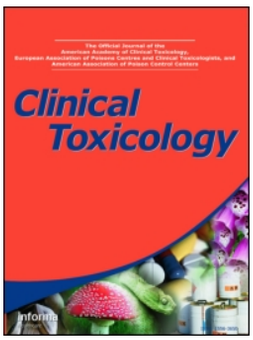

Clinical Toxicology

ISSN: 1556-3650 (Print) 1556-9519 (Online) Journal homepage: http://www.tandfonline.com/loi/ictx20

Chloroform ingestion causing severe gastrointestinal injury, hepatotoxicity and dermatitis confirmed with plasma chloroform concentrations

Dushan Jayaweera, Shawkat Islam, Naren Gunja, Chris Cowie, James Broska, Latesh Poojara, Michael S. Roberts & Geoffrey K. Isbister

To cite this article: Dushan Jayaweera, Shawkat Islam, Naren Gunja, Chris Cowie, James Broska, Latesh Poojara, Michael S. Roberts & Geoffrey K. Isbister (2016): Chloroform ingestion causing severe gastrointestinal injury, hepatotoxicity and dermatitis confirmed with plasma chloroform concentrations, Clinical Toxicology, DOI: 10.1080/15563650.2016.1249795

To link to this article: http://dx.doi.org/10.1080/15563650.2016.1249795

Published online: 28 Oct 2016.

CLINICAL TOXICOLOGY, 2016
http://dx.doi.org/10.1080/15563650.2016.1249795

Taylor & Francis
Taylor & Francis Group

SHORT COMMUNICATION

Chloroform ingestion causing severe gastrointestinal injury, hepatotoxicity and dermatitis confirmed with plasma chloroform concentrations

Dushan Jayaweera[a], Shawkat Islam[a], Naren Gunja[a], Chris Cowie[b], James Broska[b], Latesh Poojara[c], Michael S. Roberts[d,e] and Geoffrey K. Isbister[f]

[a]Department of Clinical Pharmacology & Toxicology, Western Sydney Health, Sydney, Australia; [b]Shimadzu Australasia, Sydney, Australia; [c]Intensive Care Unit, Blacktown Hospital, Sydney, Australia; [d]Therapeutics Research Centre, University of Queensland, Brisbane, Australia; [e]School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, Australia; [f]Clinical Toxicology Research Group, University of Newcastle, Newcastle, Australia

ABSTRACT

Context: Poisoning due to chloroform ingestion is rare. The classic features of acute chloroform toxicity include central nervous system (CNS) and respiratory depression, and delayed hepatotoxicity.

Case details: A 30-year-old female ingested 20–30 mL of 99% chloroform solution, which caused rapid loss of consciousness, transient hypotension and severe respiratory depression requiring endotracheal intubation and ventilation. She was alert by 12 h and extubated 16 h post-overdose. At 38-h post-ingestion, her liver function tests started to rise and she was commenced on intravenous acetylcysteine. Her alanine transaminase (1283 U/L), aspartate transaminase (734 U/L) and international normalized ratio (2.3) peaked 67- to 72-h post-ingestion. She also developed severe abdominal pain, vomiting and diarrhoea. An abdominal CT scan was consistent with severe enterocolitis, and an upper gastrointestinal endoscopy showed erosive oesophagitis, severe erosive gastritis and ulceration. She was treated with opioid analgesia, proton pump inhibitors, sucralfate and total parenteral nutrition. Secretions caused a contact dermatitis of her face and back. Nine days post-ingestion she was able to tolerate food. Her liver function tests normalized and the dermatitis resolved. Chloroform was measured using headspace gas chromatograph mass spectrometry, with a peak concentration of 2.00 μg/mL, 4 h 20 min post-ingestion. The concentration-time data fitted a 1-compartment model with elimination half-life 6.5 h.

Discussion: In addition to early CNS depression and delayed hepatotoxicity, we report severe gastrointestinal injury and dermatitis with chloroform ingestion. Recovery occurred with good supportive care, acetylcysteine and management of gastrointestinal complications.

