

Acute Paracetamol Poisoning: Two Case Studies and a Review



Curriculum Vitae

James Ker studied at the University of Pretoria and qualified with a MBCbB in 1971 and M Med (Int) in 1978. He held the following appointments: Head of Respiratory Medicine at HF Verwoerd Hospital (1980-1982), then Head of ICU at 1 Military Hospital (1982-1983). James went into private practice (1983-1989) during which time he was also part time lecturer at Medunsa. Currently he is Principal Physician in the Department of Medicine, University of Pretoria and HF Verwoerd Hospital, and a registered pulmonologist since 1993. His interests are: Asthma, Respiratory Muscle Function and Heart Failure. James is married and they have two children.

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Summary

This article presents a review on paracetamol as a therapeutic agent but also as a potential toxin, based on two patient studies. The pathophysiology, diagnostic approach and management of paracetamol poisoning is discussed.

Introduction

Paracetamol (Acetaminophen) is widely used as an analgesic and antipyretic and is readily available without prescription. It was first used in medicine by von Mering in 1893, but it only gained popularity after 1949 after being recognised as the major active metabolite of both acetanilid and phenacetin.¹

After oral ingestion paracetamol is rapidly and almost completely absorbed from the gastro-intestinal tract and 85 - 95 % is metabolised primarily by the liver and excreted in the urine as a non toxic substance. The remaining 5 - 15 % is metabolized through Cytochrome P-450 to a toxic intermediate which is detoxified by glutathione present in the liver cell. During an overdose glutathione is exhausted and then hepatic cell necrosis with subsequent liver failure develops. Paracetamol remains the commonest cause of fulminant hepatic failure in the United Kingdom, accounting for 60 - 65 % of all cases.² Paracetamol is the most commonly reported potentially toxic pharmaceutical ingestion in both adults and

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1995;16:102-6.

KEYWORDS

Poisoning;

Acetaminophen;

Physicians, Family;

Diagnosis.

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children, resulting in over 100,000 calls to United States poison centres in 1991,³ and despite the availability of a specific antidote, fatalities still occur. It was found that acute paracetamol poisoning is common in Cape Town.⁴

The purpose of this article is to discuss the clinical presentation of paracetamol poisoning using two patient studies, and to review modern concepts in the management.

Patient Studies

The first patient is a 17-year old female who was admitted to the medical ward with a history that she had taken 45 paracetamol tablets (22,5 gram) a few hours previously. The results of blood tests performed over the next few days are presented in Table I. This demonstrated high levels of liver enzymes, indicating liver cell necrosis. The prothrombin activity as well as bilirubin remained normal. She made an uneventful recovery.

The second patient is a 20-year old female who developed jaundice three days after she had ingested 35 paracetamol tablets (17,5 gram). The results of the blood tests performed on this patient during her stay in hospital is presented in Table II. This patient demonstrates extremely high levels of liver enzymes with the ALT more than eighteen thousand units. Her prothrombin activity dropped to 37 % of normal. A consultation with the liver unit was requested with the possibility in mind that she might need aggressive treatment which might include consideration for liver transplantation. She made a complete recovery and was discharged 7 days after admission.

Diagnostic Approach

Early recognition and treatment is essential. A history of ingestion is essential, but the most reliable method of diagnosis is a determination of plasma paracetamol concentration.⁵ Determination of a paracetamol plasma concentration should be done routinely in those cases with an unreliable history, because poisoned patients frequently have no clinical abnormalities until many hours after a

Paracetamol remains the commonest cause of fulminant hepatic failure in the UK.

TABLE I

	Day 1	Day 2	Day 3	Day 5	Normal values
Total Bilirubin	19	10,5	N	N	4-30 μ mol/L
Conjugated Bilirubin	<5	N	N	N	0-4 μ mol/L
Alkaline Phosphatase	-	110	106	98	26-78 IU/L
G/GT	-	77	-	80	9-34 IU/L
ALT	2 180	4 868	2 394	1 168	10-37 IU/L
AST	3 590	3 440	329	71	11-36 IU/L
LDH	-	-	239	156	6-0-200 IU/L
Albumin	-	38	-	-	39-50 g/L
Prothrombin activity	0	100 %	--	100 %	-

paracetamol overdose. Early identification of unrecognised poisoning and treatment with the specific antidote will prevent morbidity and possible mortality. Due to the common formulation of paracetamol with opioids, the possibility of paracetamol toxicity should also be considered in every case of suspected opioid ingestion.

When a reliable history is available, patients with ingestions less than 150 mg/kg in children, or 7,5 gram in adults do not require further evaluation for toxicity, provided they do not have chronic liver disease.

The poison centres in the USA received more than 100 000 calls in 1991 due to paracetamol poisoning.

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When the paracetamol plasma concentration is above 150 µg/ml at 4 hours or above 15 µg/ml after 15 hours, liver functions should be performed. The aspartate aminotransferase (AST) is used as a sensitive marker of liver injury and is of prognostic value. If AST indicates hepatocellular injury, then serial determinations of AST, alanine aminotransferase (ALT), prothrombin time (PT), bilirubin, electrolytes and glucose are warranted.⁵

Pathophysiology and Clinical Features

In adults, hepatotoxicity may occur after ingestion of a single dose of 10 to 15 gram (200 to 250 mg/kg) paracetamol and a dose of 25 gram or more is potentially fatal.¹ When high doses of paracetamol are ingested, it undergoes N-hydroxylation to form N-acetyl-para-benzoquinoneimine (NAPQI), a highly reactive intermediate metabolite which reacts with sulphhydryl groups in proteins and glutathione. When hepatic glutathione is depleted after the ingestion of large quantities of paracetamol, reaction with hepatic proteins is increased and hepatic necrosis is the result.

