Clinical Toxicology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ictx20

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To cite this article: Rowena Penafiel, David Yoo, Claire Turner, Jared A. Brown, Catherine McDonald, Jason Tran, Vanessa Shaw & Darren M. Roberts (2023) Toxicokinetics of thebaine in those consuming non-food grade poppy seeds as a tea, Clinical Toxicology, 61:9, 644-648, DOI: 10.1080/15563650.2023.2271163

To link to this article: https://doi.org/10.1080/15563650.2023.2271163

Published online: 21 Nov 2023.

CLINICAL TOXICOLOGY
2023, VOL. 61, NO. 9, 644–648
https://doi.org/10.1080/15563650.2023.2271163

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CLINICAL RESEARCH

Toxicokinetics of thebaine in those consuming non-food grade poppy seeds as a tea

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ABSTRACT

Introduction: Thebaine is an alkaloid in poppy seeds that is neurotoxic to animals. Data on its clinical effects and toxicokinetics in people are minimal. In 2022, poppy seeds high in thebaine entered the Australian food market, and people consuming tea made from these poppy seeds developed poisoning.

Methods: Three patients who drank poppy seed tea and developed neuromuscular toxicity consented for thebaine to be quantitated in serial blood samples. Blood samples were analyzed by liquid chromatography with high-resolution mass spectrometry.

Results: ***Case 1:*** A man in his 60s presented with drowsiness, vomiting, malaise and myoclonus. He developed metabolic acidosis with hyperlactataemia, acute kidney injury requiring haemodialysis, convulsions, rhabdomyolysis, and was in the hospital for 18 days. The admission thebaine blood concentration was 2.1 mg/L, and the apparent elimination half-life was 14.8 h. ***Case 2:*** A man in his 30s presented with myoclonus, rigidity, vomiting, and dizziness. He developed metabolic acidosis with hyperlactataemia, acute kidney injury, and myalgias. The admission thebaine blood concentration was 4.1 mg/L, and the apparent elimination half-life was 11.6 h. ***Case 3:*** A man in his 30s presented with myoclonus, rigidity, clonus, diaphoresis, and abdominal pain. The admission thebaine blood concentration was 2.2 mg/L, and the apparent elimination half-life was 8.3 h.

Discussion: Neuromuscular toxicity, metabolic acidosis with hyperlactataemia, acute kidney injury, and gastrointestinal symptoms were prominent clinical features in these patients after drinking poppy seed tea. Effects persisted for days, and all survived, despite thebaine concentrations far exceeding those in published forensic reports, although human data are sparse. Compared to rats, the thebaine apparent elimination half-life is much longer in humans who develop symptoms at lower concentrations.

Conclusions: Despite relatively high thebaine blood concentrations and moderate to severe poisoning, outcomes were favourable with early presentations. It is possible that acute kidney injury prolongs the apparent elimination half-life of thebaine.

ARTICLE HISTORY
Received 11 August 2023
Revised 9 October 2023
Accepted 10 October 2023

KEYWORDS
Thebaine; poppy; convulsions; strychnine; pharmacokinetics; poisoning

Introduction

The poppy plant *Papaver somniferum* and related species produce a latex residue containing several alkaloids, notably morphine and codeine, and other alkaloids to lesser extents, depending on the *Papaver* species and variant [1]. These plants have commercial uses in the food and pharmaceutical industries. A *Papaver somniferum* mutant known as *top1* yields high amounts of thebaine and oripavine and low amounts of morphine and codeine and is cultivated for the synthesis of buprenorphine and oxycodone [2].

Animal studies indicate that thebaine is a neurotoxic opium alkaloid with strychnine-like actions without opioid effects [3], with an elimination half-life of 1.1 h in rats [4]. Human data on thebaine are limited, but it is considered to have contributed to deaths, and thebaine persists in urine for up to 72 h after the ingestion of baked goods containing poppy seeds [5].

