

# PARACETAMOL POISONING AND HEPATOTOXICITY IN CHINESE - THE PRINCE OF WALES HOSPITAL (HONG KONG) EXPERIENCE

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## ABSTRACT

*From 1989 to 1991, 104 Chinese patients were admitted to the Prince of Wales Hospital with paracetamol poisoning. Only 11 subjects had a plasma paracetamol concentration above the published treatment line. Intravenous N-acetylcysteine (NAC) was completely effective when given within 8 hours (3 patients), while late treatment with NAC at 16 and 26 hours after overdose (2 patients) was ineffective in preventing liver damage as evidenced by elevations in plasma alanine transaminase concentrations. Of the 6 patients receiving NAC between 10 to 15 hours, two had liver damage. Two other subjects who presented late or in whom a plasma paracetamol concentration was not measured also developed liver damage. Fortunately, none of these 6 subjects developed hepatic encephalopathy. We recommend that a standard protocol be readily available for junior hospital staff to use when treating patients with paracetamol overdose.*

*Keywords: paracetamol poisoning, liver damage, Chinese*

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## INTRODUCTION

Paracetamol (acetaminophen) is considered to be a safe analgesic when taken in the recommended dose<sup>(1)</sup>. In overdose, however, it can cause hepatic and other organ damage<sup>(2)</sup> but with the early administration of intravenous N-acetylcysteine (NAC)<sup>(3)</sup> or oral methionine<sup>(4)</sup>, overdosage is invariably followed by recovery. Although these antidotes have been available for more than two decades, many patients still die from paracetamol poisoning largely because of late presentation<sup>(2,5)</sup>.

Ethnic difference in the proportions of paracetamol undergoing metabolic activation have been reported, suggesting possible differences in susceptibility to hepatotoxicity<sup>(6)</sup>. However, no data was available on the occurrence of paracetamol hepatotoxicity in Chinese subjects. This paper describes our experience at the Prince of Wales Hospital (PWH), Hong Kong with the treatment of paracetamol poisoning from 1989 to 1991 and emphasises the importance of a standard treatment protocol for all junior staff in any hospital.

## SUBJECTS AND METHODS

The PWH is a 1400-bed general teaching hospital situated in the north-eastern New Territories in Hong Kong. It serves a rapidly increasing population of over one million in 1989. There are 3 accident and emergency departments in this region including the one at the PWH.

To identify cases of paracetamol poisoning, a search of the admission books in the general medical wards and registry

of requests for urgent paracetamol levels in the Department of Chemical Pathology at the PWH was performed. Only Chinese patients were included in this analysis.

The data are presented as medians or means  $\pm$  SEM, as applicable.

## RESULTS

The search uncovered the records of 104 patients and these formed the basis of the present study. Most patients were young adults (median age 23 years; range 14 to 85 years). There were 78 females and 26 males.

Twenty-six patients took paracetamol (n=24) or paracetamol-containing compounds (n=6) alone. Forty-seven patients had mixed overdoses involving other drugs (n=31), alcohol (n=18) or household products (n=8). The other drugs included hypnotics (n=8), analgesics (n=6), antihistamines (n=5) and antacids (n=3).

Psychiatric assessment indicated that most patients (n=84) were young adults under 30 years of age and suffering from a temporary emotional or social crisis. Six patients had psychosis in remission or in relapse.

The median amount of paracetamol ingested in 94 patients was estimated to be 5 g (range 0.6 + 25 g). In 10 patients, the amount ingested was not known.

Most patients (n=71) presented to an accident and emergency department within four hours of ingestion (median 2 hours; range 0.5 to 72 hours).

Gastric lavage using a nasogastric tube was performed in 75 patients mostly (n=54) within four hours of overdose (median 2.5 hours; range 0.5 to 15 hours). The reasons for not performing the procedure were stated in 18, including patient refusal (n=7) and late presentation (n=9). Ipecacuanha was given in 2 other patients.

