Acute Toxicity Associated With the Recreational Use of the Novel Psychoactive Benzofuran \( \text{N}\)-methyl-5-(2 aminopropyl)benzofuran

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\( \text{N}\)-methyl-5-(2 aminopropyl)benzofuran (5-MAPB) is a novel psychoactive benzofuran, created by \( \text{N}\)-methylation of 5-(2-aminopropyl)benzofuran (5-APB), which shares structural features with methylenedioxymethamphetamine (MDMA). To our knowledge, no case of 5-MAPB–related toxicity has been published in the scientific literature. We report a case of oral 5-MAPB exposure confirmed by liquid chromatography–tandem mass spectrometry in a 24-year-old previously healthy white man. Observed symptoms and signs such as paleness, cold and clammy skin, hypertension, elevated high-sensitive troponin T level, tachycardia, ECG change, diaphoresis, mild hyperthermia, mydriasis, tremor, hyperreflexia, clonus, agitation, disorientation, hallucinations, convulsions, reduced level of consciousness, and creatine kinase level elevation (305 IU/L) were compatible with undesired effects related to 5-APB or MDMA exposure. Signs and symptoms resolved substantially within 14 hours with aggressive symptomatic treatment, including sedation with benzodiazepines, external cooling, analgesia and sedation with fentanyl-propofol, and treatment with urapidil, an \( \alpha\)-receptor-blocking agent. 5-MAPB showed first-order elimination kinetics with a half-life of 6.5 hours, comparable to the half-life of MDMA. According to the chemical structure, this case report, and users’ Web reports, 5-MAPB appears to have an acute toxicity profile similar to that of 5-APB and MDMA, with marked vasoconstrictor effect. [Ann Emerg Med. 2016; :1-4.]

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INTRODUCTION

\( \text{N}\)-methyl-5-(2 aminopropyl)benzofuran (5-MAPB), a novel psychoactive benzofuran, is the \( \text{N}\)-methyl derivative of 5-(2-aminopropyl)benzofuran (5-APB), which shares structural features with methylenedioxymethamphetamine (MDMA) (Figure).\(^1\) Benzofuran analogues of amphetamines, sold online as “benzo-fury,” represent a class of novel psychoactive substances that have gained popularity in the ever-expanding market of “legal highs” because of their alleged mood-enhancing and stimulating properties.\(^2\) A currently popular novel psychoactive substance,\(^3\) 5-MAPB is advertised and sold through the Internet as a research chemical in the form of a light tan powder.\(^4\)

To our knowledge, there is no published reliable information on clinical effects, course, toxicity, and human pharmacokinetics of 5-MAPB. The only sources of information presently are drug users’ Web discussion forums, in which euphoria, increased empathy, psychedelic effects, and slight stimulation in a dose-dependent manner are mentioned. Some users report undesired effects, including nystagmus, jaw tension, anxiety, sweating, “overheating,” and insomnia.

5-MAPB is generally used orally in doses of 100 to 140 mg and, in some reports, up to 600 mg, and by insufflation in doses of 25 to 50 mg, which is reported to cause painful nasal irritation. Effects are described to begin after 20 to 60 minutes, with a duration of 3 to 6 hours, often compared with time patterns of MDMA.\(^4,5\)

We report a case of acute toxicity after ingestion of 5-MAPB.

CASE REPORT

A 24-year-old previously healthy white man was noted to be agitated and to be cold, sweaty, and exhausted by paramedics at a first aid station during a large-scale rave party. On arrival at the emergency department, he was pale, cold, clammy, sweaty, disoriented in time and place, and inattentive, with tremor and progressive psychomotor agitation. He was conscious, with a Glasgow Coma Scale score of 15, and he admitted to the ingestion of an unknown amount of 5-MAPB for recreational purpose at an unknown time before admission. The patient denied concomitant ingestion of MDMA or other novel psychoactive substance.

The physical examination on admission revealed hypertension (blood pressure 157/105 mm Hg) and tachycardia (pulse rate 149 beats/min); respiratory rate was 20 breaths/min, temperature was 38.2°C (100.8°F), and room air pulse oximetry was 95%. The pupils were
mydriatic, with slowed reaction to light. He had increased muscle tone and symmetrically increased deep tendon reflexes without clonus, and the Babinski’s sign was negative. The remaining general physical examination result was unremarkable. The ECG showed sinus tachycardia (pulse rate 138 beats/min), with a minimal ascending ST-segment elevation and QTc prolongation (465 ms).

