

Paracetamol overdose presenting to an Accident & Emergency Department of a regional hospital in Hong Kong

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We carried out a review of the patient resuscitation records and hospital notes of paracetamol overdose patients initially treated in the Accident and Emergency Department of Tuen Mun Hospital during the period starting from January 1998 to April 1999. Altogether there were 42 patients but 46 cases were recruited in the study because 4 patients had overdose twice. Ten (22%) were male, 36 (78%) were female and young female constituted the majority of the patients. Forty-three cases (93%) took an overdose of paracetamol as a means of committing suicide and 20 cases (43%) ingested 10 grams or more of paracetamol. The most common provoking causes were adjustment disorder (18 cases, 39.1%) and acute stress reaction (8 cases 17.4%). The majority of the cases presented early and within 8 hours after the overdose. Two cases had impaired liver function, 3 had prolonged prothrombin time and 5 had transient metabolic acidaemia in the absence of liver failure. All patients recovered uneventfully. Forty one cases (89%) were given N-acetylcysteine (NAC) infusion, of these 6 had toxic paracetamol level, 24 had non-toxic level because NAC was given before the availability of paracetamol level in many cases and it was undetermined for the other 11 cases. Hypersensitivity reaction to NAC infusion was common (8 cases, 21%) but there was no long term sequelae. Highly variable approach in the use of NAC was noted, we suggest to set a clinical check-list for the management of paracetamol overdose especially concerning the time to check the serum level and the initiation of NAC. (*Hong Kong j.emerg. med.* 2000;7:73-80)

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Introduction

Paracetamol is a safe antipyretic and analgesic if it is used in the therapeutic dose but nowadays people tend to misuse it. Paracetamol is now one of the drugs most commonly used with suicidal intent in the United States¹ and is the most common drug used for self-poisoning in the UK.² In Hong Kong, analgesics are also commonly used as self-poisoning agents and account for about 13.7% of self-poisoning incidences during a study period from 1988 to 1991 in the New Territories East of Hong Kong, and paracetamol is one of the most commonly used

analgesic.³ Tuen Mun Hospital is the only acute hospital serving the Tuen Mun and Yuen Long districts with a catchment population of around 0.8 million (483,703 in Tuen Mun and 341,030 in Yuen Long in 1996 census) in Hong Kong and is a good place for a study of paracetamol overdose to be conducted as age and sex distributions are readily available in these 2 regions.

Design of study

Patient selection: all patients of paracetamol overdose that were initially treated in the resuscitation room in the Accident and Emergency Department of Tuen Mun Hospital starting from January 1998 to April 1999 were included in the study.

All patient resuscitation records starting from January 1998 to April 1999 were reviewed and the

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records of patients with paracetamol overdose were singled out, the respective hospital records were then traced. These hospital notes were reviewed by medical doctors and some laboratory results were traced (from the computer data) if they were not available in the hospital notes. Table 1 shows the parameters that were studied.

All data were interpreted in terms of range, median, mean and percentages where appropriate.

Results

There were a total of 47 patients with paracetamol overdosage whom were treated in the resuscitation room during our intended study period, but 5 hospital notes were not available therefore were excluded from the study. Of the remaining 42 patients, 4 patients had overdose twice during the study period, and making a total of 46 cases. Ten cases (22%) were male and 36 cases (78%) were female. The youngest patient was a 13-year-old girl, and the oldest patient was a 84-year-old gentleman. The majority of the patients were below 50 years of age (98%) with a median of 24 years old and most of them were young female. The Glasgow Coma Scale of all the patients was 15/15. The demographic information of the patients is tabulated in Table 1a.

None of the cases were chronic alcoholics, though 14 (35%) of them were social drinkers. Nine (20%) cases were non-drinkers and information concerning the alcohol consumption of the remaining 19 cases (45%) was not available.

None of the cases had pre-existing liver disease, based on the history, physical examination and liver function tests. Forty-three (93%) cases took an overdose of paracetamol as a means of committing suicide, 2 cases 'forgot' the reason and another one overdosed 11 tablets of paracetamol for her headache. No patients took an overdose of paracetamol by accident.

Fourteen cases (30%) ingested less than 10 grams of paracetamol, 20 cases (43%) overdosed 10 grams or more. One case claimed to have taken 50 grams and for the remaining 12 cases (27%), the amount could not be quantified. Sixteen cases (36%) took an overdose of paracetamol only, and the most common co-ingested drug was alcohol (12 cases, 27%). Other co-ingested substances included dologesic, aspirin, triact, dettol, hypnotics, amoxil, some unknown medication over the counter and Chinese herbal medicine. Four cases co-ingested 2 to 3 other medications.