Plasma paracetamol concentrations were less than 0.1 mmol/l in 36 patients including 3 patients who were admitted more than 32 hours after ingestion. Plasma paracetamol concentrations were not obtained in 9 patients because the dose ingested was considered to be small. The reason for not measuring the plasma concentration was not clear in one other patient. In the remaining 58 patients, they ranged from 0.1 to 2.0 mmol/l (mean 0.5 mmol/l) (Fig 1). Only 11 subjects had levels above that recommended for treatment. Blood samples were taken at under 4 hours after the overdose in 9 patients and in 17 patients, 2 or more separate estimations were performed.

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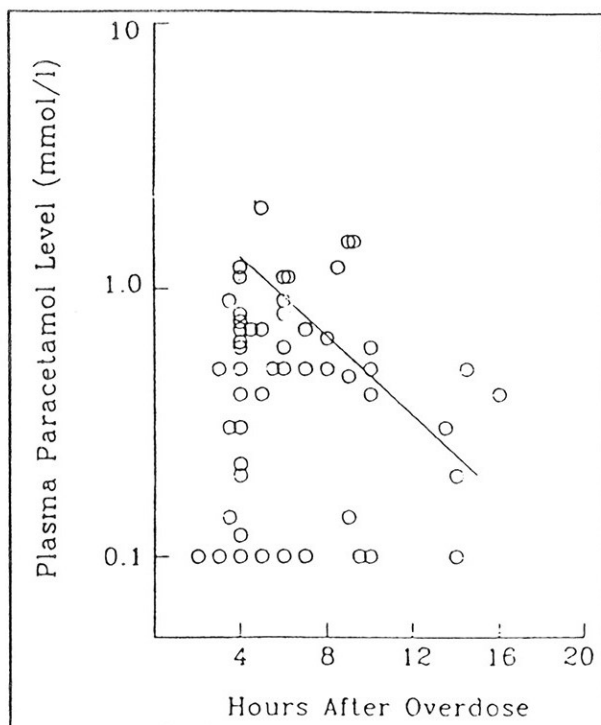
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**Fig 1 - Graph plotting plasma paracetamol levels in 42 Chinese subjects in relation to the time of ingestion. For those who had multiple estimations, only the initial reading is shown. Treatment line (—) as defined by Prescott et al, 1979<sup>(3)</sup> is also shown.**



Intravenous NAC is the only antidote available for the treatment of paracetamol poisoning in most hospitals in Hong Kong. A total of 16 patients received a full course of intravenous NAC according to the manufacturer's standard protocol, including 4 patients with non-toxic plasma paracetamol concentrations<sup>(3)</sup> and one patient presenting late (25 hours) after taking 20 g of paracetamol (level <0.1 mmol/l). A further 22 patients were given partial treatment with NAC which was subsequently stopped when the plasma paracetamol concentration was found to be below the treatment line. Four of the 48 patients receiving NAC developed a transient and uncomplicated urticarial rash.

Nausea and/or vomiting were present in 53 patients. This usually subsided soon after admission, but would have hampered oral therapy. Two patients experienced persistent vomiting lasting more than 48 hours. Five patients who took paracetamol together with "Cortal" (acetylsalicylic acid 500mg, caffeine anhydrous 30mg), "Coltalin" (paracetamol 250mg, caffeine 30mg, chlorpheniramine 2mg, phenylephrine 5 mg, thiamine 3mg) or alcohol developed minor hematemesis. At presentation, 24 patients were drowsy presumably due to the effects of other drugs (hypnotics in 7, antihistamines in 3, antidepressants in 2, narcotics in 2, and unknown in 2), alcohol (n=7) or "Dettol" (which contains phenols, n=1).

Six of the 104 patients included in this study developed liver damage as evidenced by elevations in their plasma alanine transaminase concentrations (ALT). All were female and their clinical details are shown in Table I. For comparison, clinical details of 7 others with toxic paracetamol levels but without liver damage are also shown. There was no mortality. None of the 6 subjects with liver damage developed hepatic encephalopathy and all recovered uneventfully.

