FACTORS RESPONSIBLE FOR CONTINUING MORBIDITY AFTER PARACETAMOL POISONING IN CHINESE PATIENTS IN HONG KONG

T Y K Chan, A Y W Chan, J A J H Critchley

ABSTRACT

To determine those factors responsible for continuing prevalence of liver damage after paracetamol poisoning, 222 Chinese patients presenting to the Prince of Wales Hospital, Hong Kong from 1988 to 1993 were studied. Of the 27 patients with plasma paracetamol concentrations above the recommended "treatment line", 13 developed liver damage. Time elapsed between ingestion and treatment with intravenous N-acetylcysteine (NAC) was the most important prognostic factor. Failure to give NAC appropriately (50%) and late presentation (23%) were the main reasons for the continuing morbidity. Liver damage in some of the remaining patients (30%) could have been prevented if NAC was started in the Emergency Department within 8-15 hours of ingestion. Liver damage after paracetamol poisoning remains common (5.9%) in Hong Kong because of the failure to give NAC appropriately or late presentation. We hope to improve patient management by repeatedly emphasising the importance of adherence to the standard protocols and having the toxic plasma level results phoned directly to the duty registrars.

Keywords: *paracetamol poisoning, liver damage, Chinese*

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INTRODUCTION

For the great majority of people, paracetamol (acetaminophen) is a safe analgesic/antipyretic provided it is taken in the recommended doses[1]. It is widely available under several brand names and in many proprietary combinations with other drugs.

The major problem caused by paracetamol is hepatotoxicity after large overdoses of the drug[1,2]. A fraction of the drug is converted by cytochrome P450-dependent mixed-function oxidase to a highly reactive metabolite, N-acetyl-*p*-benzoquinoneimine (NAPQI), which, with therapeutic doses, is quickly detoxified by glutathione and excreted in the urine as the cysteine and mercapturic acid conjugates of paracetamol. After a toxic dose, an increasing amount of NAPQI is formed, thus depleting the glutathione stores in the liver. NAPQI is then free to cause hepatic necrosis, which can be prevented by the early administration of glutathione precursors.

Although effective antidotes, such as N-acetylcysteine (NAC)[3] and methionine[4], have long been available for the treatment of paracetamol poisoning, hepatic damage and even deaths are still commonly seen in many countries[2,5,6]. Delay in the initial presentation to a hospital, which would preclude antidote therapy in the majority of patients, was found to be the major factor. However, it is not uncommon for treatment to be wrongly or inadvertently withheld[2,5,7].

The main objective of the present study was to determine those factors which were responsible for the continuing prevalence of liver damage in Chinese patients with paracetamol poisoning. This study included only such patients presenting to the Prince of Wales Hospital (PWH) between January 1988 and December 1993.

SUBJECTS AND METHODS

The PWH is the sole general teaching hospital in the north-east of the New Territories in Hong Kong. It served a population of about 1.1 million in 1993. There are three casualty departments in this region including the one at the PWH.

To identify the cases of paracetamol poisoning admitted to the PWH, a search was made of the admission books of the general medical wards and the registry of requests for urgent plasma paracetamol concentrations in the Department of Chemical Pathology. Only Chinese patients were included in this analysis.

The data are presented as median and ranges. Tests of statistical significance were carried out by the chi-squared test, Fisher's Exact Test or Mann-Whitney U test, where applicable.

RESULTS

A total of 222 Chinese patients (170 females, 52 males) with paracetamol poisoning were identified from the search. Most patients were young adults (median age 23 years, range 14-85 years). The mean interval from the time of ingestion to arrival at the Emergency Department was 2 hours (range 0.2 hours to 6 days).

Twenty-seven patients with plasma paracetamol concentrations above the "treatment line" joining semilog plots of 1.32 mmol/L (200 mg/L) at 4 hours and 0.2 mmol/L (30 mg/L) at 15 hours after ingestion were studied in detail. All were previously healthy and none of these subjects took alcohol on a daily basis. Thirteen patients developed liver damage as evidenced by the increased plasma alanine transaminase (ALT) levels, and this was severe (peak plasma ALT more than 1000

Department of Clinical Pharmacology
The Chinese University of Hong Kong
Prince of Wales Hospital
Shatin, New Territories
Hong Kong

T Y K Chan, MBChB, FRCP (Edin)
Associate Professor

Department of Chemical Pathology
The Chinese University of Hong Kong

A Y W Chan, FRCP (Glas), FRCPA
Lecturer

J A J H Critchley, MBChB, PhD, FRCP (Edin & Lond)
Professor and Chairman

Correspondence to: Dr T Y K Chan

IU/L) in five. All the 14 patients without liver damage and nine of the patients with liver damage received intravenous NAC according to the standard protocol[3]. One of the patients in the latter group also received a continuous intravenous infusion of NAC (6 g/day) for the next five days.