The shortest ingestion-registration interval was 12 minutes and the longest was 10 hours 4 minutes. The median was 2 hours 24 minutes. The majority of cases (40 cases, 87%) presented within 8 hours after overdose and 4 cases presented between 8 hours and 10 hours 4 minutes. Ingestion-registration interval was unknown for the remaining 2 cases because of uncertain time of ingestion. The majority of the patient presented early.

Five cases were given activated charcoal as the only treatment, and 9 cases were given NAC as the only treatment. One case had gastric lavage performed

Table 1. Parameters studied.

1	Sex	9	Treatment modalities	17	Total bilirubin
2	Age	10	Ingestion-NAC infusion interval	18	Blood glucose
3	Drinker or non-drinker	11	Allergic reaction to NAC	19	Serum paracetamol level
4	Pre-existing liver disease	12	Withdrawal of NAC	20	pH value
5	Reason of overdose	13	Prothrombin time (PT)	21	Glasgow Coma Scale
6	Amount of paracetamol ingested	14	International normalized ratio (INR)	22	Outcome of patient
7	Co-ingested medications	15	Creatinine level	23	Psychiatric diagnoses
8	Ingestion-registration interval	16	Alanine aminotransaminase (ALT)	24	Duration of stay in hospital

Table 1a. Age and sex distribution.

Age groups	Cases		
	Female	Male	Male + female
< 15	2	0	2
15-19	11	2	13
20-24	6	3	9
25-29	3	2	5
30-34	7	0	7
35-39	3	0	3
40-44	3	1	4
45-49	1	1	2
84	0	1	1
total	36	10	46
%	78.3	21.7	100

and then received NAC. Twelve cases received both activated charcoal and NAC. 18 cases had gastric lavage done first and then received both activated charcoal and NAC. The last one had both activated charcoal and NAC, but NAC was withdrawn because of allergy and methionine was used instead. Altogether 41 cases that were given N-acetylcysteine infusion, 32 cases (78%) were given within 8 hours of ingestion, the others between 8 and 16 hours. The shortest ingestion-infusion interval was 1 hour 38 minutes because the patient had taken 27.75 gram of paracetamol, and the longest was 15 hour 40 minutes. Of the 5 cases that did not receive NAC, 4 cases had non-toxic serum paracetamol level, one case did not have the serum paracetamol checked

but the amount of ingested paracetamol was only 3 grams. (Table 2)

7 cases (15%) had cutaneous anaphylactoid reaction presenting as itchy skin or itchy skin rash shortly after high dose of N acetylcysteine infusion, and all of them were given intravenous chlorpheniramine. N-acetylcysteine was withdrawn in 5 of them but for the two patients in which it was not withdrawn, one of whom had itchy skin and the other had itchy skin rash. All 7 patients did not suffer any sequelae. One patient was given oral methionine after withdrawal of NAC due to the development of shortness of breath, palpitation and skin rash. Intravenous chlorpheniramine was also given, and the symptoms subsided eventually. Of the 6 with the NAC infusion being discontinued, one had toxic paracetamol level, but fortunately the patient did not have subsequent liver damage.

N-acetylcysteine infusion was started at the Accident and Emergency Department for 8 cases because of sure history of significant overdose, while it was started in ward for the other 33 cases. For the 33 cases receiving NAC infusion in ward, NAC was started in 24 (73%) of these cases before the paracetamol levels were available. (Tables 3 & 4)

NAC was started in 9 cases when the paracetamol levels were available. One case had level above the treatment line, 4 had levels below the treatment line and the NAC was initiated by interns. The acetaminophen level was checked less than 4 hours for 4 cases, of which 2 cases had non-toxic level in

Table 2. Treatment modalities.

Treatment modalities	No of cases
Activated charcoal	5
Gastric lavage + NAC	1
NAC	9
Activated charcoal + NAC	12
Gastric lavage + activated charcoal + NAC	18
Activated charcoal + NAC + methionine	1

Note:

- 1 case had systemic anaphylactic reaction to NAC, and so NAC was withdrawn after initial dose and methionine was used instead.
- 5 cases had cutaneous anaphylactoid reaction and NAC was withdrawn after initial dose.
- 35 cases had complete NAC treatment, and 6 cases had partial NAC treatment.
- 5 cases did not have NAC treatment.

the second specimen, one case had the level checked still within 4 hours, the other had no second specimen taken.

