Case Report

Delayed onset of liver injury after intentional chloroform overdose: a case report and literature review

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Abstract

Chloroform is a recognised cause of acute liver injury, although now rarely encountered in clinical practice. We present a case of inhalational chloroform self-poisoning in a 47-year-old man that presented to hospital initially with reduced conscious level and later developed acute liver injury that was treated with intravenous acetylcysteine. This paper reviews the existing literature and presents a summary of the mechanisms of chloroform hepatotoxicity. Published cases show that there is a characteristic delay of 24 to 48 hours between chloroform exposure and elevation of liver transaminase activity. Therefore, clinicians need to provide an appropriate duration of monitoring in order to detect the occurrence of this important toxic effect.

Keywords

acetylcysteine, hepatitis, liver injury, poison, trichloromethane

Key teaching points

- Chloroform is a rare form of self-poisoning that causes rapid onset coma
- Acute liver injury is a rare but recognised complication of chloroform poisoning
- Onset of liver injury may be delayed by 24 to 48 hours after chloroform exposure
- Clinicians should be vigilant for the occurrence of late complications of chloroform even after the neurological effects have complete resolved.

Introduction

Chloroform is an organic halogenated hydrocarbon, also known as trichloromethane, CAS registry number 67-66-3. It is a volatile colourless liquid with a characteristic sweet odour, and has a boiling point around 61°C. Chloroform was discovered in 1831, and has been used as an anaesthetic agent since around 1848. Exposure to vapour and liquid causes eye and skin irritation, and lung aspiration of chloroform liquid may cause pharyngitis, pneumonitis and acute lung injury. Short term inhalation of chloroform concentrations of 100 to 1000 parts per million causes discomfort and dizziness, whereas inhalation of concentrations of 7000 to 20000 parts per million can cause rapid loss of consciousness. Deaths have been reported after inhalation of chloroform.[1-3] In the United Kingdom, the long term (time-weighted 8-hour average) workplace exposure limit is 2 parts per million, equivalent to around 9.9 milligrams per cubic metre.

Chloroform is readily absorbed by inhalation and ingestion, and bioavailability is around 60 to 70% of the inhaled dose. Its primary pharmacological mechanism of action is activation of gamma amino-butyric acid type A (GABA-A) receptors within the central nervous system.[4] It causes dose-dependent sedation, euphoria, and reduced anxiety; larger doses depress conscious level, and toxic effects include coma, seizures, and respiratory failure. Chloroform can cause cardiac effects including negative inotropy, cardiogenic shock, myocardial sensitization to catecholamines, and ventricular arrhythmias.[5]

Exposure to large chloroform doses may also cause liver and kidney damage. Chloroform-induced liver toxicity was first reported as an adverse effect of anaesthesia in the 1950s, and the rate of occurrence of liver injury is around 1 in 25000 to 50000 administrations.[6] Liver injury has been reported after occupational inhalational exposure over 40 to 45 days in two adults, which gradually recovered after removal from exposure.[7] Acute liver injury has also been reported in a 39-year-old man after dermal exposure to chloroform.[8]

Comparatively few data are available concerning the occurrence of acute liver injury after intentional, large chloroform exposures. We report a case of intentional chloroform exposure in a 47-year-old man that illustrates a delayed occurrence of acute liver toxicity, and emphasises the need for a sufficiently long period of monitoring to ensure that this adverse effect is not overlooked.

Methods

We conducted a systematic review of published cases of acute chloroform toxicity using MEDLINE

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Table 1. Initial blood investigations after presentation to hospital at around 13 hours after chloroform exposure; *values outside normal reference range.

	Laboratory value	Normal reference range
Glucose (millimoles per litre)	7.9	3.0 to 7.8
Haemoglobin (grams per litre)	145	130 to 180
White cell count (x109 per litre)	13.5*	4 to 11
Platelet count (x109 per litre)	177	150 to 450
Prothrombin time (seconds)	14.1*	10.0 to 12.5
Fibrinogen (grams per litre)	3.0	1.9 to 4.5
Sodium (millimoles per litre)	141	133 to 146
Potassium (millimoles per litre)	5.3	3.5 to 5.3
Urea (millimoles per litre)	5.4	2.5 to 7.8
Creatinine (micromoles per litre)	104	59 to 104
Bilirubin (micromoles per litre)	9	0 to 21
Alanine transaminase (units per litre)	34	0 to 45
Alkaline phosphatase (units per litre)	90	30 to 130
Albumin (grams per litre)	42	35 to 50
Paracetamol (milligrams per litre)	<5	-
Salicylates (milligrams per litre)	<15	-
Creatine kinase (units per litre)	2423*	40 to 320

and PUBMED searches, and sought case reports in the abstracts of the North American Congress on Clinical Toxicology and European Association for Poisons Centres and Clinical Toxicology between 2011 and 2018 inclusive.

