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Case Report

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Mistaking 2C-P for 2C-B: What a Difference a Letter Makes

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Abstract

2,5-Dimethoxy-4(n)-propylphenethylamine (2C-P) is a synthetic phenethylamine derivative belonging to the large family of the so-called 2C drugs. These compounds can differ significantly in receptor affinity, potency and duration of action, and an important structural difference is the ligand in the 4 position of the phenyl ring, such as propyl in 2C-P or bromine in 2,5-dimethoxy-4-bromophenethylamine (2C-B). The 2C drugs are known for their hallucinogenic properties. We present a case of a 19-year-old male admitted to the emergency department with severe hallucinations, mydriasis, tachycardia, agitation and confusion following the use of a substance sold as 2C-B. By using liquid chromatography–mass spectrometry, the more potent substance 2C-P was detected and quantified. On the basis of two blood sample concentrations, the estimated elimination half-life was 19 h. This case report illustrates and discusses the differences in potency and duration of action of 2C drugs.

Introduction

Many novel psychoactive substances (NPS) have emerged in recent years in response to market trends and legislative control (1). In total, 81 NPS were detected for the first time in a single year in Europe in 2013 and 101 in 2014 (2). These novel substances (also known as "designer drugs", "research chemicals", "bath salts", "plant food" or "legal highs") are usually analogues or derivatives of controlled substances, produced in order to circumvent regulations and imitate the effects of the controlled drugs. NPS are typically not detectable with the usual drug of abuse immunoassays. They may therefore contribute to acute toxicities and medical complications, or even deaths, but escape detection. Small modifications in the chemical structure can dramatically change the pharmacological, psychoactive and toxicological properties, thus making it difficult to predict the signs and symptoms of acute intoxication with NPS (3–5). The 2C drugs are a subgroup of the phenethylamines, with primarily hallucinogenic properties, while the better-known alpha-methylphenethylamines (or short: amphetamines) include related substances such as amphetamine, methamphetamine and 3,4-methylenedioxymethamphetamie (MDMA) (3). We now present a case of intoxication with analytical confirmation of 2C-P (2,5-dimethoxy-4-(n)-propylphenethylamine), sold and thus mistaken as the less potent 2C-B (2,5-dimethoxy-4-bromophenethylamine).

Case Report

A 19-year-old male was brought to the emergency department (ED) by the police at 4 AM after being picked up at a party in a highly agitated and hallucinating state, reportedly having ingested alcohol and 2C-B (according to friends, ~25 mg). The patient was not violently aggressive on presentation but was shouting wildly and was using an aerosol can erratically. Due to his confusion, it was not possible to obtain a medical history. The patient was clearly hallucinating, repeated a sentence stereotypically, expressed fear, and was

unable to follow instructions. On clinical examination, the patient had tachycardia (122 beats/min), hyperactive bowel sounds and marked mydriasis with reduced pupillary reflexes. The rest of the cardiopulmonary, abdominal and neurological examination was unremarkable, with normal deep tendon reflexes and blood pressure and no diaphoresis. The electrocardiogram demonstrated sinus rhythm (heart rate 119 beats/min) with no signs of ischemia or QTc interval prolongation. Routine laboratory tests—including liver and renal parameters as well as a complete blood count on presentation—showed marked leucocytosis (19.6×10^9/L, normal range: 3.5–10) and a blood ethanol concentration of 20 mg/dL. Following administration of benzodiazepines and haloperidol i.v. (a total dose of 2 mg midazolam, 15 mg diazepam and 4 mg haloperidol), the patient gradually regained situational and spatial orientation, while temporal awareness remained impaired even at the time of discharge 11 h later. A urine drug screening test using a non-instrumental immunoassay (Triage TOX Drug Screen, Alere, Köln, Germany) was positive for tetrahydrocannabinol, opiates and benzodiazepines. The latter was attributed to previous iatrogenic administration of midazolam and diazepam. An additional analysis of serum samples using multi-dimensional liquid chromatography coupled with mass spectrometry (LC–MS) revealed 2C-P, while 2C-B, the compound initially thought to have been taken, was not detected. The concentrations of 2C-P in two samples taken at 4:15 and 9:30 AM, were 17.7 and 14.7 µg/L, respectively, consistent with an estimated plasma half-life of 19 h.

Discussion

The phenethylamine structure consists of a phenyl ring with an ethyl side chain leading to a terminal amine group (Figure 1). Among the phenethylamines, the 2C compounds are characterized by two methoxy groups, at positions 2 and 5 of the phenyl (Figure 1). Within this family, compounds differ in ligands at the fourth position on the phenyl ring, e.g. bromine in 2C-B or propyl in 2C-P. The different ligands at this position can lead to great differences in metabolism and receptor affinity (6).

2C drugs are especially known for their hallucinogenic properties, mediated by serotonin $5HT_{2A}$ receptor agonism (1, 3, 6). MDMA-like entactogenic effects, including increases in well-being, have also been reported (7).

