

Treatment of severe acetaminophen-induced hepatocellular injury with prostaglandin E: Two case reports

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M KHATCHATOURIAN, H VELLEND. Treatment of severe acetaminophen-induced hepatocellular injury with prostaglandin E: Two case reports. *Can J Gastroenterol* 1995;9(4):221-224. Drugs have long been recognized as culprits in hepatocellular injury. Acetaminophen is one example of a commonly used over-the-counter medication that can cause severe centrilobular hepatic necrosis when ingested in large quantities in suicide attempts or unintentional overdoses. Acetaminophen hepatotoxicity is mediated by a toxic reactive metabolite formed from the parent compound by the cytochrome P450 mixed-function oxidase system of the hepatocyte. Conventional treatment of acetaminophen-induced liver injury consists of supportive measures and prevention of further drug absorption. In addition, in patients with high serum acetaminophen concentrations, the severity of hepatic necrosis appears to diminish with the timely use of sulfhydryl compounds such as N-acetyl cysteine. Two patients in whom acetaminophen hepatotoxicity was successfully treated using prostaglandin E₁ are described.

Key Words: Acetaminophen, Hepatotoxicity, Prostaglandins

Traitement des lésions hépatocellulaires sévères causées par l'acétaminophène à l'aide de prostaglandine E: deux rapports de cas

RÉSUMÉ : Les médicaments sont depuis longtemps incriminés dans la survenue d'atteintes hépatocellulaires. L'acétaminophène est un exemple de médicament d'usage courant vendu sans ordonnance qui peut provoquer une nécrose hépatique centrilobulaire lorsqu'il est pris en forte dose, intentionnellement ou accidentellement. L'hépatotoxicité liée à l'acétaminophène est amenée par un métabolite réactif toxique, formé à partir de la molécule-mère par le système oxydatif à fonction mixte du cytochrome P450 de l'hépatocyte. Le traitement

voir page suivante

ALL HEPATIC DISEASES BEGIN WITH injury to liver cells. Depending on the extent of damage to the hepatocytes, the injury may, at one extreme, be minor and clinically inapparent or it may lead to severe impairment of hepatocellular function associated with encephalopathy and coagulopathy – a condition known as fulminant hepatic failure (1). Similarly, the prognosis of liver disease may be quite favourable with minor insult or it may culminate in mortality of over 90% with stage IV encephalopathy in fulminant hepatic failure (2).

Etiological agents in the development of hepatic disease include drugs and toxins, viral hepatitis and vascular injury (3). Acetaminophen is one example of a commonly used over-the-counter drug that may cause severe centrilobular hepatic necrosis when ingested in large amounts in suicide attempts or accidental overdoses.

Traditional principles in the management of liver injury include supportive measures, such as fluid and electrolyte resuscitation, repletion of coagulation factors, and glucose infusion, as well as treatment of secondary sepsis (4). Liver transplantation may be life-saving, particularly early in the course of massive hepatocyte damage in a previously healthy organ (5).

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classique de la lésion hépatique imputable à l'acétaminophène repose sur le maintien des fonctions vitales et la prévention de toute autre absorption du médicament. De plus, chez les patients dont les concentrations plasmatiques d'acétaminophène sont élevées, la gravité de la nécrose semble s'atténuer lors de l'administration de composés de sulfhydryle, comme la N-acétyl-cystéine. Le présent article décrit deux cas d'hépatotoxicité liée à l'acétaminophène traités avec succès par prostaglandine E₁.

TABLE 1
Data for case 1

	NAC initiated ↓	PGE ₁ initiated at 48 h and NAC discontinued ↓				PGE ₁ tapering begun at 144 h ↓		
Hours postoverdose	24	31	56	57	66	102	151	
AST (U/L)	365	719	8760	9340	7600	996	351	
ALT (U/L)	233	513	6800	7430	7340	3550	1720	
ALP (U/L)	66	49	61	62	64	83	97	
GGT (U/L)	26	NA	28	28	33	139	133	
Bilirubin conjugated (μmol/L)	NA	<2	<2	<2	<2	3	<2	
Bilirubin unconjugated (μmol/L)	NA	18	16	16	16	25	18	
INR	1.4	1.7	2.1	2.0	2.1	1.1	1.0	
PTT (s)	29.5	34.0	35.5	35.0	35.5	28.5	30.0	
Blood glucose/accucheck (mmol/L)	4.9	10.1	5.2	5.5	5.4	3.4	6.9	
Albumin (g/L)	NA	NA	36	38	39	33	NA	
Acetaminophen level (μmol/L)	117	<66	-	-	-	-	-	

ALP Alkaline phosphatase; ALT Alanine transaminase; AST Aspartate transaminase; GGT Gamma glutamyl transpeptidase; INR International normalized ratio; NA Not available; NAC N-acetyl cysteine; PG Prostaglandin; PTT Partial thromboplastin time

Moreover, history has chronicled low survival rates in acute hepatocellular dysfunction treated with corticosteroids (6), exchange transfusions (7) and charcoal hemoperfusion (8).