ARTICLE HISTORY
Received 13 July 2016
Revised 12 October 2016
Accepted 13 October 2016
Published online 28 October 2016

KEYWORDS
Chloroform; enterocolitis; hepatotoxicity; dermatitis; acetylcysteine; toxicity

Introduction

Deliberate self-poisoning from ingestion of liquid chloroform is rare. Exposure to chloroform by inhalation and ingestion typically causes early central nervous system (CNS) depression, respiratory centre paralysis, cardiac arrhythmias and delayed liver and renal toxicity.[1] It can also cause mucosal irritation and gastrointestinal symptoms with vomiting and diarrhoea. Dermal exposure can cause systemic toxicity and skin irritation including burns.

Case details

A 30-year-old female obtained 99% liquid chloroform from a dental practice and drank 20–30 mL with suicidal intent, resulting in rapid collapse. On scene her vital signs were: Glasgow Coma Score (GCS) 3, respiratory rate (RR) 20/min, heart rate (HR) 100 bpm with a palpable pulse but an unrecordable blood pressure (BP) which improved to a systolic of 120 mmHg within 11 min. She was intubated and ventilated in the emergency department for a decreased GCS, bradypnoea and desaturation to 78% while on oxygen.

She had a normal electrocardiogram and no arrhythmias on cardiac monitoring. Initial laboratory investigations were blood glucose concentration 9.7 mmol/L (reference range (RR): 3.0–7.7 mmol/L), normal electrolytes, normal renal function and undetectable paracetamol. She had an elevated white cell count of 34×10^9/L (RR: 3.9–11.1 $\times 10^9$/L). Her initial liver function tests were aspartate transaminase (AST) 62 IU/L (RR <35 IU/L), alanine transaminase (ALT) 24 IU/L (RR <30 IU/L), bilirubin 16 μmol/L (RR <15 μmol/L) and an international normalized ratio (INR) of 1.1. She was admitted to the intensive care unit.

Her GCS improved to 9 by 7-h post-ingestion and 11 by 12 h, but she remained intubated for 16 h and was extubated without issue. Her chest radiograph did not show any evidence of aspiration. At 38-h post-ingestion, she had a normal conscious state and was haemodynamically stable but she had an increased ALT of 58 IU/L, AST 53 IU/L, bilirubin of 36 mmol/L and INR 2.3. Intravenous acetylcysteine was commenced as an infusion at 42 h (6.25 mg/kg/h). Her liver

CONTACT Geoffrey K. Isbister geoff.isbister@gmail.com Clinical Toxicology Research Group, University of Newcastle, c/o Calvary Mater Newcastle, Edith St, Newcastle, NSW 2298, Australia

function tests continued to increase peaking between 67 h and 72 h, with an ALT 1283 IU/L, AST 734 IU/L, INR 2.3 and bilirubin of 64 μmol/L (Figure 1(A)). Acetylcysteine was ceased after a 72-h period.

She had severe gastrointestinal symptoms, including persistent vomiting (pre- and post-intubation) associated with diarrhoea, which were managed with repeated doses of intravenous ondansetron 4 mg, one dose of oral promethazine 12.5 mg and suctioning. She complained of severe abdominal pain post-extubation requiring multiple boluses of intravenous fentanyl 25 mcg and a patient-controlled fentanyl infusion. There was no evidence of perforated viscous on an erect chest X-ray but chest and abdominal CT scan showed extensive, continuous small and large bowel mucosal oedema, and circumferential bowel wall thickening consistent with extensive toxin-induced enterocolitis (Figure 2(A)). An upper gastrointestinal endoscopy confirmed oesophageal erosions and severe erosive gastritis with a 6-mm erosive lesion in the lesser curvature of the stomach (Figure 2(B)). She was kept nil by mouth and treated with pantoprazole 10 mg/h, sucralfate 1 g orally three times daily for 1 week and total parenteral nutrition, which was commenced at 67-h post-ingestion and continued for 72 h.

She also developed contact dermatitis on the face and upper back, assumed to be caused by drooling saliva and pooled vomitus. This was noted around the time of extubation and was managed conservatively using 10% dimethicone barrier cream. Although any vomitus was removed immediately, she did not receive primary skin decontamination, and pooled oral secretions may have only been cleaned every hour. The patient was discharged home on Day 9, following psychiatry assessment, by which time the dermatitis had resolved, she was tolerating oral intake and her liver function tests were near normal.