Typical reported doses of 2C-B are 12–24 mg (1, 5). In clinical studies exploring the emotional effects of 2C-B, doses of 20 mg were used (7). Doses between 5 and 10 mg reportedly induce MDMA- and amphetamine-like stimulating effects, while doses between 10 and 20 mg lead to additional hallucinogenic effects (8, 9). Higher doses are known to cause unpleasant hallucinations and sympathomimetic effects, such as tachycardia, hypertension and hyperthermia (9, 10). The effects appear to peak at ~2 h, with a total duration of ~5 h (range: 2–8 h) (1, 5, 7, 9). The dose-response curve is reported to be steep for all the compounds of the 2C series (1), thus leading to a great risk of overdosing. The usual oral doses of 2C-P are reportedly lower and vary between 6 and 10 mg, with a reported duration of action of up to 10–16 h (5). According to user reports, oral doses of more than 16 mg are described as "extremely high" with "bad trips" lasting 24–36 h [drugs-forum, *2C-P Experiences*, available from: https://drugs-forum.com/forum/showthread.php?t=37905, Eve & Rave—Das Schweizer Drogenforum, *2C-P—Der mächtige Magus*, available from: http://www.eve-rave.ch/Forum/viewtopic.php?t=27501]. In a case series of five presentations following 2C-P use (11), the dose was not known in any of the cases but all patients presented with hallucinations, mydriasis and agitation, similarly to our case. Tachycardia (range: 119–149 beats/min) and leukocytosis (range: $12.4–24.2 \times 10^9$/L) were recorded in four of the five cases, while one patient presented with echolalia and was talking to himself, once again similar to our patient. Plasma concentrations (determined using different chromatographic processes) were below the limit of quantification (10 and 5 µg/L) in four of the patients, despite clinical signs of toxicity, and 20 µg/L in the fifth patient. However, 2C-P was detected in the urine of all five patients.

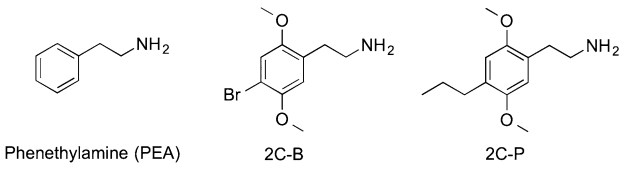

Figure 1. Chemical structures of phenethylamine, 2C-B and 2C-P.

It is not clear why 2C-P is more potent than 2C-B. The *in vitro* pharmacological receptor interactions profiles of the two compounds are quite similar, with similar binding and activation potencies at the main target, the serotonin $5\text{-}HT_{2A}$ receptor (6). Differences in blood-brain barrier (BBB) permeation and, in consequence, in concentrations in the central nervous system and access to the pharmacological target, could account for the difference in potency. Increased lipophilicity and smaller polar surface area (PSA) are both generally thought to improve BBB permeability (12). While the addition of a propyl residue to the 2C scaffold instead of bromide does not influence PSA, it does make 2C-P more lipophilic than 2C-B by a factor of about 4.5 (difference of 0.65 in the $\log_{10}$ octanol–water partitioning coefficient (logP), Table I).

A possible explanation for the difference in the duration of action may lie in differences in metabolism. While metabolism of several 2C drugs has been extensively studied in rats (13–16), less is known about human metabolism. An *in vitro* study revealed significant interspecies differences in formation of metabolites with 2C-B (10). Reported phase I activities for 2C drugs include oxidative demethylation, *N*-acetylation and deamination, the latter by monoamine oxidases (MAO) (10, 14, 17). The size of the C4-ligand has been associated with altered MAO isoenzyme affinity (17), which could be a possible explanation for the prolonged effect, as well as the polymorphic phenotype in acetylation in humans (18).

In our case, the analytical confirmation was first performed with a non-instrumental fluorescence immunoassay, a method using specific antibodies for the qualitative determination of the presence of distinct drug classes and/or major metabolites above the threshold concentrations in urine (19). Similarly to other immunoassays, the test can be performed without special knowledge or equipment and rapidly delivers results. However, it has limitations, e.g. cross reactivity with other compounds. This is a possible explanation for the positive result for opiates in our case, as there was neither

Table I. Calculated physicochemical properties of 2C-B and 2C-P

	2C-B	2C-P
Molecular mass (Da)	259.0	223.2
AlogP	1.973	2.623
PSA (Å^2)	44.48	44.48

AlogP, computed logP according to Ghose-Crippen fragment-based algorithm; PSA, polar surface area.

clinical evidence nor report of opiate use nor confirmation in the LC–MS, and cross reactivity (e.g. with acetaminophen/ codeine preparations) has been described for this assay (20). Further limitations of the immunoassay include the facts that the results are only qualitative (positive/negative), a suspected positive result does not indicate the level of intoxication (i.e. cannabis can be detected in samples days beyond the acute intoxication), and the method cannot detect most of the NPS, such as 2C drugs. Thus, the immunoassay provides only a preliminary result and other methods (e.g. GC–MS, LC–MS-MS) are needed for confirmation (19). In our case, the LC–MS not only revealed the presence of 2C-P and excluded 2C-B in blood samples, but also allowed quantification of the concentrations and an estimate of the elimination half-life. To our knowledge, this is the first published estimation of the elimination half-life of 2C-P. However, this estimation only represents an apparent serum half-life in one individual and should not be used as an estimated half-life in other contexts.

Treatment of intoxications with NPS is mainly supportive (3, 21). Recommendations include fluid replacement, as well as benzodiazepines or antipsychotic agents, such as haloperidol, though the latter should not be used as a single agent. In case of hypertension, the use of beta-blockers without alpha-blocking agents is also discouraged, because unopposed alpha-adrenergic stimulation can result in further increases in blood pressure. In cases of severe hyperthermia, physical cooling and relaxation may be needed (3).

In summary, our patient presented with hallucinations and acute sympathomimetic toxidrome after consuming 25 mg of 2C-P (usual doses 6–10 mg, duration of action 10–16 h, longer at higher doses), mistaken for the better-known and shorter-acting 2C-B (usual doses 10–20 mg, duration of action 2–8 h).

Conclusions

Our case presents the clinical findings of an analytically confirmed intoxication with 2C-P and is the first reported case with documentation of the elimination half-life of this compound. Furthermore, our case illustrates some of the risks in connection with NPS, as use of apparently similar but more potent substances can lead to more severe intoxication. Moreover, our case highlights the importance of the use of specialized analytical methods in cases of suspected NPS use.

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