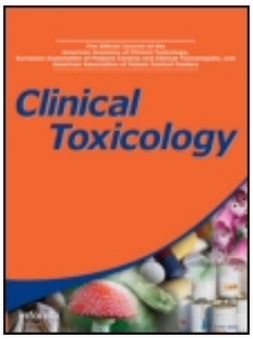

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CASE REPORT

Multiorgan failure from 1-benzylpiperazine ingestion – legal high or lethal high?

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Introduction. 1-Benzylpiperazine (BZP) is synthetic stimulant. It was legal and openly sold in New Zealand before October 1, 2008. Two cases of life-threatening toxicity associated with BZP use are reported in detail in this article. *Cases.* Case one describes an adult female who developed status epilepticus, hyperthermia, disseminated intravascular coagulation, rhabdomyolysis, and renal failure associated with a BZP ingestion. Case two developed a similar pattern of toxicity from the combined use of BZP and 3,4-methylenedioxy-*N*-methylamphetamine. Both cases required prolonged hospital care but survived. *Discussion.* There have been reports of deaths associated with the combined ingestion of BZP and 3,4-methylenedioxy-*N*-methylamphetamine. The effects may possibly be synergistic when co-ingested. Case one suggests that BZP alone has the potential to cause serious sympathomimetic toxicity.

Keywords Benzylpiperazine; BZP; Party pills

Introduction

1-Benzylpiperazine (BZP) is a synthetic stimulant. It was not scheduled as a drug of abuse in New Zealand (NZ) so was legal by default. It was openly sold and marketed as a safe, legal alternative to illicit recreational drugs. A paucity of human adverse reaction reports was construed by proponents as evidence of safety for human consumption. BZP is now illegal in NZ, the United States, and Australia but still legal in many other western countries.

Prior research had indicated that it was a stimulant with a similar pharmacodynamic profile to dexamphetamine, so therefore at potential risk of similar abuse and toxicity. A previous study reported the mild-to-severe adverse effects of recreational BZP use.[1] Two cases of life-threatening toxicity are reported in detail in this article.

Case one

A 19-year-old woman with a history of schizophrenia and substance abuse was taken into police custody at 9:00 h after being found in a confused state at a local park. Police assumed she was intoxicated and she was taken to their holding cells to sober up. Around 15:30 h guards noticed she was making unusual leg movements. A Police Surgeon assessed her and diagnosed tonic clonic seizure activity. An ambulance was called and she subsequently arrived at the Emergency Department (ED) at 17:35 h.

On arrival in the ED she displayed generalized tonic clonic activity. She was normotensive at 142/92 mmHg but was tachycardic 151 BPM, hyperthermic 40.2°C, and tachypnoeic RR 32 RPM. Her pupils were large at 7 mm and sluggishly reactive. Bleeding from the mouth and nose was evident. She was diaphoretic, had very dry mucous membranes, had clear breath sounds on auscultation, and had no audible bowel sounds. Between seizures she had 3 to 4 beats of ankle clonus. Intravenous benzodiazepines did not stop seizure activity.

She was intubated with thiopentone, fentanyl, and suxamethonium and then paralyzed with rocuronium. Urine and blood were drawn for later analysis. Initial blood gas on 100% oxygen demonstrated a significant metabolic acidosis (pH 7.14, PCO_2 40 mmHg, PO_2 200 mmHg, HCO_3 13.4 mmol/L, base excess −15). She was initially hyperglycemic (11.8 mmol/L), but became hypoglycemic for the next 24 h and required a dextrose infusion.

An electrocardiogram showed a sinus tachycardia of 110 with QT interval of 413 min and QTc 559 min. A computed tomograph of the head showed no brain lesion or hemorrhage. Biochemistry showed rhabdomyolysis with creatinine kinase (CK) of 27,601 IU/L and an acute renal injury with a creatinine of 0.27 mmol/L and urea of 16.5 mmol/L. Basic

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metabolic investigations were sodium 143 mmol/L, potassium 3.9 mmol/L, chloride 110 mmol/L, osmolality 318 mmol/kg, protein 79 g/L, albumin 46 g/L, bilirubin 23 umol/L, ALP 163 U/L, GGT 29 U/L, AST 1,144 U/L, and ALT 570 U/L.