In recent years, a family of bioactive lipids in the form of prostaglandins (PG) have been evaluated in the therapy of fulminant hepatic failure. Preliminary reports of biochemical and clinical response of fulminant viral hepatitis to PGE have been promising (9,10). This report describes two cases of severe acetaminophen-induced hepatocellular injury that improved rapidly after treatment with PGE₁.

CASE 1 PRESENTATION

A 39-year-old female was admitted with acetaminophen, codeine and doxylamine succinate overdose after attempted suicide. She had been diagnosed with multiple personality disorder three years earlier and had two prior episodes of drug overdose.

On the night preceding admission, she ingested 32.5 g acetaminophen accompanied by 126 g of alcohol (beer). Over the 12 h before presentation she felt nauseated but denied other symptoms. Medication history was otherwise unremarkable, but she admitted to consuming, on average, 216 g of alcohol (beer) a week.

Physical examination upon presentation revealed a well nourished female with blood pressure 140/85 mmHg, pulse 75 beats/min, respiratory rate 18/min and temperature 37.5°C. There was no scleral icterus. Liver span was normal and there was neither splenomegaly nor any stigmata of chronic liver disease. She was alert, fully oriented and no asterixis was elicited. The remainder of the physical examination was within normal limits.

Admission laboratory data revealed normal electrolytes, renal function and complete blood count. Pertinent biochemical and hematological data are

shown in Table 1. Hepatitis A immunoglobulin M, hepatitis B (HB) surface antigen, anti-HB surface, anti-HB core, as well as antihepatitis C (HC) virus were negative. Acetaminophen level 24 h following overdose was 117 μmol/L. The remainder of the drug screen was negative.

At presentation, an intravenous solution of 5% dextrose/water was initiated. An infusion of N-acetyl cysteine was started as per usual protocol (11). Vitamin K 10 mg orally was administered. Twenty-four hours following admission, the patient was transferred to an intensive care setting to initiate PGE₁ infusion as per the manufacturer's protocol (Upjohn) (Appendix).

As the liver enzymes and coagulopathy began to normalize, the PGE₁ infusion was tapered and stopped. The patient was assessed and discharged by the psychiatry service.

CASE 2 PRESENTATION

A 32-year-old single Chilean-born male factory worker was admitted with unintentional overdose of acetaminophen taken for severe toothache. There was no history of other medications but he consumed 54 g alcohol (beer) per week. Two days before admission he ingested 15 g acetaminophen over 90 mins. This was preceded by ingestion of 90 g of alcohol (beer). The day before admission he felt nauseous and weak; over the ensuing 4 to 5 h symptoms progressed to repeated bilious emesis and diffuse abdominal pain. He consulted his family physician who promptly referred him to the emergency department.

Physical examination upon presentation revealed a young male in mild to moderate distress due to abdominal discomfort. Blood pressure was 130/80 mmHg, pulse 72 beats/min, respiratory rate 16/min and temperature 37°C. There was no scleral icterus and dental examination showed evidence of pulpitis in an upper molar tooth on the left. There was diffuse abdominal tenderness without rebound, most prominent in the epigastrium. The liver edge was boggy and tender but the span was normal. He was somnolent but arousable and fully oriented without asterixis.

There were no stigmata of chronic liver disease.

Laboratory investigation on admission showed normal electrolytes, mildly elevated blood urea nitrogen (BUN) at 8.5 mmol/L with creatinine at 102 μ mol/L. BUN normalized with hydration. Relevant laboratory data are outlined in Table 2. Serum acetaminophen level 48 h postingestion was less than 66 μ mol/L. The drug screen was otherwise unremarkable. Screen for HB and HC was negative.

N-acetyl cysteine was administered as per the standard protocol (11), together with intravenous dextrose and saline. The patient was admitted to the intensive care unit for initiation of PGE₁ (for protocol see Appendix). Vitamin K 10 mg subcutaneously was given daily over three days. Potassium phosphate was administered intravenously to correct a serum phosphate of 0.35 mmol/L. Beginning two days following admission, PGE₁ infusion was slowly tapered and stopped as liver enzymes and coagulopathy progressively improved. The patient was discharged in stable condition with dental follow-up for tooth extraction.

DISCUSSION

Acetaminophen, a widely used antipyretic analgesic, can cause severe liver injury when ingested in large quantities. It is rapidly absorbed from the gastrointestinal tract and significant first-pass metabolism occurs in the luminal cells of the intestine and in the hepatocytes (12). The drug diffuses quickly into most tissues and concentrates mainly in the liver. A single dose of 10 to 15 g may produce clinical evidence of liver damage, whereas fulminant fatal disease is usually (although not invariably) associated with ingestion of 25 g or more.

