Case Report

Potentially Fatal Paracetamol Overdose and Successful Treatment with 3 Days of Intravenous N-acetylcysteine Regime – A Case Report

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Abstract

Introduction: Paracetamol overdose is the most common drug overdose worldwide. To our knowledge, the maximum number of paracetamol tablets ingested reported in the literature is 45 g. Clinical Picture: We describe a 21-year-old patient who acutely ingested 120 tablets, each 500 mg paracetamol (i.e., 60 g equivalent to 1200 mg/kg body weight) in a suicidal attempt. Our patient also drank 2 bottles of codeine-based cough syrup equivalent to 360 mg of codeine. At 6 hours post ingestion, her serum paracetamol level was 207 mg/L. The poor prognostic factors for paracetamol overdose in our patient included massive paracetamol ingestion (confirmed by blood levels), codeine co-ingestion and elevated serum amylase (189 U/L). Treatment: She was treated with a 3-day modified regimen of intravenous N-acetylcysteine. Outcome: The liver function tests and the prothrombin time remained normal over the second and third day of admission and the patient was discharged without complications on the fifth day. Conclusion: From this experience we feel that in very severe paracetamol poisoning, a modified regime of intravenous N- acetylcysteine for 3 days is safe and efficacious.

Ann Acad Med Singapore 2006;35:108-11

Key words: Codeine, Hyperamylasaemia, Ingestion, Suicidal

Introduction

Paracetamol overdose is one of the most common drug overdose in both children and adults in Singapore.[1] Doses of paracetamol exceeding 150 mg/kg in a patient can be life threatening.[2,3] We describe a patient with potentially lethal overdose of 60 g of paracetamol (1200 mg/kg), which led to profoundly elevated paracetamol blood levels (207 mg/L at 6 hours post ingestion), who was successfully rescued with intravenous (IV) N-acetyl cysteine (NAC) over 3 days.

Case Report

Ms AP, a 21-year-old female with a body weight of 50 kg, was admitted to the hospital on 21 June 2005 at about 5.30 pm after she deliberately ingested 120 tablets of 500 mg paracetamol each. She swallowed the tablets at about 10 am over 30 minutes that same day. She also drank 2 bottles of codeine cough syrup, each containing 180 mg of codeine. The reason behind her intentional overdose was reported as having family problems. She was not previously known to have any psychiatric problems and this was her first episode. She was brought to the emergency department (ED) at 3 pm. Gastric lavage was done and activated charcoal administered in the ED. She was started on IV NAC in the ED about 6 hours after the episode. Serum paracetamol level done at ED about 6 hours post ingestion was 207 mg/L. She had nausea but no vomiting. She had a past history of left-sided lymphocytic exudative pleural effusion in 2004. The pyogenic and acid fast bacilli cultures of her pleural fluid and sputum were negative. She was empirically treated with anti-tuberculous drugs for 9 months from June 2004 to February 2005.

On examination in the general ward, she was alert and rational. There was no evidence of asterixis or icterus. Her blood pressure was 110/70 mm Hg, pulse rate was 80 beats/minute and respiratory rate was 14/minute. Clinically, she was comfortable and there was no Kussmaul's respiration. The rest of the examination was normal. The patient was continued on IV NAC, having been initiated on 150 mg/kg over 15 minutes (completed in the ED), followed by 50 mg/

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kg in 500 mL of 5% dextrose over the next 4 hours, and then 100 mg/kg in 1000 mL of 5% dextrose over the next 16 hours in the ward. On review the next day, she was not icteric, there was no Kussmaul's respiration and the liver function tests were normal. However, due to the overwhelmingly massive paracetamol ingestion associated with high serum paracetamol levels, IV NAC 50 mg/kg in 500 mL of 5% dextrose 8 hourly was continued for the next 2 days. The liver function tests and prothrombin time remained normal over the next 2 days. The patient was discharged well on the fifth day of hospitalisation.

Her serial investigations are shown in Table 1.

Discussion

Paracetamol is one of the most common antipyretic and analgesic used all over the world. It is easily accessible over the counter and thus intentional paracetamol overdose is common. Ingestion of more than 12.5 g or 25 tablets is associated with acute liver dysfunction.[2] An extensive literature search showed that 60 g (1200 mg/kg) of paracetamol ingestion by our patient was probably the highest ingested dose ever reported.