Case Report

A 47-year-old man was found by the police unconscious in his car in a public carpark. When the car door was opened there was a pungent chemical odour, and an empty glass bottle noted. A Hazardous Area Response Team (HART) was summoned, and the patient was removed from the car and decontaminated at the scene; all clothing was removed and skin was cleansed with water. Initial clinical observations were Glasgow Coma Score 3, heart rate 76 per minute, blood pressure 94/55, oxygen saturations 98% on air, capillary refill 2 seconds, BM glucose 7.9 millimoles per litre, and pupils reactive to light. Supplementary oxygen was administered and on arrival at the Emergency Department, Glasgow Coma Score had increased to 14. The patient reported that he worked as a chemist and had attempted to commit suicide at around 10 pm on the previous evening. He had rinsed a 500 millilitre glass bottle with acetone to remove any water, and then filled it with chloroform. He poured the chloroform into the footwell of his car and then ran the car engine and heater to aid evaporation and build-up of fumes within the vehicle. He reported losing consciousness soon after. He denied having consumed alcohol or any medications. There was a past history of ocular migraine, but he was receiving no regular medications and had no known allergies.

The interval between the start of the exposure and presentation to hospital was around 13 hours. The patient described ongoing suicidal intent. He reported symptoms of paraesthesia affecting both legs, and minor aches affecting both arms and legs. A detailed neurological examination found no objective abnormality, and cardiac, respiratory and abdominal examination findings were normal. Initial investigations are summarised in Table 1.

Creatine kinase activity was abnormally high, and admission was arranged for intravenous hydration and monitoring of renal function. Creatine kinase initially increased, and then gradually decreased, with no observed deterioration of renal function, Table 2.

On day three, prothrombin time increased to 27.8 seconds and alanine transaminase was 3721 units per litre. A repeat paracetamol concentration was <5 milligrams per litre. The working diagnosis was chloroform-induced liver injury. Intravenous vitamin K 10 milligrams was administered, followed by an intravenous infusion of acetylcysteine using a standard paracetamol poisoning protocol, namely 150 milligrams per kilogram over 1 hour, then 50 milligrams per kilogram over 4 hours, and then 100 milligrams per kilogram every 16 hours.

Table 2. Creatine kinase activity and serum creatinine concentrations expressed according to the interval after chloroform exposure began.

Interval (hours)	Creatine kinase (units per litre)	Creatinine (micromoles per litre)
15	2423	104
34	5129	85
44	4605	80
60	4271	72
88	1454	88
132	206	74

Alanine transaminase activity and prothrombin time continued to increase, and peaked at 88 hours after chloroform exposure and then gradually improved; peak bilirubin concentration occurred at 180 hours (Figure 1). The acetylcysteine infusion was stopped at 180 hours, and liver biochemistry continued to improve. The patient fully recovered and was transferred to a psychiatry hospital for further assessment.

Discussion

The effects of chloroform depend upon the extent of exposure, and previous reports suggest that the fatal dose in adults may be as low as 14 grams.[9] Chloroform is predominantly excreted unchanged via the lungs, but it is also subject to metabolism, mainly in the liver and to a lesser extent within the kidney and gastrointestinal mucosa. Oxidative dechlorination gives rise to trichloromethane, whilst oxidation by cytochrome 2E1 and 2A6 gives rise to phosgene (COCL2).[10] Acute toxic effects on the heart, liver and kidneys appear to be caused by chloroform metabolites, predominantly phosgene and dichloromethyl free radicals, which disrupt molecular function and cause cell death (Figure 2). Patients with upregulated P450 activity in the liver may be at greater risk of chloroform toxicity due to more extensive formation of oxidative metabolites, and factors that increase susceptibility to liver injury include excess alcohol consumption, hypoxia, hypercapnia, dehydration and acidosis.[11]