Hepatic insult became apparent with ALT peaking at 3,461 U/L and AST at 5,245 U/L. She developed disseminated intravascular coagulation (INR 2.9, APTT 82 s, fibrinogen 0.5 g/L, platelets 23×10^9/L, and D-dimer > 1,000 mcg/L). Progressive rhabdomyolysis and renal failure were treated with crystalloid volume loading. Her creatinine peaked at 0.42 mmol/L 5 days post admission and later normalized without need for renal replacement therapy. Her CK peaked at 50,657 U/L 5 days post admission. She required infusions of fresh frozen plasma and platelets to treat her coagulopathy, which persisted for a further 10 days. Her INR peaked at 4.2.

Blood and urine were taken 10 h after she had been taken into custody. Urine immunoassay screen revealed a strong color change for amphetamine-type compounds (cross reaction from BZP), metabolites of benztropine (one of her long-term medications), as well as caffeine and nicotine. The screening panel (EMIT®; DAU kit, Dade-Behring, Newark, Delaware, USA) comprised immunoassays (with detection limits) for amphetamine-type compounds (300 ng/mL), barbiturates (200 ng/mL), benzodiazepines (200 ng/mL), cannabinoids (50 ng/mL), cocaine metabolites (300 ng/mL), ethanol (24 mg/dL), methadone (300 ng/mL), and opiates (300 ng/mL). Thin-layer chromatography was also used to cover antipsychotics, antidepressants, anticonvulsants, opioids, and analgesics to varying degrees of sensitivity. These tests for drugs of abuse and ethanol were negative.

Plasma BZP level was measured using solid-phase extraction followed by derivatization and analysis by gas chromatography mass spectrophotometry. Plasma 1-BZP was 0.2 mg/L. Gas chromatography mass spectrophotometry did not show any other amphetamine-like drugs other than BZP.

The patient initially had no motor responses for 7 days. Some neurological improvement was then observed with motor responses to painful stimuli. She remained febrile and tachycardic for over 10 days with intermittent muscle rigidity unresponsive to boluses of benzodiazepines and orphenadrine. Her blood pressure was labile. Initial hypotension gave way to hypertension in the range of 160/100 mmHg by day 6. Intravenous bolus dosing of clonidine 30 mcg was used, then a higher dose infusion was started. Clonidine totaling 300–870 mcg/24 h was required to control blood pressure over 4 days.

She was extubated on day 9. At this stage she was nonverbal but able to obey commands and remained disorientated to time and place. A total of 30 days hospitalization was required in total including 11 days in the intensive care unit (ICU). After 5 months she underwent psychometric testing to assess for long-term neurological sequelae. Significant disability in the areas of working memory and speed of processing were detected on the Weschler Adult Intelligence Scale (3rd Ed) when compared with a test taken 4 years previously. Further therapy and follow-up testing were planned.

Case two

A 22-year-old man was at a local party and allegedly consumed 3–4 "party pills" containing 1-BZP. After 2 h he collapsed and had a brief seizure. He was taken to the ED of a small peripheral hospital with hyperthermia T 41.4°C, tachycardia 180 BPM, muscle rigidity, hypotension 73/31 mmHg, and a Glasgow Coma Score of 6/15. He was intubated, paralysed, and cooled before transport to a tertiary referral hospital.

On arrival to the ICU he remained hyperthermic and tachycardic. He was diaphoretic, had dilated pupils at 7 mm, and dry mucous membranes. He had significant metabolic acidosis (pH 7.19, PCO_2 51 mmHg, PO_2 71 mmHg, HCO_3 19.3 mmol/L, base excess −9), coagulopathy (INR 3.1, APTT 51 s, platelets 23×10^9/L), rhabdomyolysis (CK 32,263 IU/L), and an acute kidney injury with a creatinine of 0.15 mmol/L. Biochemistry results were sodium 144 mmol/L, potassium 3.5 mmol/L, chloride 116 mmol/L, albumin 37 g/L, bilirubin 4 umol/L, ALP 75 U/L, GGT 22 U/L, AST 247 U/L, and ALT 55 U/L. He was treated with large volumes of crystalloid to maintain urine output. He was also noted to be persistently hypoglycemic requiring a dextrose infusion for 24 h. He was given 8 units of fresh frozen plasma to treat his coagulopathy over the first 36 h.

Initial blood toxicology at 3 h post admission revealed a 1-BZP level of 2.23 mg/L and a 3,4-methylenedioxy-*N*-methylamphetamine (MDMA) level of 1.05 mg/L. Repeat sampling at 9 h post admission showed a 1-BZP level of 0.1 mg/L and MDMA was just detectable. No other illicit drugs or ethanol were detected on urine screen.

