

Measuring plasma paracetamol concentrations in all patients with drug overdose or altered consciousness: Does it change outcome?

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Abstract

Objective—To assess whether measuring plasma paracetamol concentrations in all patients with drug overdose or collapse (altered consciousness) changes outcome.

Method—A retrospective survey was performed of all patients attending the Accident and Emergency Department at Guy's Hospital, London over a 12 month period who had plasma paracetamol concentrations measured (it is hospital policy that patients presenting after any drug overdose, or with a collapse/altered consciousness have a plasma paracetamol concentration).

Results—A total of 440 patients were identified who had plasma paracetamol concentrations measured, of whom 411 were eligible for the study. Altogether 115 patients presented after a collapse and paracetamol was detected in four of these. A total of 296 patients presented after a drug overdose—136 denied overdose with a paracetamol containing product and paracetamol was not detected in any of these 136 cases. Of the remaining 160 patients who gave a positive history for overdose with paracetamol, 122 presented within 24 hours and 94 had detectable paracetamol values with 16 cases above the treatment line, 12 presented more than 24 hours after ingestion, and 26 presented with a staggered overdose. One patient died as a result of paracetamol overdose.

Conclusions—This is the first study in the United Kingdom to evaluate the clinical value of routine paracetamol levels in patients presenting to the emergency department after any overdose or a collapse. Taking blood samples for plasma paracetamol estimation in patients who deny taking paracetamol is of little clinical value. However, there is the potential for missing significant paracetamol poisoning in patients presenting with collapse and so screening with a plasma paracetamol concentration is clinically justified in these patients. Such an approach can only be justified in a country in which paracetamol poisoning is prevalent, such as the United Kingdom.

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Keywords: paracetamol; acetaminophen; overdose; screening; prognosis; predictive value

Paracetamol is the commonest drug taken in overdose in the United Kingdom (UK),^{1,2} accounting for up to 48% of all poisoning admissions to hospital³ and an estimated 200-300 deaths per year in the UK.^{4,5} In 1998 approximately 10% of calls to the National Poisons Information Centre (London) were as a result of paracetamol overdose (personal communication: JN Edwards). Paracetamol poisoning is also common in the United States—paracetamol and paracetamol containing preparations were involved in 119 807 (5.5%) of the 2 192 088 cases reported to the American Association of Poison Control Centres Toxic Exposure Surveillance System in 1997.⁶ *N*-Acetylcysteine (NAC) is the most widely used antidote for paracetamol poisoning, which, if given within eight hours of overdose, provides almost complete protection against liver necrosis, acute renal failure and death.⁷ In the UK, the Prescott nomogram⁷ is used to identify patients requiring treatment, which is indicated in patients with a paracetamol level above the line joining plots of 200 mg/l at four hours and 30 mg/l at 15 hours after ingestion.⁷

Paracetamol poisoning has no specific clinical features in the early phase. As a consequence, diagnosis is usually based on a history of ingestion and measurement of plasma paracetamol concentrations related to the estimated time of ingestion. Because of the potential for severe toxicity after paracetamol overdose, the high prevalence of paracetamol poisoning in the UK and the availability of an effective antidote, many clinicians routinely take blood samples for estimation of plasma paracetamol concentration in all patients presenting after a drug overdose, regardless of the history. Worldwide, there have been few systematic studies performed to evaluate this common practice⁸⁻¹³ and none have been performed in the UK.

At the Accident and Emergency Department, Guy's Hospital, London, all adult patients presenting after a possible drug overdose or after a collapse (decreased level of consciousness or confusion and a suspicion of drug overdose) are routinely screened for paracetamol and salicylate poisoning. We performed a retrospective study to evaluate the clinical value of paracetamol screening in this group of patients in relation to their subsequent management and outcome.