The dose of paracetamol ingested and the time lag between ingestion and initiation of treatment with NAC is very important. If the dose ingested is more than 150 mg/kg, specific antidote should be given. If the time lag is less than 8 hours, treatment is most effective. When the time lag approaches 8 to 15 hours, the efficacy of treatment starts to decline. The efficacy of treatment is significantly limited if initiated more than 15 hours and doubtful beyond 24 hours of the overdose.[3]

Within therapeutic doses, paracetamol biotransformation involves conjugation with glucoronide and sulphate. A small amount of paracetamol is metabolised by mixed function oxidase enzymes to form highly reactive compound N–acetyl-p-benzoquinoneimine (NAPQ1), which is immediately conjugated with glutathione and subsequently excreted as cysteine and mercapturic conjugates. In overdoses, large amounts of paracetamol are metabolised by oxidation because of saturation of the sulphate conjugation pathway. Liver glutathione stores become depleted so that the liver is unable to deactivate the toxic metabolite (NAPQ1). The paracetamol induced renal damage results from a mechanism similar to that which is responsible for hepatotoxicity.[3,4]

The severity of paracetamol-induced organ damage is dose related. There is, however, some variation in individual susceptibility to paracetamol-induced hepatotoxicity. Patients with high risk for paracetamol toxicity (Table 2) should be treated with NAC at plasma paracetamol concentrations lower than normally used for interpretation.[3]

The clinical course of paracetamol toxicity is divided into four phases.[4]

Phase 1 appears 0.5 to 24 hours post ingestion. The patients are either normal or present with anorexia, nausea or vomiting.

Phase 2 appears 24 to 48 hours post ingestion. Patients may present additionally with right hypochondrial pain. Elevated transaminase levels and bilirubin, and prothrombin time may be prolonged.

Phase 3 starts 72 to 96 hours post ingestion and is characterised by hepatic necrosis including jaundice, coagulation defects, renal failure and hepatic encephalopathy.

Phase 4 continues 4 to 14 days post ingestion and if the

Table 1. Serial Laboratory Investigations in Our Patient

Investigations	Day 1	Day 2	Day 3	Day 4	Day 5
Hb (g/dL)	14.18				
Total white count (/L)	11.5 x 10^9				
Platelets (/L)	296 x 10^9				
Albumin (g/L)	49		43		44
Bilirubin (μmol/L)	8	11	7	7	5
ALT (U/L)	14	10	9	11	10
AST (U/L)	23	19	16	14	15
ALP (U/L)	65	59	61	58	69
GGT (U/L)		12	14	14	15
Amylase (U/L)		189			
Creatinine (μmol/L)	65		55	54	
Serum paracetamol (mg/dL)	207				<10
Salicylate levels (mmol/L)	<0.1				
PTT (N 28-39)	33.1	35.6	33.1	32.9	32.8
PT (N 11-14.5)	13.4	14.3	13.2	13.5	12.8
INR	1.04	1.13	1.00	1.05	0.96

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma glutamyl transpetidase; Hb: haemoglobin; INR: international normalised ratio; PT: prothrombin time; PTT: partial thromboplastin time

Table 2. Risk Factors for Paracetamol Toxicity

No	High-risk group
1	Preexisting liver disease
2	Alcohol intake
3	Poor nutrition
4	Enzyme inducing drugs
5	Anorexia nervosa
6	Human immunodeficiency virus infection

patient survives, complete resolution of hepatic dysfunction occurs and the liver heals without any evidence of fibrosis.

Renal failure secondary to acute tubular necrosis occurs in 25% of patients with severe hepatic damage and in a few without evidence of serious disturbance of liver function. Specific antidotes for paracetamol overdose are NAC or methionine. NAC can be given in IV or oral form. The oral NAC is not preferred as it induces vomiting. The recommended standard treatment regime of IV NAC is 150 mg/kg over 15 minutes, then 50 mg/kg in 500 mL of 5% dextrose over next 4 hours and then 100 mg/kg in 1000 mL of 5% dextrose over the next 16 hours. Bridger et al[5] recommended treatment with NAC if blood paracetamol levels are more than 150 mg/L at 4 hours and more than 30 mg/L at 12 hours. Serious liver damage occurs in 60% of patients with paracetamol levels more than 200 mg/L at 4 hours and 90% over more than 300 mg/L if not treated. They recommended that all patients with paracetamol blood levels more than 150 mg/L at 4 hours and more than 30 mg/L at 12 hours should be treated with NAC. If high risk factors are present (Table 2), treatment should be instituted with paracetamol blood level more than 100 mg/L at 4 hours. Methionine is given orally in a dose of 2.5 g initially followed by 2.5 g 4 hourly for 3 doses (total of 10 g over 12 hours). Methionine is given to patients who are allergic or cannot tolerate NAC.[3,4] Wright et al[6] recommended that 2.5 g of oral methionine should be given to all patients with simple paracetamol poisoning whatever the paracetamol levels. Oral charcoal should not be used as it may impair absorption of oral methionine. Four doses of oral methionine should be completed, and IV NAC should be started immediately as per recommendation of Bridger et al.[5] Thomas[7] reported that an absolute cut off point between a non-toxic and toxic paracetamol overdose does not exist. In judging whether to use the antidote, the clinician should always err on the side of caution. When using treatment normograms, they should assume the longest interval betwee