Liver function tests were initially normal but hepatic injury became evident later with an ALT peaking at 5,296 U/L and bilirubin peaking at 76. Coagulopathy and hypoglycemia continued for 4 days. He had ongoing problems with hyperthermia, tachycardia, hypertension, and rigidity for 16 days. CK peaked on days 2 and 14 at 56,717 and 11,418 IU/L, respectively. He had three doses of cyproheptadine (4 mg), which had no apparent effect on his dysautonomia. His renal injury resolved without need for dialysis.

The patient's blood pressure began to rise at 24 h to 160/80 mmHg. Blood pressure remained stable at this level till day 4 when it rose to 190/90 mmHg. A glyceryl trinitrate infusion was commenced and had a transient effect but pressures rose to 195/80 mmHg by day 6. Bolus dosing of nasogastric labetalol (100 mg t.d.s. for 3 days) settled the hypertension. There was another delayed hypertensive spike with pressures of 195/105 mmHg on day 16. Clonidine was used with good effect at doses of 900–1,800 mcg/24 h for 4 days then the blood pressure normalized.

His course was complicated by ileus, lung injury, and slow neurological recovery. He had a tracheostomy at day 16 because of slow weaning from ventilation. He was in the ICU for 19 days and had a total of 25 days in hospital. On discharge, his renal, hepatic, and lung injuries had resolved, and he had ongoing mild sequelae of brain injury. At 3 months he

had not had a formal cognitive assessment but had returned to work part time.

Discussion

1-BZP is a piperazine-based central nervous system stimulant and is classified as a synthetic designer drug. In many countries it has not formally been scheduled, so by default is not illegal. Distributors have marketed BZP as a "legal high." BZP is similar in structure and effect to amphetamine.[2] One study showed that experienced stimulant users could not distinguish it from dexamphetamine.[3]

It has a high adverse effect profile including nausea, vomiting, tachycardia, anxiety, and confusion. Serious effects reported to date have been toxic seizures, metabolic acidosis hyponatremia, renal injury, and toxic psychosis.[4] Although QTc prolongation has been observed, no incidences of arrhythmia have been encountered or reported. Experienced users report a slow onset of action. Pharmacokinetic studies show that after oral dosing BZP takes 75 min to reach its maximum plasma concentration (C_{max}).[5] Some naive users are disappointed by the early lack of effect and take further doses before the C_{max} is reached – thereby increasing the risk of toxicity.

The two cases described are the first detailed reports of severe hyperthermia, central nervous system toxicity, and multi-organ failure associated with BZP ingestion. Rhabdomyolysis, hepatotoxicity, and clinically significant coagulopathy are also effects that have not been previously reported. Both cases were not initially expected to survive based on increasing physiological derangement resistant to treatment.

Toxicology confirmed the presence of BZP in both patients. Case one had a low absolute level (0.2 mg/L) probably because of the delay of at least 9 h between ingestion and presentation to hospital. BZP in low oral dosing appears to have elimination half-life of approximately 5.5 h.[5] Plasma levels were measured in a cohort of 96 patients who attended hospital for adverse effects from self-reported recreational BZP use.[1] Levels ranged from 0.0 to 6.29 mg/L. Those with levels between 0.0 and 0.50 mg/L tended to report symptoms of anxiety, palpitation, and vomiting. Agitation, anxiety, and confusion were more frequent above 0.5 mg/L. Seizures were associated with levels as low as 0.05 mg/L but increased with higher levels and were consistent when plasma levels were above 2.15 mg/L.

In case two MDMA was also present at a lesser concentration. The contribution of MDMA is difficult to estimate. Plasma levels do not correlate well with toxicity. A level of 1.05 mg/L is generally accepted to be in the neurotoxic range and falls within the range seen post mortem in MDMA-associated deaths (0.11–2.1 mg/L).[6] However, levels as high as 0.84 mg/L have been recorded in clinically asymptomatic party-goers.[7]

Case one could be consistent with sympathomimetic poisoning syndrome arising from BZP alone. The differential for case one would have included serotonin syndrome and possibly neuroleptic malignant syndrome. The patient was known to have been on olanzapine and benztropine but was also known to be noncompliant with dosing. Olanzapine was not detected in urine testing, and there was no past history of neuroleptic malignant syndrome. Metabolites of benztropine were only a faint positive on urine immunoassay. An interaction between benztropine and BZP is possible with overlap of anticholinergic and sympathomimetic features, but causality from BZP alone seems more plausible.