In 2022, non-food grade poppy seeds high in thebaine entered the human food supply chain in Australia. From October 2022, more than 40 people drinking tea made from poppy seeds developed clinically significant symptoms, including muscle cramps and spasms, convulsions, acute kidney injury, rhabdomyolysis, cardiac arrest, and death [6,7]. Cases were reported from across Australia, leading to a national recall of batches containing non-food grade poppy seeds.

We describe the clinical manifestations and toxicokinetics of thebaine in three patients with thebaine poisoning after consuming poppy seed tea. These data are compared to existing data from animal and human studies.

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Methods

We identified patients with thebaine poisoning using clinical criteria of neuromuscular excitation (myoclonus, rigidity) after consuming poppy seed tea. Thebaine poisoning was confirmed after excluding other differential diagnoses and performing specific toxicological testing. Testing of blood and urine samples was undertaken as clinically indicated.

Three patients in this cluster had two or three measured thebaine concentrations. We obtained informed consent from patients for reporting their clinical and laboratory findings.

We measured opium alkaloids in whole blood using either ultra-performance liquid chromatography quadrupole time of flight mass spectrometry (UPLC-QTOF-MS) or ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS). The limits of detection are thebaine 0.01 mg/L, morphine 0.002 mg/L, codeine 0.002 mg/L, papaverine 0.01 mg/L, noscapine 0.01 mg/L, and laudanosine 0.001 mg/L.

In each patient, we determined the maximum concentration observed and plotted subsequent data on a semi-logarithmic graph to determine if changes in concentration were first order. The method used to calculate the apparent elimination half-life depended on the number of samples with quantifiable thebaine. For multiple samples, the apparent elimination half-life and 95% confidence interval were calculated using a monoexponential decay using GraphPad Prism version 9.1.1 for Windows, GraphPad Software, San Diego, CA, USA. If thebaine concentrations were available in only two samples, the apparent half-life ($T_{1/2}$) was calculated using the equation $\ln(C_t) = \ln(C_o) - ket$, then $T_{1/2} = \ln 2/ke$. Here, C_o is the initial concentration, and C_t is the concentration after time t when elimination occurs with a rate constant of *ke*.

Opium alkaloids were measured in retail poppy seeds in samples of both recalled and non-recalled products available in New South Wales at the time.

The Sydney Children's Hospitals Network Human Research Ethics Committee approved the inclusion of patients identified by the New South Wales Poisons Information Centre (Approval number 2021/ETH00165). Sydney Local Health District Human Research Ethics Committee approved the inclusion of patients admitted to Royal Prince Alfred Hospital (Approval number LNR/18/RPAH/651).

Results

Of the approximately 40 patients identified across Australia with thebaine poisoning [7], multiple blood samples were available in three patients. The maximum thebaine concentration was noted at the first sample available in each case (Figure 1).

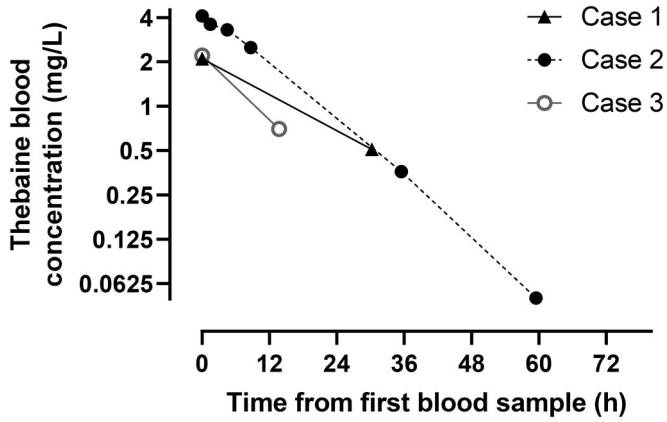

Figure 1. Concentration-time curves of thebaine in three patients with serial samples.