The molecular absorbent recirculating system (MARS) is a new detoxification method based on albumin dialysis. It removes both protein bound and water soluble substances of low and middle sized molecular weight. Koivusalo et al[8] have described their experience with albumin dialysis on 5 patients. They suggested that a combination of NAC and MARS is effective when toxic dose of paracetamol is ingested with high blood levels even before severe hepatic failure develops. One of their 5 patients was a 24-year-old woman who ingested 17.5 g of paracetamol and was started on standard NAC treatment within 5 hours after ingestion. In spite of the early treatment with NAC, she developed liver failure and was started on MARS. Her paracetamol level was 49.1 mg/L (325 μmol/L) at 30 hours after ingestion. This suggests that NAC in severe paracetamol poisoning may not be 100% effective in its usual regime when given over 24 hours only. Furthermore, MARS can be associated with complications like venous related haematomas and thrombocytopaenia with extracorporeal circulation. MARS treatment is contraindicated in the presence of active bleeding and coagulopathy which are not uncommon in liver failure.

In our patient who ingested 60 g of paracetamol, NAC was instituted within 6 hours. The blood levels at about 6 hours after ingestion were 207 mg/L. We continued NAC

Table 3. Severe Paracetamol Overdose: Treatment and Outcome

Authors	Koivusalo et al	Pajoumand et al	Bridger et al	McIntyre et al	Sule et al
No. of patients	5	1	4	1	1
Maximum number of paracetamol tablets ingested in gm (per kg body weight)	45 g (473 mg/kg)	32.5 g (Weight not given)	32 g (Weight not given)	40 g (Weight not given)	60 g (1200 mg/kg)
Paracetamol blood levels (maximum)	261.48 mg/L (1731 μmol/L) at 24 hours	Not done	178 mg/L at 4 hours	151 mg/L (1 mmol/L) After 36 hours	207 mg/L At 6 hours
Initiation of NAC treatment	After 18 hours	After 24 hours	After 48 hours	After 36 hours	Within 6 hours
Duration of NAC treatment	24 hours	20 hours	24-36 hours	Not given	72 hours
Liver failure	Yes	Yes	Yes	Yes	No
Need of dialysis or MARS	Yes	No	No	Yes	No
Outcome	Death	Survival	Death	Survival	Survival
No. of days in hospital	12 days	12 days	6 days	26 days	5 days

MARS: molecular absorbent recirculating system; NAC: N-acetyl cysteine
Please note: Conversion factor 1 mg/L x 6.62 = 1 μmol/L

for 3 days even though the liver function and prothrombin time was normal after 24 hours. In view of the massive paracetamol ingestion, high paracetamol blood level at 6 hours and the possible failure of antidote effectiveness as shown by others in massive overdoses, we felt that it was safer to continue NAC for a total of 3 days in an attempt to prevent potential liver toxicity after a careful risk versus benefit analysis. Our patient also had high serum amylase of 189 U/L, which was associated with poor prognosis. Schmidt et al[9] studied 602 patients transferred to a specialised unit with severe paracetamol poisoning and 212 unselected patients admitted from the local region. An elevated serum amylase (>100 U/L) occurred in 28 (13%) of the unselected patients, in 218 (36%) of the transferred patients, and in 118 (80%) of 148 patients with fulminant hepatic failure. Only 33 cases of paracetamol-associated acute pancreatitis were diagnosed. A threshold serum amylase of 150 U/L to discriminate non-survivors had 76% sensitivity, 85% specificity, 33% positive predictive value, and 97% negative predictive value. In a logistic regression analysis, a serum amylase more than 150 U/L was associated with an excess mortality (odds ratio 5.0). A serum amylase exceeding 1.5 times the upper normal limit indicates a poor prognosis**.** Moreover, there were case reports that acute pancreatitis with paracetamol-codeine combination correlates with a poor prognosis.[10,11] Our patient had ingested around 360 mg of codeine in total along with paracetamol 60 g which is associated with increased mortality and poor prognosis.[10,11]

Metabolic acidosis is also a poor prognostic marker.[12,13] However, an arterial blood gas was not done in our patient as she was not clinically acidotic. Ethnic and inter-subject differences in paracetamol metabolism may exist and the reason that our patient may have done so well with a longer period of treatment with intravenous NAC may be a result of inherently different metabolic handling of paracetamol. However, there is no data to support this in literature.