Acetaminophen hepatotoxicity is mediated by a toxic reactive metabolite formed from the parent compound by the cytochrome P450 mixed-function oxidase system of the hepatocyte. Under normal circumstances the metabolite reacts with glutathione to form a harmless end-product. However, the consumption of large doses of acetaminophen depletes glutathione and

TABLE 2
Data for case 2

	PGE ₁ and NAC initiated at 56 h		NAC discontinued at 68 h	PGE ₁ tapered beginning at 96 h and discontinued at 120 h	
	↓	↓	↓	↓	↓
Hours postoverdose	48	64	73	86	237
AST (U/L)	9920	333	2010	914	74
ALT (U/L)	>11,000	660	5870	4210	663
ALP (U/L)	115	73	72	94	74
GGT (U/L)	365	311	316	301	216
Bilirubin conjugated (μ mol/L)	11	13	22	9	<2
Bilirubin unconjugated (μ mol/L)	29	42	42	28	12
INR	2.9	2.0	1.6	1.3	NA
PTT (s)	29.5	32.0	29.0	28.0	NA
Blood glucose/accucheck (mmol/L)	4.3	7.7	6.2	5.3	3.9
Albumin (g/L)	46	36	36	36	NA
Acetaminophen level (μ mol/L)	<66	–	–	–	–

ALP Alkaline phosphatase; ALT Alanine transaminase; AST Aspartate transaminase; GGT Gamma glutamyl transpeptidase; INR International normalized ratio; NA Not available; NAC N-acetyl cysteine; PG Prostaglandin; PTT Partial thromboplastin time

APPENDIX

Protocol for administration of prostaglandin E₁ (Prostin VR, alprostadil, Upjohn)

ADMINISTRATION

PREADMINISTRATION

- record patient's baseline vital signs
- central or peripheral line can be used; central line is preferred as Prostin can cause vessel irritation
- administer as a 24 h infusion via infusion device
- medication bag to be changed every 24 h at same time each day
- discard unused portion
- usual dilution is 500 μ g/500 mL 5% dextrose/water (1 μ g/mL)
- for fluid restrictions 500 μ g/250 mL 5% dextrose/water (2 μ g/mL)

INFUSION RATE

- initial rate 0.2 μ g/kg/h
- each 1/2 hour interval increase by 0.1 μ g/kg/h to a maximum tolerated dose or to 0.6 μ g/kg/h, whichever is lower
- dosage may be titrated up or down during infusion depending on patient's response

SIDE EFFECTS

- hypotension (arteriolar dilation)
- diarrhea
- headache
- stomach pain
- nausea and vomiting
- fever
- feeling of warmth
- joint and muscle pain

AVAILABILITY

- Prostin IV 500 μ g
- Prostin oral form (misoprostil, prostin VR)

the metabolite is covalently bound to nucleophilic hepatocyte molecules; this process is believed to lead to hepatocyte necrosis (12). The precise sequence and mechanisms are unclear but it is well known that liver injury may be potentiated by prior alcohol intake (13), the so-called alcohol-

acetaminophen syndrome. Moreover, combinations of two or more single agents used together may have synergistic toxicity, for example acetaminophen used with isoniazid (14).

Treatment of acetaminophen toxicity involves supportive measures and prevention of further drug absorption

using gastric lavage or activated charcoal, ideally within the first 30 mins after ingestion. In patients with a high serum acetaminophen level (greater than 4.4 mmol/L at 4 h or greater than 2.2 mmol/L at 8 h postingestion), the use of sulfhydryl compounds such as N-acetyl cysteine, ideally within 12 h of ingestion, appears to reduce the severity of hepatic necrosis. Late administration of these compounds is of uncertain value but is nevertheless advocated by some clinicians (12).

Based on the cases presented and published data on PG use in fulminant viral hepatitis, the use of PG as

adjunctive therapy in acetaminophen-induced hepatic toxicity is an attractive concept. The mechanisms of this beneficial effect remain to be elucidated, yet initiation of PG therapy appears to result in a marked and sustained decrease in transaminases (9,10). The immunosuppressive properties of PG may be instrumental in reversing the liver injury in cases of drug-induced damage. It has been shown that PG decreases expression of class I and II antigens known to be induced in liver disease (15-17) and that PGE₁ inhibits T cell-mediated cytotoxicity against isolated murine he-

patocytes (18). Moreover, several groups have demonstrated beneficial effects of PG in animal models of hepatic failure due to a variety of toxins including acetaminophen (19).

CONCLUSIONS

We describe two cases in which PGE₁ was used to treat acute acetaminophen-induced hepatotoxicity successfully. Controlled and randomized clinical trials are undoubtedly fundamental in establishing efficacy and benefit of this therapy, and in extending the use of PG to other forms of hepatotoxicity.

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