Methods

A 12 month retrospective analysis was performed on all adult patients (over the age of 16

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years) attending the Accident and Emergency Department at Guy's Hospital, London between the July 1997 and June 1998. The chemical pathology computer was used to identify all patients who had plasma paracetamol concentrations estimated during this period. The hospital records of all of these patients were traced and reviewed. A standard evaluation form was used by one author (SL) to obtain the following data from the hospital records: (a) demographic data; (b) medications taken in overdose, with particular attention to paracetamol containing products; (c) quantity of medication taken; (d) timing of the overdose; (e) whether risk factors for paracetamol poisoning were present; (f) investigations performed during admission; (g) management; and (h) outcome. For statistical analysis, com-

parison of categorical data was carried out using the χ^2 test. Where expected cell values were less than 5 in more than 20% of the cells, Fisher's exact test was used. A value of $p < 0.05$ was considered to be statistically significant, with corrections for multiple analyses.

Results

Between July 1997 and June 1998, approximately 42 000 patients were seen in the Accident and Emergency Department at Guy's Hospital. A total of 440 patients (1.0%) were identified who had plasma paracetamol concentrations estimated over this period (fig1). Twenty seven case notes (0-3 per month, all with undetectable paracetamol concentrations) were missing (6.1%) and a further two were excluded from further analysis as they

