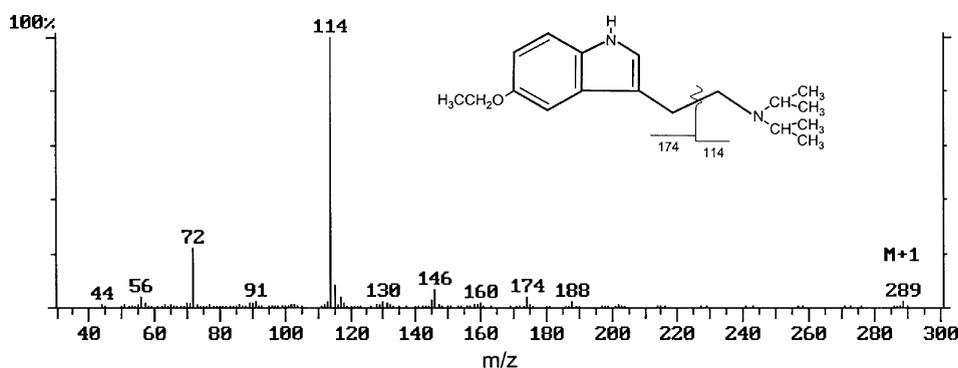


Fig. 3. Ion trap mass spectrum of the ethyl derivative of peak C, presumptively 5-ethoxy-DIPT.

providing further evidence that 5-OH-DIPT was absent in the serum sample.

Quantitation of 5-MeO-IAA and 5-OH-IAA in the patient's urine resulted in concentrations of 0.17 and 3.2  $\mu\text{g}/\text{mL}$ , respectively.

## 5. Discussion

Use of modified tryptamines, such as Foxy, appear to be increasing in the United States as attested by increased emergency room reports and law enforcement seizures. Few current reports have provided significant analytical data as an aid to identification of these substances and their relative toxicological risk.

This patient's presenting symptoms are somewhat different to those previously described following 5-MeO-DIPT ingestion [1,4,6]. Here, there were no auditory or visual hallucinations but rather a diffuse sense of formication (tactile hallucinations) and a feeling of paranoia. The patient did not admit to recent cannabis consumption on direct questioning. We do not think the symptoms were a direct result of marijuana use. According to the clinical impres-

sions of his attending doctor while in the emergency department (GM), he was probably not a naïve marijuana user. There is the possibility that the presenting symptoms are the result of concomitant use of marijuana and 5-MeO-DIPT. However, an observed 3 to 6 h drug effect with rapid onset is in keeping with ingestion of 5-MeO-DIPT [1,6].

Analytical results following the work-up of this patient are summarized in Table 1. The serum concentration of 5-MeO-DIPT is 0.14  $\mu\text{g}/\text{mL}$ , an order of magnitude smaller than that in the urine, 1.6  $\mu\text{g}/\text{mL}$ . Other metabolites, namely 5-MeO-IPT, 5-MeO-DIPT-*N'*-oxide and 5-OH-DIPT, were not detected in the serum, but were detected in the urine. There was insufficient sample to attempt analysis of 5-MeO-IAA or 5-OH-IAA in the serum. Also, in Table 1, the urine results found in our patient are compared to those of a previously described subject [4]. The urine concentrations of 5-MeO-DIPT are essentially the same, 1.6  $\mu\text{g}/\text{mL}$  versus 1.7  $\mu\text{g}/\text{mL}$ . For comparison purposes, visual estimates of peak areas were used to guess the concentrations of 5-MeO-IPT, 5-MeO-DIPT-*N'*-oxide and 5-OH-DIPT in the two urine samples. The urine creatinine measurements indicate normally concentrated samples. In contrast, our patient excreted a large amount of the presumptively identified 5-OH-DIPT

Table 1  
Comparison of analytical data from two foxy case reports

	Serum	Urine	Urine (ref [4])
5-MeO-DIPT (Foxy)	0.14 µg/ml	1.6 µg/mL	1.7 µg/mL
5-MeO-IPT (presumed)	None	Estimate 0.1 µg/mL	Estimate 2 µg/mL
5-MeO-DIPT- <i>N'</i> -oxide (presumed)	None	Estimate 0.1 µg/mL	Estimate 0.1 µg/mL
5-OH-DIPT (presumed)	None	Estimate 1.6 µg/mL	None
5-MeO-IAA	nd	0.17 µg/mL	1.3 µg/mL
5-OH-IAA	nd	3.2 µg/mL	3.0 µg/mL
Δ <sup>9</sup> -THC-COOH	nd	88 ng/nL	44 ng/mL
Creatinine	0.9 mg/dL	1220 mg/dL	1945 mg/dL