In case two the interaction of BZP and MDMA is likely to have precipitated severe hyperthermia with resultant multiorgan failure. Severe serotonin toxicity was also considered in his differential. In animal studies BZP is known to increase central synaptic concentrations of dopamine, serotonin (5-HT), and noradrenaline by stimulated release and uptake inhibition.[8,9] Serotinergic excess was possibly a contributor to toxicity in these cases but difficult to clinically differentiate from pure sympathomimetic toxicity. Core temperatures above 40°C are a marker of severity and prognostic indicator in both sympathetic and serotinergic toxicities.[10]

The combination of BZP and MDMA in case two could have caused additive or synergistic toxicity. Case fatalities associated with the recreational use of BZP with MDMA have been reported from Sweden[11]and Zurich.[12] In recent news media reports, BZP co-ingested with MDMA has been linked to sudden deaths in the United Kingdom[13,14] and Canada.[15] BZP has also been marketed as "legal highs" in these countries. Together these reports raise further concerns about toxic synergism from these stimulants. The legal status of BZP is currently under review in both these countries.

Addendum

On August 25, 2009, the Home Secretary for the United Kingdom announced that BZP would be categorized as a Class C drug, thereby banning its sale and possession. The decision was based on advice from the government's Advisory Council on the Misuse of Drugs. Accessed at http://news.bbc.co.uk/2/hi/uk_news/8061693.stm

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

References

1. Gee P, Gilbert M, Richardson S, Moore G, Paterson S, Graham P. Toxicity from the recreational use of 1-benzylpiperazine. Clin Toxicol (Phila) 2008; 46(9):802–807.
2. Bye C, Munroe-Faure A, Peck A, Young P. A comparison of the effects of 1-benzylpiperazine and dexamphetamine on human performance tests. Eur J Clin Pharmacol 1973; 6:163–169.
3. Campbell H, Cline W, Evans M, Lloyd J, Peck A. Comparison of the effects of dexamphetamine and 1-benzylpiperazine in former addicts. Eur J Clin Pharmacol 1973; 6:170–176.
4. Austin H, Monasterio E. Acute psychosis following ingestion of "rapture". Australasian Psychiatry 2004; 12(4):406–408.
5. Antia U, et al. Pharmacokinetics of "party pill" drug *N*-benzylpiperazine (BZP) in healthy human participants. Forensic Sci Int 2009; 186(1):63–67.
6. Lynton RC, Albertson TE. Amphetamines and designer drugs. In: Dart RC, ed. Medical Toxicology. 3rd ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 2004:1075.
7. Rodney J, Irvine RJ, Keane M, Felgate P, McCann UD, Callaghan PD, White JM. Plasma drug concentrations and physiological measures in "Dance Party" participants. Neuropsychopharmacol 2006; 31:424–430. doi:10.1038/sj.npp.1300896
8. Baumann M, Clark R, Budzynski A, Partilla J, Blough B, Rothman R. *N*-substituted piperazines abused by humans mimic the molecular mechanism of 3,4-methylenedioxymethamphetamine (MDMA, or "Ecstasy"). Neuropsychopharmacology 2005; 30:550–560.
9. Tekes K, Tóthfalusi L, Malomvölgyi B, Hermán F, Magyar K. Studies on the biochemical mode of action of EGYT-475, a new antidepressant. Polish J Pharm Pharm 1987; 39:203–211.
10. Rusyniak D, Sprague J. Toxin-induced hyperthermic syndromes. Med Clin North Am 2006; 89(6):1277–1296.
11. Wikström M, Holmgren P, Ahlner J. A2 (*N*-benzylpiperazine) a new drug of abuse in Sweden. J Anal Toxicol 2004; 28:67–70.
12. Balmelli C, Kupferschmidt H, Rentsch K, Schneemann M. [Fatal brain edema after ingestion of ecstasy and benzylpiperazine]. Dtsch Med Wochenschr 2001; 126(28–29):809–811.
13. Wright E, Davies R, Warne C. New killer drug alert as mortgage adviser dies. Sheffield Telegraph 2009; June 16. http://www.sheffield-telegraph.co.uk/news2/New-killer-drugalert.5251039.jp. Accessed 8 January 2010.
14. Coroner calls for law change after man's "party drug" death. Nottingham Evening Post 2009; May 28. Accessed at http://www.thisisnotting-ham.co.uk/news/Coroner-calls-law-change-man-sparty-drug-death/article-1030905-detail/article.html#StartComments. Accessed 8 January 2010.
15. Hammer K. After club-goer's death, Health Canada looks at BZP. Globe and Mail 2008; Thursday, July 10.