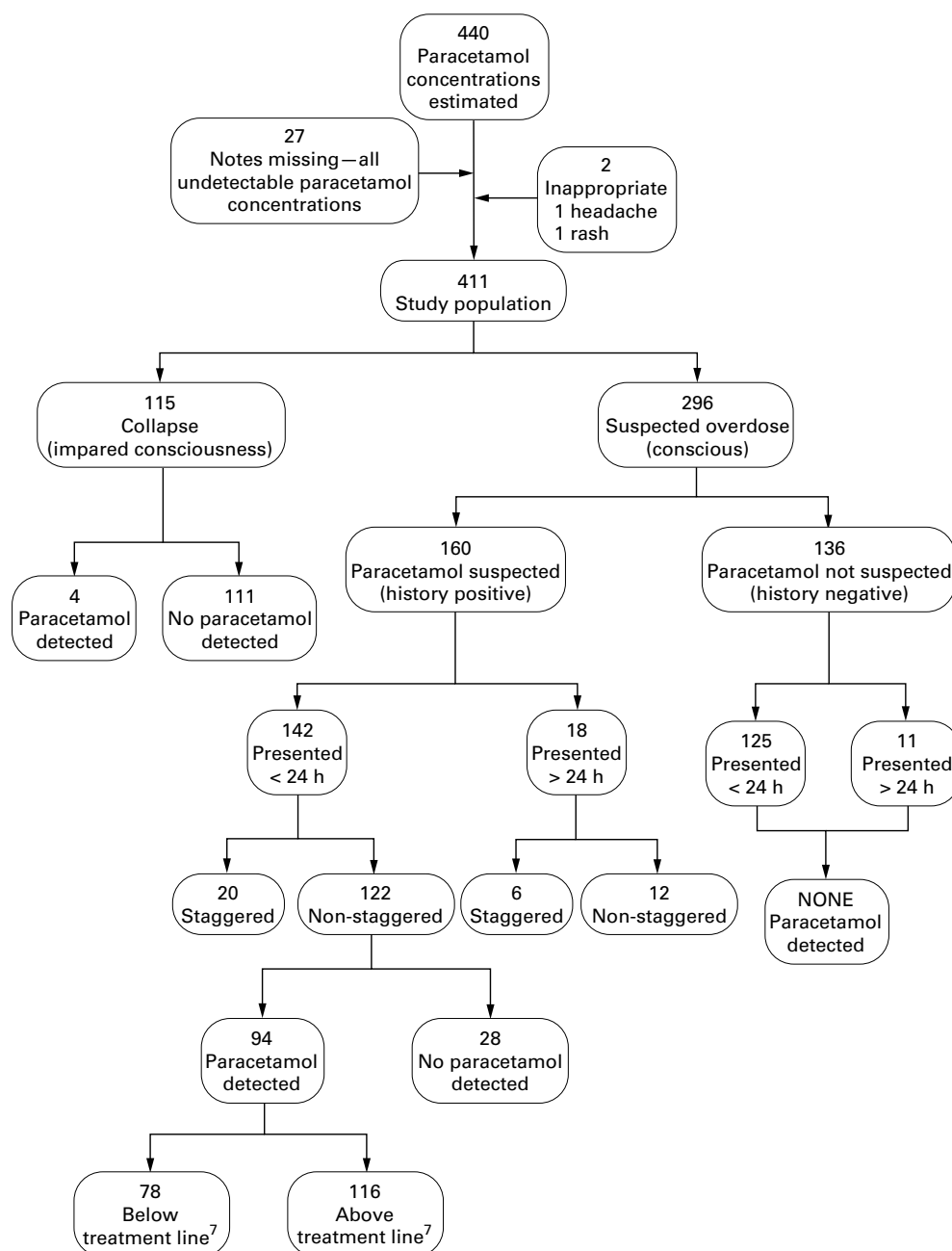


Figure 1 Breakdown of all patients in the study.

Table 1 Apparent causes of collapse (n=115)

Cause	Number (%) of patients
Alcohol intoxication	54 (47.0)
Drug overdose	
Intravenous drug misuse	14 (12.1)
Other overdose	8 (7.0)
Paracetamol involved	4 (3.5)
Seizure	13 (11.3)
Infection	
Septic shock	4 (3.5)
Meningitis	2 (1.7)
Pyelonephritis	1 (0.9)
Unknown source	1 (0.9)
Assault/trauma	4 (3.5)
Diabetic coma	2 (1.7)
Other	
Status asthmaticus	2 (1.7)
Panic attack	2 (1.7)
Subdural haematoma	1 (0.9)
Fainting episode	1 (0.9)
Hepatic encephalopathy (not paracetamol)	1 (0.9)
Dead on arrival (unknown cause—presumed cardiovascular)	1 (0.9)

were considered to be inappropriate (paracetamol concentrations taken in one patient presenting with headache and in another presenting with an erythematous rash). The remaining 411 form the basis for the study (fig 1) and involved 222 women (54%) and 189 men (46%). Of the 411, 115 (28.0%) presented with collapse and so were unable to give a history and 296 (72.0%) presented after a suspected overdose, 160 of these gave a history of overdose with a paracetamol containing product.

CASES PRESENTING WITH COLLAPSE

There were 115 episodes of collapse (table 1) over the 12 month study period (28.0% of 411

patients screened). An overdose was involved in 26 cases (22.6%). Paracetamol was involved in four cases of collapse (3.5%), including (a) a 28 year old female alcoholic, intravenous drug user found unconscious on the street who had a plasma paracetamol concentration of 61 mg/l; (b) a 43 year old woman who collapsed in a pub while drinking with her friends who had a plasma paracetamol concentration of 191 mg/l; (c) a 66 year old woman found drunk at home who had a plasma paracetamol concentration of 86 mg/l; and (d) an 86 year old woman found at home in respiratory arrest who had a plasma paracetamol concentration of 215 mg/l. All four cases involved multiple drug overdoses. All four patients received a full course of NAC as soon as paracetamol was detected and liver function tests, renal function and INR were normal at the end of the course of NAC in all four cases.

CASES PRESENTING WITH DRUG OVERDOSE

There were 296 (72.0%) cases of suspected overdose over the 12 month study period. Figure 2 shows the paracetamol concentration in all of the patients who presented with a suspected drug overdose plotted against the time after ingestion that the sample for paracetamol concentration was taken. In four cases (1.4%) blood for a plasma paracetamol concentration was taken at less than four hours after ingestion.

Of the 296 overdose cases, 160 (54%) gave a history of overdose with a paracetamol containing product (history positive, HP) and 136 (46%) denied overdose with a paracetamol containing product (history negative, HN). None of the 136 HN patients had detectable paracetamol, giving a negative predictive value of 100% for HN patients.