There are other conditions which are associated with depletion of hepatic glutathione. These conditions cause the liver to have an increased susceptibility to the toxic effects of paracetamol. These patients are therefore high-risk patients and may develop toxic effects at a lower dose of ingestion. Chronic alcohol abuse, malnutrition, patients on anticonvulsants and rifampicin all constitute this high risk group.

Symptoms of acute poisoning during the first 2 days do not reflect the

potential seriousness of the intoxication. Nausea, vomiting, anorexia and abdominal pain occur during the initial 24 hours and may persist for a week or more. Clinical indications of hepatic damage become manifest within 2 to 4 days of ingestion of toxic doses. Severe liver damage (with levels of aspartate aminotransferase activity in excess of 1000 IU per liter of plasma) occurs in 90% of patients with plasma concentrations of acetaminophen greater

A 20 year old needed aggressive treatment after ingesting 35 paracetamol tablets - even liver transplantation was considered!

TABLE II

	Day 1	Day 3	Day 5	Normal values
Total Bilirubin	98	79,6	67,8	4-30 µ mol/L
Conjugated Bilirubin	43,6	25,6	53,1	0-4 µ mol/L
Alkaline Phosphatase	-	-	132	26-78 IU/L
G/GT	-	-	300	9-34 IU/L
ALT	18,945	8,340	3 295	8-30 IU/L
AST	16,985	1 805	156	11-32 IU/L
LDH	-	-	190	60-200 IU/L
Albumin	-	-	36,7	39-50 g/L
Prothrombin activity	-	37 %	100 %	

than 300 µg/ml at 4 hours, or 45 µg/ml at 15 hours after ingestion of the drug. Minimal hepatic damage can be anticipated when the drug concentration is less than 120 µg/ml at 4 hours, or 30 µg/ml at 12 hours after ingestion.

The clinical course of paracetamol poisoning can be divided into 4 stages.⁶

Stage I: 0,5 to 24 hours after ingestion, is characterised by anorexia, nausea, vomiting, malaise, pallor and diaphoresis.

Determine the plasma paracetamol concentration routinely.

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Stage II: 24 to 48 hours after ingestion, entails the resolution of stage I and the development of right upper quadrant abdominal pain and tenderness, elevated serum bilirubin, prothrombin time and hepatic enzymes, and oliguria.

Stage III: 72-96 hours after ingestion, is characterised by peak liver function abnormalities while anorexia, nausea, vomiting, malaise may reappear.

During stage IV: 4 days to 2 weeks after ingestion, resolution of hepatic dysfunction usually takes place. Fatalities generally occur between 3 and 5 days after overdose but have been reported at other times³ and hepatic regeneration becomes complete in survivors. The rate of recovery varies but is complete by 5 to 7 days, although recovery can be longer in severely poisoned patients.

Management

According to Sommers⁷ *all* patients suspected of paracetamol poisoning should be admitted to hospital for observation. Gastric lavage and activated charcoal are only of benefit if given within 4 hours of ingestion of an overdose of paracetamol. If a mixed ingestion of paracetamol and another drug is suspected, then charcoal should be used as indicated regardless of the time delay and without regard to the specific treatment of paracetamol toxicity.

N-acetylcysteine (NAC) is the current treatment of choice for paracetamol overdose. NAC supplies additional glutathione to enhance glutathione supply.⁸ NAC may have other actions that ameliorate organ damage after injury has occurred.

The efficacy of acetylcysteine as an antidote for paracetamol has been defined, but the optimal time of dosing is still under debate. The ideal time to start acetylcysteine treatment is within 8 hours of ingestion of paracetamol.⁹

Neither intravenous nor oral NAC has been shown to be the superior route of administration, because each dosing protocol is very effective when treatment is initiated within 10 hours of ingestion.¹⁰ The dosage schedule for oral treatment is 140 mg/kg, followed by 70 mg/kg every 4 hours for 17 doses (total of 18 doses equaling 1330 mg/kg in 68 hours), and for intravenous treatment 150 mg/kg IV as a bolus over 15 minutes, then 50 mg/kg over 4 hours, then 100 mg/kg over 16 hours (total of 300 mg/kg in 20 hours).

Treatment with acetylcysteine up to 24 hours after the overdose is both safe and beneficial.⁹ All patients with evidence of severe toxicity should be given acetylcysteine regardless of the duration after which they present.² The use of acetylcysteine up to 72 hours postoverdose significantly decreases both the progression of hepatic encephalopathy and mortality.¹¹

Cimetidine has been considered as an adjunctive agent due to its ability to inhibit cytochrome P-450. Cimetidine may have an additional protective effect when used with acetylcysteine in paracetamol overdose.^{12,13}

The improvements in intensive care and the advent of orthotopic liver transplantation have allowed the rescue of a previously untreatable small group of patients with this poisoning.^{2,14}

Poisoned patients often show no clinical abnormalities until many hours after the overdose.

"All patients suspected of paracetamol poisoning should be admitted to hospital for observation"

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Start acetylcysteine treatment 8 hours after taking paracetamol – safe and beneficial

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