5-MeO-DIPT: 5-methoxy-diisopropyltryptamine; 5-MeO-IPT: 5-methoxy-isopropyltryptamine; 5-MeO-DIPT-*N'*-oxide: 5-methoxy-diisopropyltryptamine-*N'*-oxide; 5-OH-DIPT: 5-hydroxy-diisopropyltryptamine; 5-MeO-IAA: 5-methoxy-indole acetic acid; 5-OH-IAA: 5-hydroxy-indole acetic acid; Δ<sup>9</sup>-THC-COOH: 11-nor-Δ<sup>9</sup>-tetrahydrocannabinol-9-carboxylic acid; nd = not done.

metabolite, whereas the previously described subject had none. Conversely, our patient had very little of the 5-MeO-IPT, 5-MeO-DIPT-*N'*-oxide and 5-MeO-IAA metabolites, whereas the previously described subject had significant amounts of all three. We expect this can be best explained

by genetic based differences in metabolism. Ethnic and sex differences do not lend an explanation, since both patients were young adult Caucasian males.

In their research on 5-methoxy-dimethyltryptamine in male Sprague-Dawley rats, Agurell et al. [7] conclude that

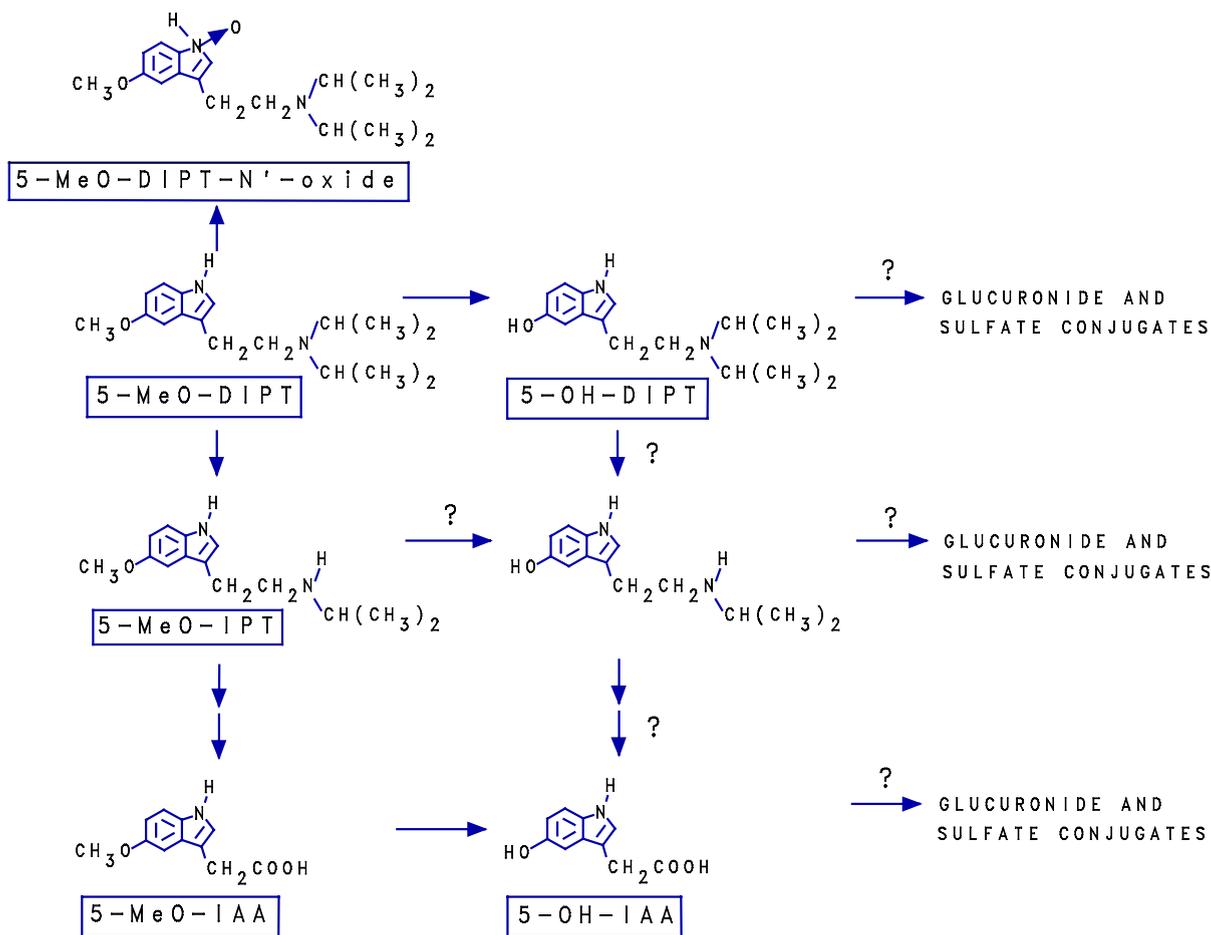


Fig. 4. Proposed metabolic pathway for 5-MeO-DIPT in humans.

*O*-demethylation is a major metabolic route. A predominant *O*-demethylation pathway would thus result in minor metabolite contributions from competitive pathways, such as *N*-dealkylation, *N'*-oxidation and oxidative deamination to respective indole acetic acids. In their model, the amount of unconjugated 5-hydroxy-dimethyltryptamine excreted depends upon the capacity for  $\beta$ -glucuronidation, presumably in the liver. Using this model, it is possible that increased conjugation made for undetectable concentrations of free 5-OH-DIPT in the first report [4].

In contrast, Sitaram et al. [8], who also studied 5-methoxy-dimethyltryptamine in male Sprague–Dawley rats, concluded that the *O*-demethylation pathway was relatively unimportant, and that *N'*-oxidation and oxidative deamination to 5-MeO-IAA were the major metabolic routes. Their experiments on rats help support the metabolite findings of the previously reported [4] human 5-MeO-DIPT subject; it does not however explain the significant amount of 5-MeO-IPT seen in that urine sample.