Case 1

A man in his 60s developed drowsiness, nausea, vomiting, malaise and myoclonus, resulting in a fall within hours of drinking poppy seed tea. The tea was made by adding 500 g poppy seeds to 1 L warm water with tartaric acid. He presented to the hospital 5 h post-ingestion and was noted to have a metabolic acidosis with hyperlactataemia (lactate concentration 11.5 mmol/L), acute kidney injury (creatinine concentration 142 µmol/L [1.61 mg/dL]) and a left shoulder fracture and dislocation requiring operative repair. At 7 h post-ingestion, he had a generalized tonic-clonic convulsion and was administered intravenous midazolam 5 mg. He was intubated, sedated with propofol and fentanyl, commenced on an epinephrine infusion for hypotension and transferred to the intensive care unit until extubation on day 3. His admission was complicated by oliguric acute kidney injury (peak creatinine concentration 705 µmol/L [7.97 mg/dL]) treated with continuous kidney replacement therapy on days 2–4 and haemodialysis on three occasions until day 9 and rhabdomyolysis (peak creatine kinase activity of 18,657 U/L). Following rehabilitation for the fracture, he was discharged on day 18. At follow-up, more than 6 months post-ingestion, persistent chronic kidney disease (eGFR 60 mL/min/1.73 m^2) with no residual neurotoxicity was found.

Of 13 blood samples analyzed over 11 days, thebaine was detected in only two samples. The thebaine blood concentration 11 h post-ingestion was 2.1 mg/L, which decreased with an apparent elimination half-life of 14.8 h. The codeine concentration measured on the admission blood sample was 0.04 mg/L; morphine was not detected, laudanosine was present (<0.05 mg/L) and codeine-6-glucuronide, morphine-3-glucuronide, fentanyl and hydrocodone were also present. These other substances produced only a minor contribution to the presentation and reflected lesser components of the poppy plant or metabolites and fentanyl administration for intubation.

Analysis of a sample of poppy seed tea used by this patient showed a thebaine concentration of 830 mg/L, a codeine concentration of 17 mg/L and a morphine concentration of 2 mg/L.

Case 2

A man in his 30s presented with myoclonus and rigidity, episodes of tonic-clonic activity lasting 15–30 s with preserved consciousness, nausea, vomiting, dizziness, tachycardia, and

nystagmus. This involuntary activity was precipitated by the slightest noise (e.g., birds tweeting) or touch. Admission blood samples showed metabolic acidosis with hyperlactataemia (lactate concentration 5.8 mmol/L) and acute kidney injury (serum creatinine concentration 123 μmol/L [1.39 mg/dL]). A history of ingesting poppy seed tea was not provided at the time, and neurological review and investigations, including computed tomography of the brain and angiogram, were normal. Public health messaging to healthcare workers and the public about the emerging cluster of poppy seed tea poisonings prompted a review of the history, which confirmed that the patient had consumed poppy seed tea on three occasions over the preceding 24 h. The patient mixed 1 kg poppy seeds with 750 mL water and 250 mL lemon juice; symptoms did not develop until the final 250 mL of the 1 L solution was consumed. He was treated with oral diazepam. Overall clinical outcomes included myalgia and constipation. The peak serum creatinine concentration on day 2 was 186 μmol/L (2.1 mg/dL), and the creatine kinase activity was 855 U/L; both had resolved by day 4 when he was discharged home.

Thebaine was quantitated in all six samples sent for analysis. The thebaine blood concentration 4 h after the last ingestion was 4.1 mg/L, with an apparent elimination half-life of 11.6 h (95% CI: 9.2–14.5 h). The admission codeine concentration was 0.11 mg/L; morphine was not detected, but laudanosine (<0.05 mg/L), codeine-6-glucuronide, morphine-3-glucuronide, morphine-6-glucuronide, and hydrocodone were also present. These other substances had a minor contribution to the presentation and reflected lesser components of the poppy plant or metabolites.

Case 3

A man in his 30s presented to the hospital with muscle rigidity and cramping with myoclonus, with body arching, inducible clonus, diaphoresis, tachycardia, back and abdominal pain after ingesting poppy seed tea earlier that day. He had mixed 200 g poppy seeds with four cups of hot water with added lemon juice. He performed this routine 3–4 times/day and purchased the current stock of poppy seeds 1–2 days earlier. Admission blood samples showed respiratory alkalosis (pH 7.5, PCO_2 28 mmHg [3.73 kPa]), a lactate concentration of 3.2 mmol/L and normal kidney function (serum creatinine concentration 71 μmol/L [0.8 mg/dL]). He was treated with intravenous midazolam, intravenous morphine and fentanyl, and oral diazepam and transferred to another hospital for admission to the intensive care unit overnight. He was transferred to the ward the next day for weaning from oral diazepam until discharge on day 5.