In summary, of all the cases with NAC given, 6 cases (14.6%) had toxic levels, 25 cases (60.0%) had non-toxic level, and it was undetermined for the other 10 cases (24.4%) because the blood specimen was taken less than 4 hours after ingestion (8 cases), the time of ingestion of paracetamol was

uncertain (1 case), or the serum paracetamol level was not available (2 cases). In the calculation of the interval between ingestion of paracetamol and collection of serum paracetamol, the laboratory reception time was taken as the time of blood taking because time of blood taking was seldom stated in the laboratory form. There was inevitably some error in the calculation of the ingestion-blood-taking interval although the specimens were meant to be sent urgently to the laboratory. (Table 5)

Table 3. Serum paracetamol level of patients with NAC given in accident and emergency department.

No of cases with level checked 4 hours or more after ingestion	5 1 case has level above treatment line 4 cases have levels below treatment line
No of cases with level checked less than 4 hours after ingestion	3 1 case has 2 nd level above treatment line 1 case has 2 nd level below treatment line 1 case the 2 nd level was not available for review
Summary of findings • 2 cases had toxic paracetamol level. • 5 cases had non-toxic level. • 1 case had undetermined level.	Total of 8 cases with NAC started in the A&E Department

Table 4. Subsequent serum paracetamol level of patients with NAC infusion given in ward before the availability of serum paracetamol level.

No of cases with level checked less than 4 hours after ingestion	9 1 case has 2 nd level above treatment line 4 cases have 2 nd level below treatment line 4 cases, the 2 nd level was not available for review
Information for the other 15 patients	2 cases have toxic paracetamol levels 10 cases have non toxic paracetamol levels 1 case had uncertain time of ingestion 2 cases have missing paracetamol levels
Summary of findings • 3 cases had toxic paracetamol level • 14 cases had non-toxic level • 7 cases had undetermined status	Total of 24 cases with NAC started in the in-patient ward

Table 5. Summary of cases treated with NAC.

	NAC given in A & E Dept.	NAC given in ward before paracetamol level available	NAC given in ward after paracetamol level available	Total cases
Paracetamol level toxic	2	3	1	6
Paracetamol level non-toxic	5	14	6	25
Status undetermined	1	7	2	10

Four cases had prolonged prothrombin time. Case no. 5 overdosed 25 gram acetaminophen, whose INR was 1.3 and the serum paracetamol was checked less than 4 hours after admission. Case no. 13 overdosed 5 gram paracetamol, whose INR was 1.8, the first serum paracetamol level was checked less than 4 hours after admission but the second level checked was non-toxic. Case no. 16 ingested 7 gram paracetamol, the INR was 2.8 and the level was checked within 4 hours. Case no. 35 only ingested 2 gram paracetamol, the INR was greater than 4.5, the first level was checked less than 4 hours after admission and the second level was non-toxic. They did not have any specific risk factors. However, their subsequent INR were all normal. The INR of the patient whose first INR was greater than 4.5 was re-checked immediately on the same day, the value was less than 1. Very likely, there must have been some error during blood taking for this case. All these 4 patients received NAC infusion. None of these 4 cases had abnormal liver function. The INR was normal for the other 40 cases and was not available in 2 cases.

The creatinine level was within normal level for all patients except for the 84-year-old gentleman whose creatinine was 149, but these was no further deterioration in his renal function. No further deterioration of renal function was detected in 35 cases, and the second renal function test was not available in the remaining 11 cases. No patients had hypoglycemia, based on the spot glucose (38 cases) and bed-side glucometer assay in 8 cases whose spot glucose was not checked. Twenty-seven cases (58.7%) had normal pH values, pH values of another 14 cases (30.4%) were not available. A summary of

the remaining 5 cases with abnormal pH value is tabulated in Table 6.

Five cases had metabolic acidaemia, but none had any associated biochemical abnormalities. Three cases were given NAC infusion but the other two cases were not given because their respective serum paracetamol level was below treatment line. The mechanism for paracetamol-induced metabolic acidosis in the absence of liver failure is still speculative, but it may be related to inhibition of mitochondrial aerobic metabolism by uncoupling of sites I and II on the electron transport or through covalent binding of essential mitochondrial enzymes, both these 2 mechanisms can cause lactic acidosis.¹

Two cases had impaired liver function, their serial levels of alanine transaminase is summarised in Table 7.