## DISCUSSION

Hepatotoxicity from paracetamol overdose results from the

formation of a highly reactive metabolite, N-acetyl benzoquinoneimine (NAPQI), which, at lower doses, is rapidly inactivated by conjugation with reduced glutathione and excreted in the urine as cysteine and mercapturic acid conjugates of paracetamol<sup>(1)</sup>. After a toxic dose, hepatic glutathione is depleted, allowing NAPQI to react with and destroy hepatocytes. The protective actions of NAC after paracetamol overdose are primarily owing to replenishment of hepatic glutathione stores and detoxication of NAPQI<sup>(7,8)</sup>. In addition, NAC may act as a source of sulphate to enable conjugation of paracetamol, or as an antioxidant to prevent inflammatory response initiated by oxidative damage<sup>(9)</sup>. NAC may also allow repair of oxidative damage by regenerating cysteine or glutathione.

Intravenous NAC administered within 10 hours in a dose of 300 mg/kg over 20 hours is highly effective in preventing hepatic necrosis, renal failure and death in patients with severe paracetamol poisoning<sup>(3,10)</sup>. When given within 8 hours, NAC is effective in preventing even trivial liver and renal damage. Intravenous therapy with NAC after 15 hours have elapsed was considered to be ineffective because it failed to prevent severe liver damage, defined by a rise in the aspartate transaminase above 1000 iu/l.

In the present study (Table I), NAC was completely effective when given within 8 hours (patients 9, 11, 13). Of the 6 patients receiving NAC between 10 to 15 hours, two had liver damage (patients 5, 6). Late treatment with NAC at 16 and 26 hours after overdose was ineffective in preventing liver damage (patients 1, 3).

More recently, several studies have shown that late treatment with NAC (after 15 hours) may still be beneficial in patients with severe paracetamol poisoning. In a retrospective review of oral NAC treatment, therapy up to 24 hours after ingestion was associated with a lower incidence of hepatotoxicity (41%) compared with historical controls<sup>(11)</sup>. In a prospective study of 20 patients treated with intravenous NAC 12 to 24 hours (median 15.5 hours) after ingestion, 10 patients had plasma paracetamol levels which were associated with a 90% risk of severe liver damage. This complication, however, only occurred in 4 patients (40%)<sup>(12)</sup>. In a retrospective analysis of 100 patients with paracetamol-induced fulminant liver failure<sup>(13)</sup>, mortality was 37% in patients who received intravenous NAC 10 to 36 hours (median 17 hours) after the overdose, compared with 58% of those not given the antidote; similarly, fewer patients who received NAC progressed to grade III/IV coma compared with those who did not receive the antidote (51% versus 75%, respectively).

Chronic alcoholics and patients taking drugs that induce hepatic enzymes (eg carbamazepine, rifampicin) are alleged to develop liver and renal damage at lower paracetamol concentrations, possibly due to increased production of NAPQI relative to other metabolites<sup>(14,15)</sup>. For this reason, it has been proposed by others that the treatment threshold should be halved in these subjects<sup>(9,16)</sup>. However, studies of paracetamol metabolism in epileptic patients on anticonvulsant therapy do not show evidence of increased oxidative metabolism despite glucuronide conjugation being enhanced<sup>(17)</sup>. Furthermore, similar studies in chronic alcoholics only show evidence of increased oxidative metabolism in a few individuals<sup>(18)</sup>. Probably of more importance in this locality is that some patients with chronic hepatitis B infection and hepatocellular carcinoma show greatly increased oxidative metabolism of paracetamol<sup>(19)</sup>. Thus, we suggest that the treatment threshold should be lowered in patients with histories of high alcohol intake and hepatitis B related liver diseases.

A significant proportion of the patients (n=36) in our study

**Table I - Clinical details and laboratory investigations in 13 Chinese subjects with\* (patients 1 to 6) or without (patients 7 to 13) liver damage following significant overdoses with paracetamol**