A notable finding in the present case is the delay between exposure and onset of acute liver damage. The occurrence of liver injury was not predicted from the investigations undertaken at the time of presentation to hospital, some 15 hours after exposure. This is in keeping with reports elsewhere that identified a delay between chloroform exposure and development of acute liver injury.[12-19] In some cases, patients have recovered fully from the neurological effects of chloroform before any liver injury has become apparent, raising a concern that patients might have inadvertently been considered safe for discharge from hospital before liver injury had become apparent. Existing case reports indicate an interval of at least 24 to 48 hours between chloroform exposure and a detectable increase in prothrombin time or transaminase activity (Table 3). A delayed onset of liver injury can be explained by the duration of chloroform being metabolised to toxic metabolites, and the time taken for hepatocyte glutathione stores to become deplete. Similar delays are observed for other drugs that cause liver toxicity

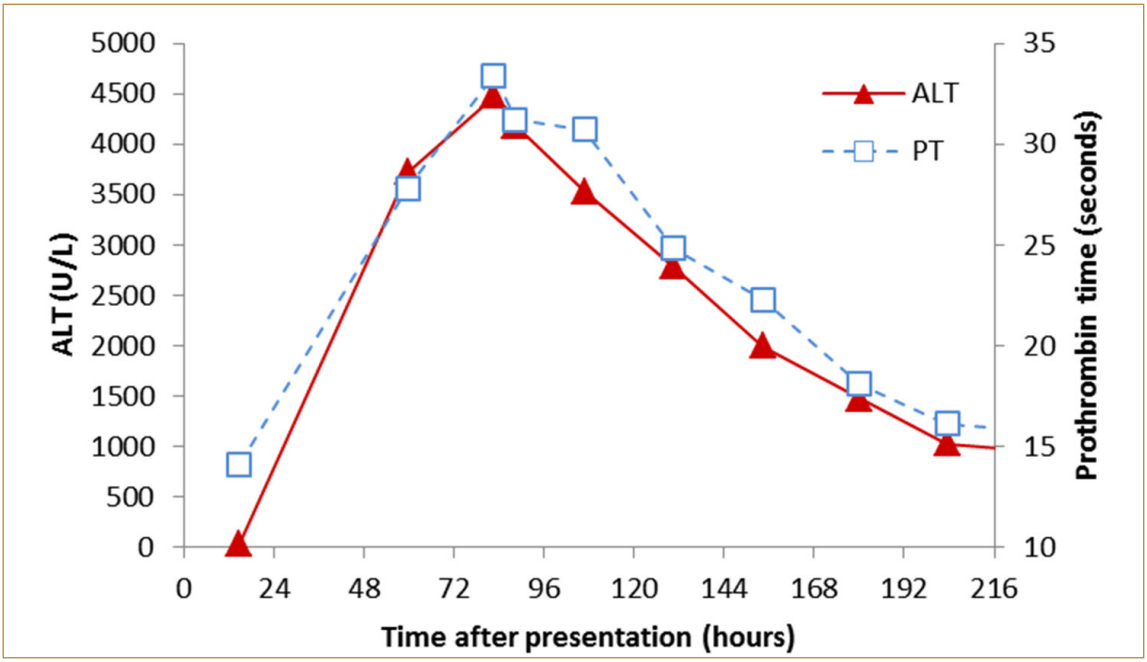

Figure 1. Serum alanine transaminase activity (closed triangles) and prothrombin time (open squares) at various intervals after chloroform exposure began.