Laboratory analysis revealed increased levels of creatine kinase (305 IU/L; reference <190 IU/L), myoglobin (maximum 94 μg/L; reference 28 to 72 μg/L), highsensitive troponin T (maximum 31 ng/L; reference <14 ng/L), and prolactin (21.8 μg/L; reference 4 to 15.2 μg/L).

Blood glucose level (6.6 mmol/L) and serum electrolyte levels, as well as other parameters, were within normal limits, except for a mild leukocytosis (12.76×10⁹/L; reference 3 to 9.6×10⁹/L), and a blood alcohol level of 0.48% (10.6 mmol/L).

The patient was initially treated with intravenous fluid replacement, a total of 6 mg lorazepam sublingual for sedation, and external cooling with ice packs. There was no improvement in clinical state, except a slight decrease in body temperature to 37.9°C (100.2°F).

Three hours after admission, the patient became seriously agitated and hallucinations occurred; therefore, he was treated with midazolam (6 mg intravenously, cumulative dose), but arterial hypertension and tachycardia persisted. The patient experienced a single, short (<1 minute), generalized seizure, which was successfully treated with an additional bolus of 3 mg midazolam intravenously. Subsequently, the patient lost consciousness and he was intubated and transferred to the ICU, where he arrived with central nervous system depression and a Glasgow Coma Scale score of 5. Propofol and fentanyl were administered. The patient remained hypertensive (blood pressure 190/105 mm Hg), hyperreflexia persisted, and myoclonus of the lower limb was inducible. Therefore, intravenous midazolam sedation was repeated, with additional antihypertensive treatment with urapidil (continuous infusion, 5 to 15 mg/h). The blood pressure decreased to 140/60 mm Hg during 7 hours, and the pulse rate normalized (80 beats/min). Sedation was stopped 11 hours after admission and the patient extubated himself. The ECG changes resolved, and the patient required no further antihypertensive treatment, but he remained somnolent for another 24 hours. Because of partial respiratory insufficiency (carbon dioxide 51.7 mm Hg; oxygen 119.3 mm Hg), noninvasive ventilation with pressure support (end expiratory pressure of 5 mbar; inspiratory pressure 15 mbar) was intermittently necessary. The subsequent clinical course was uneventful, and the patient was discharged to home 37 hours after admission.

The immunologic urine toxicology screen result (initial catheter urine) was positive for amphetamines and benzodiazepines, and negative for cocaine, cannabinoids, opioids, barbiturates, methadone, and phencyclidine. Test results for lysergic acid diethylamide were positive because of a cross-reaction with fentanyl but were not confirmed by the liquid chromatography–tandem mass spectrometry (LC-MS) screening method in urine or plasma.

Targeted screening in 2 urine and 4 serum samples was conducted with an LC-MS toxicologic screening method with turbulent flow online extraction. Quantification of 5-MAPB and 5-APB was conducted.
with the same LC-MS method, but coupled to high-resolution LC-MS.

The serum and urine samples contained 5-MAPB and its metabolites (Table). 5-MAPB showed first-order elimination kinetics with a half-life of 6.5 hours. No further substance except those listed in the Table were identified by complete-library-based LC-MS screening including approximately 1,000 xenobiotics.

**DISCUSSION**

Psychoactive benzofurans structurally related to MDMA are used recreationally for their primarily entactogenic, stimulant, and hallucinogenic properties. These phenethylamines were first synthesized in the 1990s by researchers investigating non-neurotoxic MDMA analogues. Since 2010, these compounds have reached widespread use internationally. 5-MAPB has been available in online research chemical markets since late 2011, and users started to discuss its effects. Although psychoactive benzofurans have been scheduled recently as controlled substances or were controlled by analogue acts in many countries, 5-MAPB still seems to be a very popular novel psychoactive substance.

As is usually the case, information on the health risk for novel psychoactive substance in general and psychoactive benzofurans specifically is limited to a small number of scientific reports with confounders such as concomitant exposures, postmortem evaluation, or lack of analytical confirmation.

Users of 5-MAPB report that the effects resemble that of MDMA but are more intense. The same experience is described by users of other psychoactive benzofurans, including 5-APB.

Signs and symptoms observed in our patient such as hypertension, tachycardia, diaphoresis, hyperthermia, mydriasis, tremor, agitation, disorientation, hallucinations, reduced level of consciousness, clonus, seizures, and creatine kinase level elevation were compatible with the effects induced by 5-APB or MDMA.