Five per cent of patients who received NAC treatment developed complications which included rash, angioedema, hypotension or bronchospasm.[3] These reactions are generally related to the initial bolus; they are seldom serious and slowing the infusion rate is useful. In severe cases, chlorpheniramine 10 to 20 mg IV in an adult may be given.[2,3] Our patient tolerated NAC well without any side effects.

Conclusions

Review of literature shows that paracetamol overdose of more than 30 g is associated with severe acute hepatic dysfunction, need for dialysis and even death in spite of NAC (Table 3).[4,5,8,14] Our patient had consumed probably the highest paracetamol overdose (60 g) ever reported in the medical literature thus far. She had poor prognostic factors like high paracetamol blood levels, high serum amylase and co-ingestion with codeine. She was treated with IV NAC for 3 days without any side effects. From this experience, in very severe paracetamol poisoning, we feel that NAC for 3 days is safe and probably more efficacious than NAC treatment over 24 hours and MARS. Randomised controlled trials are recommended to confirm our experience.

REFERENCES

1. Ng KC. Paracetamol ingestions at the Children's Emergency Department – a three-year series. Singapore Med J 2003;44:79-83.
2. Hawton K, Ware C, Misrty H, Hewitt J, Kingsbury S, Roberts D, et al. Paracetamol self poisoning. Characteristics, prevention and harm reduction. Br J Psychiatry 1996;168:43-8.
3. Benjamin N, Rawlins M, Vale JA. Drug therapy and poisoning. In: Kumar P, Clark M, editors. Kumar and Clark Clinical Medicine. 5th ed. United Kingdom: WB Saunders, 2002:985-7.
4. Pajoumand A, Jalali N, Abdollahi M, Shadnia S. Successful treatment of acetaminophen overdose associated with hepatic failure. Hum Exp Toxicol 2003;22:453-8.
5. Bridger S, Henderson K, Glucksman E, Ellis AJ, Henry JA, Williams R. Deaths from low dose paracetamol poisoning. BMJ 1998;316:1724-5.
6. Wright B, Crowe M. Deaths from low dose paracetamol poisoning. Use of oral methionine for overdose below threshold for acetylcysteine. BMJ 1998;317:1656-7.
7. Thomas SH. Deaths from low dose paracetamol poisoning: if in doubt use the antidote. BMJ 1998;317:1655-6.
8. Koivusalo AM, Yildirim Y, Vakkuri A, Lindgren L, Hockerstedt K, Isoniemi H. Experience with albumin dialysis in five patients with severe overdoses of paracetamol. Acta Anaesthesiol Scand 2003;47:1145-50.
9. Schmidt LE, Dalhoff K. Hyperamylasaemia and acute pancreatitis in paracetamol poisoning. Aliment Pharmacol Ther 2004;20:173-9.
10. Hastier P, Demarquay JF, Maes B, Caroli-Bosc FX, Dumas R, Delmont J, et al. Acute pancreatitis induced by codeine-acetaminophen association: a case report with positive rechallenge. Pancreas 1996;13:324-6.
11. Renkes P, Trechot P. Acetaminophen-codeine combination induced acute pancreatitis. Pancreas 1998;16:556-7.
12. Koulouris Z, Tierney MG, Jones G. Metabolic acidosis and coma following a severe acetaminophen overdose. Ann Pharmacother 1999;33:1191-4.
13. Mutimer DJ, Ayres RC, Neuberger JM, Davies MH, Holguin J, Buckels JA, et al. Serious paracetamol poisoning and the results of liver transplantation. Gut 1994;35:809-14.
14. McIntyre CW, Fluck RJ, Freeman JG, Lambie SH. Use of albumin dialysis in the treatment of hepatic and renal dysfunction due to paracetamol intoxication. Nephrol Dial Transplant 2002;17:316-7.