Of the 160 HP patients, 18 (11.2%) presented more than 24 hours after overdose (six after a staggered overdose, and 12 after a single overdose) and a further 20 (12.5%) had taken a staggered overdose. This left a total of 122 patients (76.2%) in which the paracetamol level could be used as a prognostic guide. Of these 122 patients, 28 (23%) had no detectable paracetamol, 94 (77%) had paracetamol detected—78 (63.9%) below the relevant treatment line, 16 (13.1%) above the relevant treatment line (in four of these 16 patients the lower treatment line of 100 mg/l at four hours was used because they were in a high risk category¹⁴—three because of chronic alcoholism and one as a result of a positive HIV status). Of the 94 patients with detectable paracetamol, 80% presented within four hours, 90% within eight hours and 95% within 12 hours.

Confirmed paracetamol overdose was more common among women than men (40 of 117, 34.2% of all men compared with 92 of 179, 51.4% of all women taking an overdose; $\chi^2=8.48$, $p<0.005$). Confirmed paracetamol overdose was particularly common among women in the younger age groups (77.2% of women <30 years compared with 22.8% of women >30 years; $\chi^2=54.4$, $p<0.0001$). This effect was not seen among the 87 women

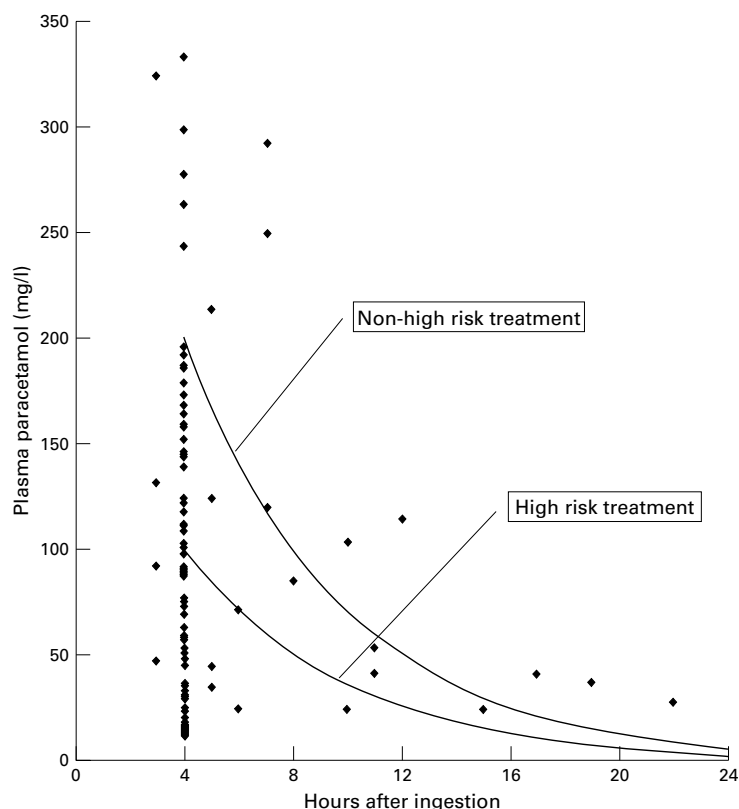


Figure 2 Paracetamol concentrations of all overdose patients shown together with the standard treatment lines for paracetamol poisoning.⁷

taking other overdoses (46% of women <30 years compared with 54% of women >30 years, $\chi^2=1.13$, $p=0.29$) or among men taking a paracetamol overdose (45% of men <30 years compared with 55% of men >30 years, $\chi^2=0.8$, $p=0.37$).

Attempted suicide was the reason for the overdose in 116 patients (87.9%) of the 132 cases of paracetamol overdose, there were 16 cases of accidental overdose (all of which were below the treatment line).