Of the three blood samples analyzed, thebaine was detected in two samples. The admission thebaine blood concentration was 2.2 mg/L with an apparent elimination half-life of 8.3 h. On the admission blood sample, the codeine concentration was 0.36 mg/L, and morphine concentration was 0.06 mg/L; laudanosine (<0.05 mg/L), codeine-6-glucuronide, morphine-3-glucuronide, morphine-6-glucuronide, oxycodone and hydrocodone were also present. These other substances all made a minor contribution to the presentation and largely reflected lesser components of the poppy plant or metabolites.

As only two quantified blood samples were reported in Cases 1 and 3, there is some uncertainty about the calculated apparent half-life. On subsequent review of the chromatogram, it was possible to estimate the concentration in a third sample, although this concentration was below the limit of detection, which adds uncertainty to its reliability. Nevertheless, incorporating this third sample and performing a regression analysis yielded similar results. In Case 1, the apparent half-life was 14.6 h (95% CI: uncertain lower limit to 31.3 h), and in Case 2, the apparent half-life was 8.3 h (95% CI: 8.1–8.9 h).

Opium alkaloids measured in retail poppy seeds

Analyses noted extremely high amounts of thebaine compared to other opium alkaloids in the recalled products compared to non-recalled products (Figure 2).

Discussion

We report three cases of confirmed thebaine poisoning following ingestion of a tea made with non-food grade poppy seeds. All patients had neuromuscular excitation. In addition, one patient had severe toxicity (fractures, convulsions, hyperlactaemia and oliguric acute kidney injury) and required admission to the intensive care unit); two had moderate toxicity, one was admitted to the intensive care unit and the other to a medical ward.

A clear dose-toxicity relationship was not observed in these patients. However, each had differing exposures and timing of blood testing. The larger case series reporting on this cluster noted that convulsions, acute kidney injury, metabolic acidosis, and cardiac arrest were potentially dose-dependent [7]. The elimination half-life of thebaine varied between 8.3 h and 14.8 h, which is sufficiently long to allow thebaine to accumulate with repeated doses, as noted in Case 2 and possibly Case 3. A potential contributor to the interindividual variability in elimination half-life is kidney function, given that half-life was longest in the patient with

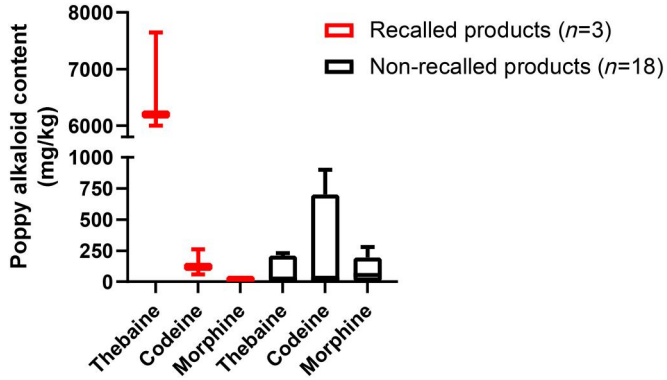

Figure 2. Opium alkaloids in recalled and non-recalled poppy seed retail products available in New South Wales at the time of the cluster. Box-and-whiskers graph showing median, interquartile range and range of concentrations.

the most severe acute kidney injury and shortest in the patient with normal kidney function.