When compared to patients without liver damage, those with liver damage tended to present late to the Emergency Department (7.7 vs 4.4 hours) (Table I). Consequently, gastric lavage or induced vomiting had been performed less frequently. Also largely because of the late presentation, those with liver damage were given intravenous NAC after a longer delay (13.5 vs 7.1 hours).

Table I – Clinical details of 27 Chinese patients with (n=13) or without (n=14) liver damage.

	With liver damage	No liver damage	p value
Females: males	12:1	9:5	0.164
Ages (years)	22 (16-34)	19.5 (14-85)	0.519
Dose (g)	12 (7-25)	15.5 (6.5-40)	0.155
Ingestion-admission intervals (h)	7.7 (0.6-72)	4.4 (1-11.5)	0.068
Nausea/vomiting (%)	85	79	1.000
Gastric lavage/ induced vomiting (%)	31	79	0.013
Admission-NAC intervals (h)	2.7 (0.6-19.7)[a]	2.9 (0.4-7.0)	0.439
Ingestion-NAC intervals (h)	13.5 (10-26)[a]	7.1 (3.8-15)[b]	0.003

Medians and ranges.
[a] 9 patients treated with intravenous N-acetylcysteine.
[b] 14 patients treated with intravenous N-acetylcysteine.

There was a female predominance amongst patients with liver damage, but this difference in sex distribution did not reach statistical significance. The 21 females did not differ significantly ($p \geq 0.1$) from the 6 males with regards the amount of paracetamol ingested, the ingestion-admission interval and the ingestion-treatment interval.

Three of the 13 patients with liver damage presented to the Emergency Department 18 to 72 hours after ingestion. None of these received intravenous NAC because at that time late treatment was considered to be ineffective.

Ten other patients with liver damage presented 0.6 to 14 hours after ingestion to the Emergency Department (Table II). Plasma paracetamol concentration measurement was not requested for subject 2 and NAC was not given. There was a long delay in giving NAC to subjects 1, 5, 8 and 10 because plasma paracetamol measurement results were not obtained or assessed immediately. Intravenous NAC could have been started earlier in the Emergency Department in subjects 3, 4, 7 and 9. The alleged ingestion time in subjects 6 and 10 was probably incorrect.

All patients recovered completely, including subject 9 who had developed stage I hepatic encephalopathy.

DISCUSSION

The management for paracetamol poisoning is now well established[1]. In the UK[3] and Hong Kong[7], a standard 20-hour protocol using intravenous NAC in a dose of 300 mg/kg has been found to be highly effective in preventing liver damage, renal failure and deaths in patients with plasma paracetamol concentrations above the "treatment line" when started within 10 hours[3]. NAC is completely effective in preventing even trivial liver damage if commenced within eight hours[3].

Despite the availability of effective antidotes and standard protocols for the treatment of paracetamol poisoning[3,7,8], liver damage and even deaths are still commonly seen. In the UK[5], delay in initial presentation (85% > 16 hours) to hospital was found to be a major factor responsible for severe liver damage in 147 patients referred to a liver unit in 1982-83, and failure to give NAC or methionine appropriately was responsible for 11 cases.

In Hong Kong, our experience at the Prince of Wales Hospital indicated that paracetamol is increasingly used for self-poisoning[9]. In view of this trend and existence of avoidable cases of liver damage[7], local guidelines on the management of paracetamol poisoning have also been developed and updated periodically[7,10,11]. However, despite our efforts, the proportion of patients having liver damage has not decreased during the periods 1989-91 (5.8%) and 1992-93 (6.9%) (Table III). There

Table II – Clinical details of 10 Chinese patients with paracetamol induced liver damage who presented to the Emergency Department within 15 hours of ingestion.