Patient	Sex/age	Estimated dose (g)	Ingestion treatment interval (hours)	Plasma paracetamol (hours after overdose) (mmol/l)	Maximum ALT (iu/l) (iu/l)	Maximum bilirubin (umol/l)	Maximum prothrombin-time ratio
1*	F/25	8	26	0.5 (10 h)	426	73	1.26
2*	F/26	15	No treatment	Not available	99	4	0.96
3*	F/22	17.5	16	0.4 (16 h)	9530	145	2.71
4*	F/29	15	No treatment	<0.1 (72 h)	475	9	1.20
5*	F/19	12	10	1.5 (9 h)	222	22	1.28
6*	F/28	25	11	1.5 (9 h)	3920	87	1.32
7	M/33	8	13.5	0.3 (13 h)	41	10	1.13
8	M/20	17.5	11	0.6 (10 h)	6	16	1.11
9	F/18	13	6.5	1.1 (6 h)	11	19	Not available
10	F/17	7.5	14.5	0.5(14.5h)	11	18	1.04
11	F/16	10	6	1.1 (6 h)	24	11	1.22
12	F/85	6.5	15	1.2 (8.5)	10	7	1.09
13	F/27	8	5	2 (5 h)	17	14	1.24

**Table II - Outline management plan for paracetamol overdose.**

1. As with all poisoning, immediate attention should be given to the airway and respiration (although paracetamol alone does not depress respiration).
2. In the absence of a contraindication, perform gastric aspiration and lavage (with appropriate airway care) in patients admitted within 4 hours of overdose.
3. Measure plasma paracetamol concentration urgently in *all* patients but not earlier than 4 hours after ingestion.
- 4.\* If the plasma paracetamol concentration is above the "treatment" line joining semilog plots of 1.32 mmol/l (200 mg/l) at 4 hours and 0.20 mmol/l (30 mg/l) at 15 hours after ingestion, give intravenous N-acetylcysteine (NAC), 150 mg/kg in 200 ml dextrose 5% over 30 to 60 minutes, then 50 mg/kg in 500 ml dextrose 5% over 4 hours, then 100 mg/kg in 1000 ml dextrose 5% over 16 hours.
5. For those patients who have taken a significant overdose (eg. over 7.5 g in adults) and who are seen at or after 8 hours after ingestion, commence intravenous NAC while awaiting result of plasma paracetamol assay.
6. Use of NAC from 15 to 24 hours is controversial but some recent evidence suggests that it is beneficial.
7. Look out for hepatic and renal damage. Peak disturbance of liver function occurs 2 to 4 days after an overdose. Monitor liver enzymes and prothrombin time. The latter is often the best guide to recovery.

\*(a) Manufacturers recommend giving loading dose over 15 minutes but irregularities in administration rate may then lead to very high plasma concentrations initially<sup>(20)</sup> possibly associated with the side effects such as flushing and urticaria. Thus we recommend generally using a slower rate of loading dose administration except in patients presenting near to or after 8 hours.

(b) It is controversial whether the treatment threshold should be lowered in patients receiving hepatic enzyme-inducing drugs and in chronic alcoholics (see discussion). However, there is more convincing evidence of its lowering in patients with histories of high alcohol intake and hepatitis B related liver disease.

had admission plasma paracetamol concentrations below 0.1 mmol/l despite admission in 31 cases being within 8 hours of ingestion. Apart from the patient who was admitted 3 days after an overdose (patient 4 in Table I) and the 7 patients in whom the ingested dose was unknown, the alleged amount

ingested in the remaining 28 patients was small (median 2.5 g). Other possible explanations include the common occurrence of early vomiting, early presentation to hospital for gastric lavage and/or an unreliable history. Because the amount claimed to be ingested may be inaccurate or indeterminable, it is important that an urgent paracetamol concentration measurement is ordered in all cases.

Our findings also suggest that a protocol for managing any patient who takes an overdose of paracetamol should be readily available for junior staff in any hospital (Table II). In this survey, for example, plasma paracetamol levels were ordered in 9 patients less than 4 hours after ingestion when absorption may be incomplete. In others, measurements were repeated unnecessarily while in two (patients 1 and 2 in Table I), blood levels were not traced or ordered leading to NAC therapy being delayed or not given with consequent liver damage.

In summary, paracetamol taken in overdose may result in liver damage in Chinese and this can be prevented by the early administration of intravenous NAC. We recommend that a standard protocol (such as given in Table II) be readily available for junior hospital staff to use when treating patients with paracetamol overdose.

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## 8TH INTERNATIONAL WORKSHOP ON THERAPEUTIC ENDOSCOPY

organised by The Chinese University of Hong Kong and

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