The in vitro pharmacologic profile of 5-MAPB has not been published; nevertheless, because of the similar structure it is probable that it acts like MDMA and 5-APB, which are potent monoamine-transporter blockers and monoamine...

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**Table.** Concentrations of 5-MAPB and its metabolite 5-APB in serum and urine, and other detected substances.

<table>
<thead>
<tr>
<th>Time After Admission, h:min</th>
<th>5-MAPB in Serum, μg/L †</th>
<th>5-MAPB in Urine, mg/L †</th>
<th>Metabolites of 5-MAPB in Serum †</th>
<th>Metabolites of 5-MAPB in Urine †</th>
<th>Other Substances in Serum †</th>
<th>Other Substances in Urine †</th>
</tr>
</thead>
<tbody>
<tr>
<td>0:20</td>
<td>502</td>
<td>44</td>
<td>5-APB, hydroxylated 5-MAPB, 3-hydroxyethyl-4-hydroxy methamphetamine</td>
<td>5-APB, hydroxylated 5-MAPB, hydroxylated 5-APB, 3-carboxymethyl-4-hydroxy methamphetamine, glucuronidated 3-carboxymethyl-4-hydroxy amphetamine, 3-hydroxyethyl-4-hydroxy methamphetamine, glucuronidated 3-hydroxyethyl-4-hydroxy amphetamine, 3-dihydroxyethyl-4-hydroxy amphetamine, 3-dihydroxyethyl-4-hydroxy methamphetamine</td>
<td>Caffeine, lorazepam, midazolam, metabolite of nicotine</td>
<td>Caffeine, fentanyl, lidocaine, lorazepam, midazolam, metabolites of nicotine and acetaminophen, quinine</td>
</tr>
<tr>
<td>0:40</td>
<td>33.1</td>
<td>1.6</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1:39</td>
<td>480</td>
<td>48</td>
<td>22.3</td>
<td></td>
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<tr>
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<td>308</td>
<td>47</td>
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</tr>
<tr>
<td>6:30</td>
<td>274</td>
<td>39</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* † Identification and quantification by a high-resolution LC-MS method.

† Identification by LC-MS toxicologic screening analysis.
receptors. On a receptor level, affinity has been reported for 5-hydroxytryptamine (5-HT) receptors (5-HT₂A and 5-HT₂B) and adrenoreceptors (α₂C and α₁A/2Ae) in vitro or in animal models.\textsuperscript{11,12}

Our patient showed prolonged systolic and diastolic hypertension unresponsive to benzodiazepines, probably because of increased vasoconstriction caused by complex mechanism, as described with MDMA and 5-APB in animal models.\textsuperscript{11,13} Accordingly, urapidil, which has primarily an α-receptor–blocking effect but also has a central sympatholytic effect,\textsuperscript{14} led to a decrease of blood pressure in our patient.

ECG changes and increased troponin T level observed in our patient were consistent with myocardial ischemia caused by coronary vasoconstriction. To our knowledge, myocardial infarction has not yet been described with psychoactive benzofurans, but chest pain has been reported.\textsuperscript{5} However, MDMA-induced acute myocardial infarction has rarely been described.\textsuperscript{15,16}

The main metabolite of 5-MAPB is 5-APB,\textsuperscript{1} which was detected in plasma and urine, but it is also used recreationally.\textsuperscript{2} The metabolite:parent drug ratio after ingestion of an unknown dose of 5-MAPB was 0.2 to 0.3.\textsuperscript{1} In our patient, a ratio of 0.008 was found. Therefore, simultaneous consumption of 5-APB was unlikely. All detected substances other than 5-MAPB and its metabolites were used therapeutically in our patient or were beverage ingredients (Table). The positive amphetamine result in the immunologic urine toxicology screen was probably due to the amphetamine metabolites of 5-MAPB (Table).

The pharmacokinetic findings of 5-MAPB in this case, such as rapid onset of symptoms, the half-life of 6.5 hours, marked improvement after 14 hours, and plasma concentrations of 271 to 502 μg/L, resemble those of MDMA after comparable doses.\textsuperscript{10}

In conclusion, 5-MAPB appears to have pharmacokinetics comparable to those of MDMA and an acute toxicity profile similar to that of other psychoactive benzofurans and MDMA, with pronounced vasoconstriction. On the basis of the limited evidence available, management of patients presenting with acute toxicity related to 5-MAPB use should be similar to that used for other psychoactive benzofuran compounds.

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