Blood samples were collected, centrifuged, serum separated and frozen for subsequent analysis (see Appendix).[2] Initial plasma chloroform concentration was determined as 0.1667 μg/mL 74 min post-ingestion with a highest plasma concentration of 2.00 μg/mL measured at 4-h 20-min post ingestion. The concentration time data was fitted to a 1-compartment model with an elimination half-life of 6.5 h (Figure 1(B)).

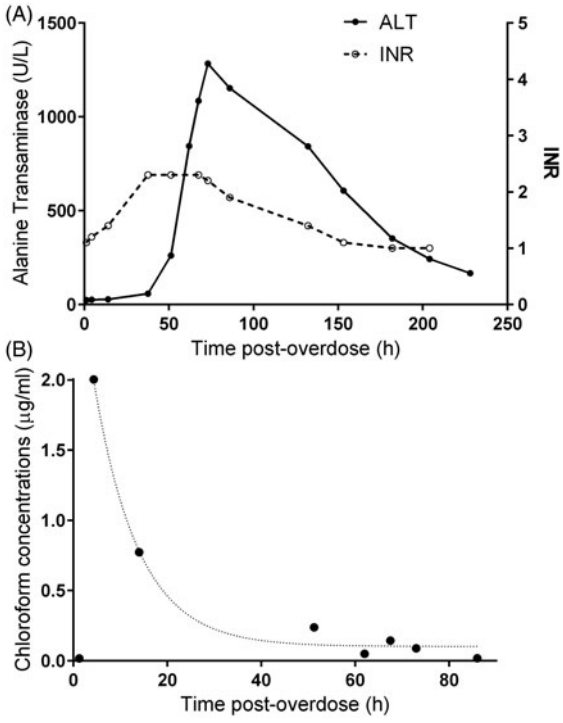

Figure 1. Plot of the alanine transaminase (ALT) and international normalized ratio (INR) versus time (A) and time course of chloroform concentrations (B).

Discussion

Our patient ingested a concentrated solution of chloroform, which caused rapid loss of consciousness and respiratory depression. Her condition improved over 12 h and she was extubated 16-h post-overdose. Her major problems were delayed hepatotoxicity without liver impairment and severe gastrointestinal effects.

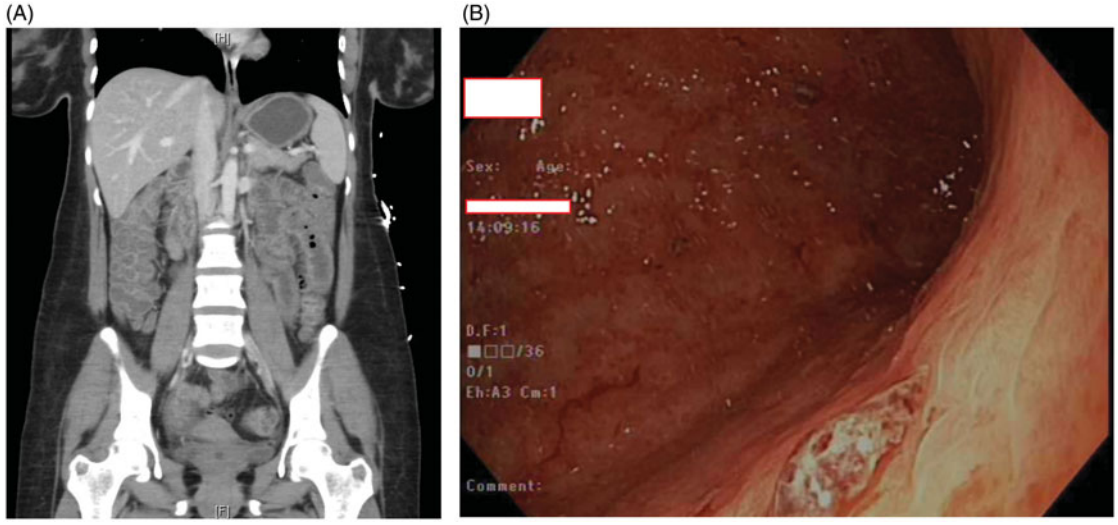

Figure 2. Computer tomography scan of the patient displaying extensive small and large bowel oedema and thickening, consistent with toxin-induced enteritis/colitis (A); Upper gastrointestinal endoscopy image of the patient demonstrating severe erosive gastritis with ulcer (B).