One patient was transferred to Castle Peak Hospital, a psychiatric hospital because of schizophrenia. Three patients were transferred to the psychiatric ward at Tuen Mun Hospital, 2 of whom had depression and another had anorexia nervosa. Most of the patient were found to have adjustment disorder (18 patients, 39%) and acute stress reaction (8 patients, 17%), the commonest reasons were unhappy relationship with spouse, boyfriends, or other family members. Financial problem was not uncommon as a reason for suicide. Five patients had depression, one had schizophrenia and another had anorexia nervosa. One case had impulsive drug overdose and 5 other cases had no psychiatric condition after assessment by the psychiatrists.

Table 6. Paracetamol dosage, major investigation results and antidote treatment in cases with abnormal pH.

case	pH	Arterial or venous	2nd pH if available	Paracetamol ingested	ALT	INR	creatinine	NAC given
11	7.34	arterial	N/A	15 gm	30	< 1	91	yes
12	7.29	venous	N/A	5 gm	8	1	65	yes
24	7.34	arterial	N/A	N/A	35	< 1	69	yes
32	7.11	arterial	7.38	5 gm	11	< 1	82	no
34	7.19	venous	N/A	5.5 gm	21	< 1	81	no

Table 7. Summary of the patients with impaired liver function.

Case	Serial alanine transaminase levels	History	Paracetamol level	NAC administered	Remarks
Case no. 14:	40, 36, 79, 108, 105	Ingested a total of 30 tablets of paracetamol and (cokaben - containing paracetamol, chlorpheniramine, phenylephrine & caffeine.	Above treatment line for both cases NAC was started before level was available for both	Infusion started at 8 hours 35 minutes after ingestion in AED	In both cases, there was no elevation of total bilirubin or any associated biochemical abnormalities
Case no. 39:	23, 80, 121, 583, 1110, 122	Unknown amount of paracetamol		NAC infusion started 12 hours 35 minutes after ingestion in ward.	Uneventful recovery

Seven patients had no psychiatric diagnoses because they either discharged themselves against medical advice or were found missing before assessment by psychiatrists. Table 8 summarises the psychiatric diagnoses made by the psychiatrists.

The median duration of stay in hospital was 2 days 1 hour, and the mean was 2 days 18 hours. The shortest duration of stay was 17 hours in a patient who discharged herself against medical advice. The longest duration of stay was 21 days 21 hours for a lady because of fractured sacrum resulting from jumping from height in addition to drug overdose.

Discussion

Young female patients constituted the majority of this acute paracetamol poisoning, which was consistent with the result of another study conducted at the Prince of Wales Hospital in the New Territories East in 1994.⁵ This reflects the impact of the stress of unhappy relationship with their partners, either spouses or boyfriends, imposed on these young female, which was the main cause of the overdose.

Table 8. Psychiatric diagnoses made by psychiatrist.

Psychiatric diagnoses	Cases	%
schizophrenia	1	2.2
depression	5	10.9
anorexia nervosa	1	2.2
adjustment disorder	18	39.1
acute stress reaction	8	17.4
impulsive drug overdose	1	2.2
no psychiatric diseases	5	10.9
not available	7	15.2
total	46	100

In therapeutic doses, paracetamol is largely (around 92%) conjugated in the liver to the inactive sulphates and glucuronides. About 8% is metabolized to a highly toxic intermediate metabolite, N-acetyl-p-benzoquinone imine (NAPQI), which is immediately inactivated under normal condition by conjugation with the hepatic reduced glutathione and subsequently excreted in the urine as cysteine and mercapturic acid conjugates. On overdose, the excessive NAPQI rapidly deplete the hepatic reserve of glutathione and the NAPQI consequently bind irreversibly with the macromolecules in the