	Sex/ age	Dose (g)	Ingestion-admission intervals (h)[a]	Plasma paracetamol concentrations (h after ingestion) (mmol/L)	Admission-NAC intervals (h)	Ingestion-NAC intervals (h)	Main reasons for the significant delay in giving intravenous NAC
1.*	F/25	8	7.3 (8.3)	0.5 (10 h)	19.7	27	Plasma paracetamol conc. not traced
2.*	F/26	15	3.5 (5)	Not requested	–	–	NAC not given
3.*	F/22	17.5	13.3 (16)	0.4 (16 h)	2	15.3	NAC not given until arrival in ward
4.*	F/19	12	7.7 (8.7)	1.5 (9 h)	2.7	10	–
5.*	F/28	25	0.6 (1.1)	1.5 (9 h)	0.6	10.7	Plasma paracetamol conc. not traced
6.	F/18	10	7.2 (8)	0.5 (8 h)	0.8	8	–
7.	F/18	12	14 (15)	0.6 (16 h)	2.7	16.7	–
8.	F/24	7	2.5 (6)	0.8 (8 h)	12.5	15	Plasma paracetamol conc. not traced
9.	F/19	13	13.5 (14.5)	0.7 (14 h)	1.5	15	–
10.	M/34	15	2.7 (4.1)	1.2 (5 h)	7.5	10.2	Plasma paracetamol conc. not traced

*From Chan TYK et al., 1993[7]
[a] Time elapsed between ingestion and admission to the Casualty Department and, in parenthesis, ward.

Table III – Chinese patients presenting to the Prince of Wales Hospital, Hong Kong with paracetamol-induced liver damage between 1988 and 1993.

	1988[a]	1989-91[b]	1992-93	Total
Total no. of patients	16	104	93	213
At risk[c]	0	13	14	27
No. with liver damage (%)	0	6 (5.8)	7 (6.9)	13 (5.9)

[a] Admissions to six of the eight general medical wards only.
[b] From Chan TYK et al., 1993[7].
[c] Plasma paracetamol concentration above the "treatment line".

is therefore an obvious need for a more detailed study of those factors responsible for the continuing morbidity in these patients.

The present study has shown that the time elapsed between ingestion and treatment with NAC is the important prognostic factor in paracetamol overdose (Table I). Probably because of the small size of our study, the difference between patients with and without liver damage reached statistical difference with regards the ingestion-treatment interval but not for ingestion-admission or admission-treatment intervals.

Other studies also reported the ingestion-treatment interval as the most important determinant of liver damage after paracetamol poisoning[12]. Chronic alcohol abuse was associated with a significantly worse prognosis in some[12,13] but not[5] all studies. Long-term anticonvulsant therapy was reportedly found to worsen outcome in paracetamol-induced fulminant hepatic failure[14]. However, the scientific basis for this observation is unclear since studies of paracetamol metabolism do not show evidence of its increased oxidative metabolism in patients on anticonvulsants[15]. On the other hand, a population of patients with alcoholic and other liver diseases do show evidence of increased metabolic activation of paracetamol[15-17]. Chronic alcoholics may also be predisposed to paracetamol-induced liver toxicity because of reduced glutathione stores[18].

Our study also shows that the main reasons for the morbidity following paracetamol poisoning in our patients are late presentation (23%) and failure to give NAC appropriately (50%) (subjects 1, 2, 5, 8 and 10 in Table II). The liver damage in some of the remaining patients (30%) could have been prevented if intravenous NAC was commenced in the Emergency Department (<15 hours after ingestion) (subjects 3, 7 and 9 in Table II).

Among the more recent reports of the incidence of liver damage following paracetamol poisoning[12,19,20], the study from Sydney[12] was the only one in which intravenous NAC was used almost exclusively as the antidote. Of the 306 patients studied (median age 24 years, range 1-88 years), 28% consumed >80 g of alcohol per day. The median interval between ingestion and presentation was 4 hours. All the 55 patients (18%) with toxic plasma paracetamol concentrations were given NAC. There were no deaths but 24% had plasma ALT >45 IU/L. The incidence of liver damage amongst our patients was much lower at 5.9%, possibly because of their earlier presentation and the absence of chronic alcoholism.

There may be several ways to improve outcomes in paracetamol poisoning. Firstly, there is a need for strict adherence to standard assessment and treatment protocols. Secondly, steps should be taken to ensure rapid availability of paracetamol assay results to doctors responsible for managing such patients. We are aiming to do this by getting our hospital laboratory to inform our duty registrars directly of all toxic level results so that treatment delays and morbidity are minimised.

In conclusion, liver damage after paracetamol poisoning remains common (5.9%) in Hong Kong because of the failure to give NAC appropriately or late presentation. We hope to improve patient management by repeatedly emphasising the importance of adherence to the standard protocols and having the toxic plasma level results phoned directly to the duty registrars.

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