Chloroform is readily absorbed from the gastrointestinal tract and distributed to fat tissue, central nervous system, liver and kidney.[1,3] The rapid distribution to the central nervous system results in the rapid onset of coma and respiratory depression seen in this and other cases.[4,5] Early death from chloroform is due to ventricular arrhythmias caused by direct sensitizing effects of chloroform on the myocardium and hypoxia. It can cause shock from negative inotropy and vasodilation arising from vagal stimulation.[1]

Chloroform is metabolized by cytochrome P450 to phosgene and free radicals, which cause mitochondrial damage and cell death in the liver.[6,7] Chloroform also causes proximal tubular necrosis in the kidney which is unlikely to be due to liver-generated phosgene because it is unlikely to be transported out of the liver due to its high reactivity.[8] Hepatotoxicity associated with chloroform use was first reported in 1923 and is often seen after inhalation and skin exposure.[9] Hepatotoxicity manifests clinically as delayed elevation of transaminases. Interestingly the ALT did not rise until 36 h, similar to a previous report [10] and consistent with the delay seen in rodent hepatotoxicity as a consequence of phosgene formation.[11] It is also a longer delay than seen in paracetamol hepatotoxicity where aminotransaminases are elevated by 12–24 h,[12] which led to delayed commencement of acetylcysteine in our case. There are previous cases of patients receiving both oral and intravenous acetylcysteine aiming to prevent chloroform-induced liver injury.[5,10] There is little evidence to suggest that acetylcysteine prevents chloroform hepatotoxicity. In one previous case, acetylcysteine was commenced early, which potentially reduced the liver injury because the patient was more severely poisoned with a serum concentration of chloroform on admission of 91 μg/mL but had a lower ALT peak compared to our case.[5]

Our patient had prominent gastrointestinal distress, including protracted vomiting, increased oral secretions and diarrhoea. The pooled secretions behind her upper back were sufficient to cause a painless contact dermatitis which resolved by Day 8.[13] There was severe gastritis, ulceration and extensive small and large bowel inflammation with mucosal oedema and circumferential wall thickening found continuously in both small and large bowel. This is more consistent with a toxin-induced pathology and not ischaemic, infective or inflammatory aetiologies. This has not been previously described in chloroform poisoning. We used sucralfate and pantoprazole, which resulted in a rapid resolution of symptoms.

The first-order elimination of chloroform over the first 24 h was consistent with the improvement in central nervous system effects (Figure 1B). There were two unusual increases in the chloroform concentration at 51 h and 67.5 h. It is not clear why this occurred; these increases cannot be explained by redistribution, but may be simply unexplained random variation due to the assay. However, ongoing absorption from the dermal exposure is another possibility.[14] This would suggest that initial primary decontamination by washing the patient is important as well as preventing any contact with oral secretions, both for the patient and staff. Our case confirms that oral chloroform causes rapid central nervous system and respiratory depression and hepatotoxicity. In addition, we report severe gastrointestinal injury and dermatitis, possibly with ongoing dermal absorption. Recovery occurred with good supportive care, acetylcysteine and meticulous attention to management of gastrointestinal secretions.

Disclosure statement

The authors report no declarations of interest.

Funding

This work was supported by the National Health and Medical Research Council, 10.13039/501100000925 [1002611,1061041,1055176].