PRESENTATION AT GREATER THAN 24 HOURS

Eighteen of the 160 cases (11.3%) of suspected paracetamol overdoses (HP) presented at least 24 hours after ingestion—nine were men (9 of 40, 22.5% of all men) and nine were women (9 of 94, 9.8% of all women). Six cases involved staggered overdose and their management is discussed below. All the remaining 12 patients (including four high risk cases) were assumed to have taken a significant overdose and received complete treatment. Nine patients had detectable paracetamol concentrations at presentation, three had no paracetamol detected. None of these 12 patients suffered any complications and in all cases liver and renal function tests and INR were normal after the course of NAC.

PARACETAMOL CONCENTRATIONS 150–200 MG/L

Of the 99 patients who presented within four hours of ingestion of a paracetamol containing product, 67 (67.7%) had detectable paracetamol levels at four hours after ingestion below the current treatment line of 200 mg/l, and 11 (11.1%) of them had serum paracetamol levels between 150–200 mg/l at four hours. Two patients claimed to have taken a very significant overdose and were treated with NAC within four hours, two patients received activated charcoal only (at presentation, before the level was taken) and seven patients received no treatment. Three of the untreated patients had mildly raised INR (< 1.5) at presentation. None of the 11 patients suffered any complications and in all cases liver and renal function tests and INR were within normal limits at discharge.

STAGGERED OVERDOSE

Twenty six patients presented with a history of a staggered overdose of a paracetamol containing product and three of these were considered to be in a high risk category.¹⁴ Twenty (76.9%) presented within 24 hours (all had detectable paracetamol levels), the remaining six were all assumed to have taken a significant overdose and were fully treated. There were nine cases of accidental overdose mainly for pain (for example, backache, osteoarthritis, and dental extraction); all nine patients were discharged with no sequelae. No treatment was given to 16 patients (all of these patients were discharged with no sequelae), nine were treated with NAC on presentation (either because they presented more than 24 hours after ingestion or because they claimed to have taken a very large

overdose) and one was treated when a detectable paracetamol concentration was found.

Three of the patients who presented after staggered overdose suffered adverse consequences, of whom one died:

(1) A 32 year old man, a known alcoholic with chronic pancreatitis, took an unknown amount of paracetamol over the two days before presentation. At the time of admission, blood tests showed INR 3.33 with serum alanine aminotransferase (ALT) 4326 U/l, he was given a full course of NAC followed by two maintenance infusions of NAC before his INR returned to 1.08 and ALT to 2567 U/l and he was discharged to the care of the psychiatric team.

(2) A 37 year old woman who took two paracetamol tablets every hour for 12 hours two days before admission was admitted with abdominal pain and vomiting. At the time of admission, paracetamol level < 10 mg/l, INR 2.5, ALT 9300U/l. Her condition gradually deteriorated with a decreasing level of consciousness and she was admitted to the intensive care unit. She received a full course of NAC and four further maintenance infusions. Her INR initially rose to 3.3 on day 2 after admission then returned to 1.0 on day 7 at which stage her ALT was 1454 U/l and she was discharged to the care of the psychiatric team.

(3) A 20 year old woman with a history of depression and several previous suicide attempts—some involving paracetamol, including one in the previous month—presented with vomiting after taking 48 paracetamol and aspirin over the 24 hours before admission. NAC was started on admission before blood test results were available, these showed: paracetamol level 129 mg/l, ALT 171 U/l, bilirubin 30 $\mu\text{mol/l}$. The day after admission she had episodes of hypoglycaemia and developed a severe metabolic acidosis (pH 7.18, pCO_2 2.95, BE -17, lactate 11.8). She was transferred to the King's College Hospital liver unit for further management. She was treated with further maintenance NAC but developed a grade III encephalopathy, acute renal failure and her INR continued to rise, peaking at 14.5 on day 5. Despite full supportive care she continued to deteriorate and died after developing adult respiratory distress syndrome and subsequent multi-organ failure on day 10.