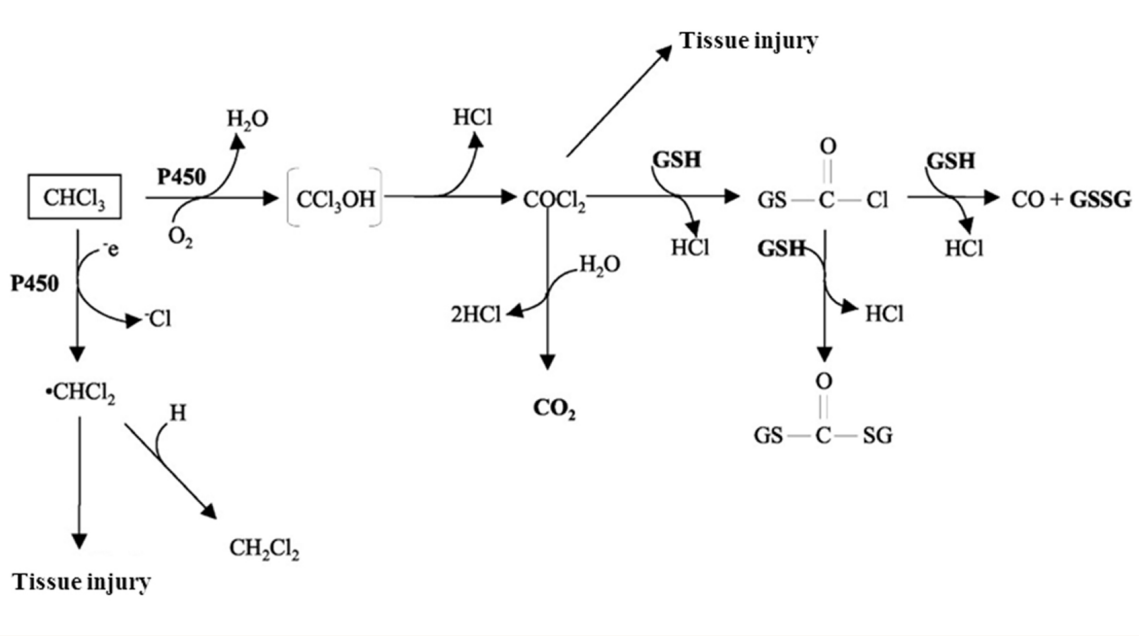

Figure 2. Schematic representation of chloroform (CHCl3) metabolism by the P450 oxidation system causing formation of free radicals and reactive metabolites capable of provoking cell and tissue injury, including dichloromethane (CHCl2), which may be detoxified by glutathione (GSH).

Table 3. Summary of published clinical cases of chloroform exposure that indicate a delay between exposure and onset of liver injury; F=female, M=male, NAC=N-acetylcysteine administered.

Age	Route (dose)	Clinical features	Onset liver injury (hours)	Peak liver injury (hours)	NAC	Outcome
46 F	Inhalation	Coma, respiratory failure, acute liver failure and rhabdomyolysis. Ventilation, haemodialysis	27	52	No	Death[12]
23 M	Ingestion 75 mL	Reduced conscious level followed by acute liver injury, jaundice; discharged on day 14	48	120	No	Recovery[13]
30 F	Ingestion 20-30 mL	Coma, hypotension, respiratory failure, erosive oesophagitis and enteritis, contact dermatitis; ventilation, recovery on day 9	38	72	Yes	Recovery[14]
31 M	Ingestion 50 mL	Coma, liver injury, acute kidney injury. Gastric lavage, activated charcoal, ventilation, haemodialysis; discharged on day 10	72	120	Yes	Recovery[15]
19 M	Ingestion 75 mL	Coma followed by liver injury; ventilated, discharged on day 4	72	96	Yes	Recovery[16]
42 F	Inhalation	Alert on arrival; kidney and liver failure, coagulopathy; vitamin K, fresh frozen plasma, haemodialysis, recovery by day 21	50	60	Yes	Recovery[17]
90 M	Ingestion "sip"	Coma, bradycardia, hypoxaemia, liver injury and kidney injury; ventilated, forced diuresis, vasopressors, recovery on day 16	>48	120	Yes	Recovery[18]
14 M	Ingestion 32 mL	Agitation, rapid reducing consciousness, hypotension, tachycardia; ventilated	-	192	Yes	Recovery[19]

via a toxic metabolite, for example paracetamol or isoniazid.[20,21]

Administration of acetylcysteine has been described in several previous reports of chloroform-induced liver injury, although evidence of improved outcome are lacking. We administered intravenous acetylcysteine to our patient because we postulated that it might serve as an effective antidote against liver toxicity by allowing restoration of hepatic glutathione stores. Glutathione protects against oxidative liver injury, and exposure to chloroform and phosgene causes depletion of glutathione within the liver.[22] The mechanism of action of chloroform toxicity appears similar to that of paracetamol-induced liver damage, where acetylcysteine is an established antidote treatment.[23] Acetylcysteine protects against liver damage by restoring hepatocellular glutathione concentrations, but even in the context of paracetamol poisoning, the optimal dose and duration of treatment is uncertain.[24,25] Whilst it is impossible to be certain that treatment shortened the duration of liver injury in our patient, the risks of acetylcysteine treatment are comparatively low so empirical treatment seemed justifiable.

A limitation of the present findings is the lack of chloroform concentrations, which would have provided confirmatory evidence of chloroform poisoning. Nonetheless, the patient history was considered to be consistent and reliable, and data elsewhere show a reasonable correlation between patient reports and laboratory analyses.[26]

In conclusion, chloroform exposure can cause acute liver injury, and the onset of elevated transaminase activity may be delayed by 24 to 48 hours. Patients should have an appropriate duration of monitoring in order to detect this important adverse effect. Clinicians should consider the use of intravenous acetylcysteine to prevent or reverse liver injury.

Declaration of competing interests

Nothing to declare.

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