References

[1] International Programme on Chemical Safety (IPCS). Chloroform. Poisons Information Monograph. PIM 121. Geneva: WHO; 1989–2002.
[2] Lee J, Kim S, Lee J, et al. Rapid determination of volatile organic compounds in human whole blood using static headspace sampling with gas chromatography and mass spectrometry. Bull Korean Chem Soc. 2012;33:3963–3970.
[3] Chloroform toxicological overview [Internet]. 2007 [cited 2015 Nov 5]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/338535/Chloroform_Toxicological_Overview.pdf.
[4] Sridhar N, Krishnakishore C, Sandeep Y, et al. Chloroform poisoning – a case report. Ren Fail. 2011;33:1037–1039.
[5] Dell'Aglio DM, Sutter ME, Schwartz MD, et al. Acute chloroform ingestion successfully treated with intravenously administered N-acetylcysteine. J Med Toxicol. 2010;6:143–146.
[6] Pandit AST, Bafna P. Drug-induced hepatotoxicity: a review. J Appl Pharm Sci. 2012;2:233–243.
[7] Pohl LR, Bhooshan B, Whittaker NF, Krishna G. Phosgene: a metabolite of chloroform. Biochem Biophys Res Commun. 1977;79:684–691.
[8] Fang C, Behr M, Xie F, et al. Mechanism of chloroform-induced renal toxicity: non-involvement of hepatic cytochrome P450-dependent metabolism. Toxicol Appl Pharmacol. 2008;227:48–55.
[9] Kang YJ, Ahn J, Hwang YI. Acute liver injury in two workers exposed to chloroform in cleanrooms: a case report. Ann Occup Environ Med. 2014;26:49.
[10] Boyer ELS, Perrone J, de Roos F. Limited hepatotoxicity following a massive chloroform ingestion treated with oral N-acetyl-cysteine. J Toxicol Clin Toxicol. 1998;36:427–534.
[11] Wang PY, Kaneko T, Tsukada H, et al. Time courses of hepatic injuries induced by chloroform and by carbon tetrachloride: comparison of biochemical and histopathological changes. Arch Toxicol. 1997;71:638–645.
[12] Green TJ, Sivilotti ML, Langmann C, et al. When do the aminotransferases rise after acute acetaminophen overdose? Clin Toxicol. 2010;48:787–792.
[13] Vlad IA, Armstrong J, Gault A. A painless burn: systemic toxicity after dermal exposure to chloroform. Emerg Med Australas. 2014;26:648–649.
[14] Dick D, Ng KM, Sauder DN, Chu I. In vitro and in vivo percutaneous absorption of 14C-chloroform in humans. Hum Exp Toxicol. 1995;14:260–265.

Appendix

Chloroform assay details

100 μL of internal standard (IS) chlorobutanol (Sigma Aldrich, NSW, Australia) was added to 200 μL of thawed plasma and the volume

adjusted to 1 mL with MilliQ water. Samples were vortexed and head space analysed by gas chromatograph mass spectrometer (GCMS) using an assay adapted from Lee et al.[2]

GCMS analysis

Column used was Agilent RXI-5MS, 0.35 μm df, 0.25 mm × 30.0 m. Gas Chromatography was performed using a Shimadzu GCMS-TQ 8040 triple quadrupole gas chromatograph mass spectrometer with a CTC auto injector. Head space analysis was fibre based using Solid Phase Micro Extraction (SPME), 75 μm CAR/PDMS fused silica fibre, pre incubation of 1 min at 30 °C with extraction time of 1 min and fibre bake out of 20 min. Helium was used as the carrier gas with a linear velocity of 1.0 mL/min. Injector temperature was 280 °C with splitless injection, sampling time 1 min then split ratio of 50 with the temperature gradient of 45 °C for 3 min, then 10 °C/min to 100 °C, then 25 °C/min to 200 °C. Mass detector was operated in SIM mode with the following ions (*m/z*) tracked: for chloroform, the target *m/z* 83; qualifier *m/z* 85 with ion ratio 70; *m/z* 47 with ion ratio 14, for the internal standard the target *m/z* 56; qualifier *m/z* 41 with ion ratio 65; *m/z* 43 with ion ratio 45 and for phosgene: target *m/z* 99, qualifier *m/z* 63. The ion ratio ranges used were 30%. Standard curve consisted of the following standards: 0.1, 10 and 20 μg/L of plasma with $r^2 = 0.9997$. Limit of quantification (10× blank) was 0.02 μg/L, linear to 50 μg/L with limit of detection (3× blank) was 0.006 μg/L.