The proposed metabolic pathway in Fig. 4 illustrates the two *N*-oxidation pathways and the *O*-dealkylation pathway being competitive; they employ differentiable enzyme systems and act upon the existing concentration of the parent substance. It is also known that there is genetic variability in the expression of these enzyme systems. A sound explanation might involve selective inhibition in the earlier reported [4] case subject due to the presence of another drug or another environmental agent either dietary or physiological. The converse explanation is that *O*-demethylation may be activated in the current case subject by other agents with opposite attributes. While we cannot rule out the potential for interaction by naturally occurring and environmental substances, we think it unlikely that another drug is at fault, because no other substances, with the exception of cannabinoids were identified in the history or by analysis. Finally, it is possible that 5-OH-DIPT is not a metabolite of 5-MeO-DIPT at all, but a byproduct of 5-MeO-DIPT synthesis. The synthesis of 5-MeO-DIPT as described by Shulgin and Shulgin [6] uses 5-methoxytryptamine as starting material, which is obtainable in pure form. Differing batches or synthetic schemes, however, might account for the presence of 5-OH-DIPT here, but not in other cases. Though there are alternative explanations, the common occurrence of aromatic *O*-dealkylation makes metabolic formation the most likely explanation for our findings. Of note is that another

predictable metabolite, 5-hydroxy-*N*-isopropyltryptamine, was not detected. While 5-OH-IAA, formed sequentially from *N*-deamination and *O*-demethylation, is potentially an additional metabolite, it is also present endogenously from serotonin metabolism and cannot be used to validate one explanation over another.

The broader question of the relative danger of Foxy ingestion cannot be answered in this report. As in the previous report [4], our patient presentation demonstrated limited but predictable pharmacological manifestations and little of obvious toxicological impact. Of great importance is the degree to which the pharmacology and toxicology are affected by other acute factors, such as dose, purity, physiological and psychological state, concurrent medications and drugs of abuse, and chronic factors, such as cumulative dosing, environmental stressors, genetic predispositions, and disease state. We expect that additional quantitative and pharmacokinetic data will be useful and important in assessing these considerations in future occurrences.

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