Animal studies provide toxicological insights into thebaine. In rats, thebaine 5 mg/kg subcutaneously resulted in a maximum plasma concentration of 1 mg/L with no apparent clinical effects and an elimination half-life of 1.1 h [4]. In contrast, thebaine 20 mg/kg subcutaneously induced subconvulsive spasms, jerking and convulsions, indicating a dose-response relationship for thebaine [4]. Conjugated metabolites of thebaine increased in the plasma over 24 to 48 h post-administration, and 17% of the dose was renally excreted unchanged at 96 h [4]. Rats appear less susceptible to thebaine toxicity compared to humans, given lesser signs of toxicity at similar thebaine concentrations noted in this and our accompanying report [7] and a shorter elimination half-life in rats [4]. The relatively small proportion of thebaine eliminated unchanged in the urine of rats predicts that changes in kidney function do not have a major impact on thebaine elimination half-life [8]. However, non-metabolized thebaine predominates in the urine of monkeys administered thebaine subcutaneously [9], suggesting differences in pharmacokinetics between rodents and primates.

There are minimal clinical toxicology data for thebaine in humans. A United States study measuring thebaine in the urine of asymptomatic volunteers ingesting baked goods (strudel or bagel) purchased from a store noted mean urine concentrations approaching 80 mg/L, which peaked around 6 h post-ingestion [5]. We estimated the mean apparent elimination half-life of thebaine using these urine concentrations and non-linear regression according to the methods described in this report, yielding 10 h for the strudel and 5 h for the bagel with very wide 95% confidence intervals. Reasons for the differences in urine thebaine concentrations and elimination half-lives between the two baked products could not be ascertained from the information provided. However, despite the limitations of performing pharmacokinetic calculations using spot urine concentrations (e.g., changing hydration status), the thebaine apparent elimination half-lives calculated from these data (5 h–10 h) approximate those in our clinical series (8 h–15 h). The high urine thebaine concentrations noted in this volunteer study [5] and another [10] may indicate that similar to monkeys [9], a much higher proportion of thebaine is renally eliminated in humans, compared to 17% noted in rats [4].

While these data lead us to speculate that reduced kidney function may prolong the thebaine elimination half-life, as noted in our cases, other factors may also contribute to interindividual differences in thebaine persistence in urine [5,10]. The longer elimination half-lives noted with these human data indicate that people are at increased risk of thebaine accumulation with repeat dosing, as noted in Case 2 and possibly Case 3.

Sparse forensic reports have explored the contribution of thebaine to death. A 32-year-old man with a history of epilepsy consumed poppy extract while in a poppy field, suffered generalized seizures for 30 min, and later died [11]. His post-mortem thebaine concentrations were 0.1 mg/L in blood and 7.12 mg/L in urine [11]. These concentrations are much lower than concentrations in this cluster [7] and the volunteer study [5]. A 42-year-old man was found dead at home with evidence of consumption of poppy extract, and the post-mortem thebaine blood concentration was 0.07 mg/L [12]. Therefore, data from the 2022 cluster implies that thebaine had a minor contribution to these deaths. More data are required to explore the thebaine concentration-toxicity relationship in humans.

A limitation of this study is the relatively few thebaine concentrations available to better define the maximum thebaine concentrations and calculate the elimination half-life. This was due to delayed presentations by patients, reliance on samples collected for clinical use, which were relatively infrequent compared to the half-life of thebaine, and thebaine being undetected in many samples. As such, particularly for the two patients for whom only two concentrations were available, there is some uncertainty regarding the calculated half-life. However, the apparent half-lives calculated in these three patients are similar to those determined using urine data from another study [5], so they appear to be reasonable estimates.

Conclusions

Humans appear more susceptible to thebaine compared to rats, due to convulsions at lower concentrations and a longer elimination half-life. In comparison to prior forensic case reports, the serial blood thebaine concentrations were higher in survivors described here, which can inform future forensic investigations.

Acknowledgements

The Prescription, Recreational and Illicit Substance Evaluation (PRISE) program is a public health program providing access to extensive toxicology testing for cases of severe and unusual substance-related toxicity or clusters of overdoses in New South Wales. It is part of the collaborative state-wide rapid surveillance and public health response program to improve the health and well-being of people at risk or experiencing harms from alcohol and other drug use.

We are grateful to Anne McIntosh (Manager – Food Incident Response and Complaints, Department of Primary Industries) for coordinating the testing of poppy seeds and providing permission for the results to be shared.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

The authors reported there is no funding associated with the work featured in this article.

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