hepatocytes causing necrosis⁴ The sulphate and glucuronide pathways become saturated if the ingested paracetamol is greater than 140 gm/kg, 10 gram paracetamol can cause marked liver necrosis and a single dose of 15 gram can cause death. In our sample, 43% of all the cases ingested 10 gram or more which can definitely endanger their lives if treatment is not given promptly. Fortunately, the majority of the patients presented early so that the antidote, NAC, could be given promptly. Late presentation and failure to give NAC appropriately are two important factors responsible for continuing morbidity after paracetamol overdose in Chinese patients in Hong Kong,⁶ patients of paracetamol overdose are usually given NAC before the availability of serum paracetamol level if the amount ingested is large or unsure. Moreover, our chemical pathology laboratory will phone our on duty doctor promptly if the serum paracetamol level is above toxic level. This kind of practice is pretty safe as there was no a single case of delayed infusion of NAC in our sample. Nevertheless, a high price (about HK\$700 for 15 gm of NAC at a cumulative dosage of 300 mg / kg of a 50-kg patient) had been paid because quite a significant number of our patients (25 cases, 64%) were given NAC at a non-toxic serum paracetamol level. Therefore it is still controversial as to whether NAC should be started before the availability of serum paracetamol level. However it is clear that NAC should be discontinued if the serum paracetamol level is below treatment line and the investigation results are normal.

Unnecessary prescription of NAC is not cost effective, moreover we have to bear in mind the possibility of side effect of the prescribed drug. In our sample side effects are common with NAC infusion (8 cases, 21%) and it was 14% in a similar study conducted at the Prince of Wales Hospital in Hong Kong.⁷ The side effects are dose-dependent and they usually occur shortly after the initial high concentration of NAC infusion.⁸ The incidence of adverse reactions can be reduced by slowing the infusion time from 15 minutes to 60 minutes for the first high dose of NAC.⁹ Should NAC infusion be withdrawn if such common side effects as skin rash or fever appear? In our sample, the adverse

reactions of the 2 cases, one had itchy skin and another had skin rash, were controlled with intravenous chlorpheniramine while the NAC was continued. Similar results were found in another study⁷ by YK Chan et al. It seems that it is safe to continue NAC with intravenous chlorpheniramine to suppress the anaphylatoid reaction. Perhaps it may be appropriate to stop the NAC temporarily and start the NAC again when the side effects are controlled with chlorpheniramine, especially if the serum paracetamol level is available and above the treatment line.

Only 5 cases (1%) had liver damage, as evidenced by the elevated alanine aminotransferase or prolonged prothrombin time, fortunately, none developed hepatic encephalopathy and all of them recovered. We exclude the case whose INR was greater than 4.5 as it was likely to be due to handling error. Those who had impaired liver function did not have prolonged prothrombin time, and vice versa in our sample. Early presentation, prompt treatment with NAC and none of the patients being chronic alcoholics (alcohol induces hepatic microsomal oxidases and hence raises the vulnerability to paracetamol toxicity by increasing the production of toxic metabolites, NAPQI) probably account for this low figure.

Highly variable approach in the use of NAC was noted, we suggest to set a clinical check-list for the management of paracetamol overdose especially concerning the time to check the serum level and the initiation of NAC. The suggested approach in the check-list is based on the fact that NAC treatment is most effective if started within 8 hours of ingestion and paracetamol level versus hours post ingestion normogram is most validated within 15 hours of ingestion.

We recommend a checklist with the following:

1. Note down the amount and time of ingestion.
2. On any hepatic enzyme-inducing drug: alcohol, carbamazepine, phenobarbitone, phenytoin, rifampicin.
3. Suggested approach in Table 9.¹⁰

Table 9. Table summarises the management approach to paracetamol poisoning

<8 hour	<ol style="list-style-type: none"> 1. Gut decontamination if indicated. 2. Blood on admission for paracetamol, INR, R/LFT, CBP, pH. 3. Blood at 4 hour for paracetamol level, consider further sample if co-ingestions slowing gastric emptying. 4. NAC infusion if <ol style="list-style-type: none"> a) any 1 of the level > treatment line or b) level not available by 8 hour & greater than 150mg/kg ingested. 5. Stop NAC if level < treatment line. 6. Discharge if asymptomatic & post treatment investigations are normal.
8-15 hour	<ol style="list-style-type: none"> 1. Blood for paracetamol level, INR, R/LFT, CBP, pH. 2. NAC infusion if > 150 mg/kg ingested. 3. Stop NAC if level < treatment line. 4. Discharge patient if asymptomatic & post treatment investigations are normal.
>15 hour	<ol style="list-style-type: none"> 1. Blood for paracetamol level, INR, R/LFT, CBP, pH. 2. NAC infusion if > 150 mg/kg ingested or investigation abnormal. 3. Consider continuing NAC if still symptomatic or post-treatment investigation abnormal.
remark	<ol style="list-style-type: none"> 1. If on enzyme-inducer, NAC infusion if level > high risk treatment line. 2. Make it a habit to state the time of blood taking for serum paracetamol level.

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