Discussion

Paracetamol is the commonest drug ingested in overdose in the UK and is found in a variety of both prescription and over the counter preparations. There are few indications for urgent measurement of drug concentrations in clinical toxicology and emergency assays should only be carried out if the result can be related to the severity of poisoning and can be used to guide treatment and prognosis. Paracetamol rarely results in specific clinical features in the early stage of poisoning, the risk of liver damage can only be predicted from the plasma paracetamol concentration and so the estimation of plasma paracetamol concentrations is important in all patients who present

with a history of a paracetamol overdose. However, many physicians routinely measure plasma paracetamol concentrations in all patients presenting with a history of overdose or in whom an overdose is suspected. This is the first study in the UK to evaluate the clinical value of this practice.

In this study we have shown that paracetamol was not detected in any of the 136 patients who denied taking paracetamol (HN). On the basis of this result we feel that paracetamol screening is not clinically justifiable in patients presenting after a drug overdose who deny taking paracetamol. The exception to this is if there is clinical doubt as to the validity of the history, or if the patient has ingested unknown white tablets. Our findings are similar to those of a previous study in Hong Kong⁸ in which paracetamol was not detected at toxic levels in any of 208 HN patients (paracetamol was detected at non-toxic levels in four HN patients and was not detected in the other 204 cases). However, in a study in the United States¹² one patient among 365 HN patients had a potentially toxic concentration (and there were seven HN patients in whom paracetamol was detected at non-toxic concentrations).

In our study, among 115 patients presenting with collapse paracetamol was detected in four (3.5%) cases and all four were treated with NAC. On the basis of our results we feel that the potential for missed paracetamol poisoning in such patients warrants the routine use of paracetamol screening in all patients presenting to the emergency department with a history of collapse (altered consciousness). In a previous study in the United States⁹ paracetamol was detected in five (0.3%) patients who were either HN or in whom a reliable history could not be obtained because of an altered mental status; no distinction between these categories was made in this study.

Of the 99 patients who presented within four hours of ingestion of paracetamol, 11 had a paracetamol level between 150–200 mg/l at four hours after ingestion. In all 11 patients liver function tests, renal function and INR were normal at the time of discharge (seven patients received no treatment, two received NAC and two received activated charcoal only). This is in contrast with a recent case series¹⁵ of four patients who developed hepatotoxicity despite having paracetamol concentration apparently below the conventional treatment line. The authors of this study advocated that on the basis of their four cases the level at which treatment with NAC should be started should be lowered to 150 mg/l at four hours. This study stimulated considerable debate on the issue of the treatment threshold for paracetamol overdose—the consensus in a subsequent editorial¹⁴ was that there was not sufficient evidence to warrant lowering the treatment threshold. Although the number of patients in our study who presented with a paracetamol level of 150–200 mg/l is small, our results are in support of the treatment level of 200 mg/l at four hours being a safe threshold.^{7, 15}

There were three patients among the 26 who presented with a staggered overdose that devel-

oped severe hepatotoxicity. Risk assessment in patients who present after a staggered paracetamol overdose is difficult because the plasma paracetamol concentration cannot be used prognostically or to guide treatment. The three patients who developed severe hepatotoxicity were all treated with NAC on arrival; but all three presented at greater than 24 hours after ingestion at which point the efficacy of NAC treatment is much reduced.¹⁶

This is the first study in the UK to evaluate the clinical value of routine paracetamol levels in all patients presenting to the emergency department after an overdose or collapse. On the basis of this study taking blood samples for plasma paracetamol estimation in patients who deny taking paracetamol seems to be of little clinical value.

However, we have shown that among patients presenting with collapse there is the potential for missed paracetamol poisoning and because the consequences of missing this diagnosis are potentially life threatening, we believe that screening with paracetamol levels is clinically justified in these patients. Such an approach can only be justified in a country in which paracetamol poisoning is prevalent, such as the UK.

Contributors

Shamez Ladhani was responsible for data collection, helped with analysis of the data and reviewed and commented on drafts of the paper. Paul Dargan designed the protocol, helped with analysis of the data and coordinated the writing of the paper. Alison Jones helped with analysis of the data and reviewed and commented on drafts of the paper. All three authors will act as guarantors.

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