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Renal injury at first presentation as a predictor for poor outcome in severe paracetamol poisoning referred to a liver transplant unit

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Abstract

Background Paracetamol poisoning remains a leading cause of morbidity and mortality. Identifying indices of poor prognosis at first presentation is key to both improving clinical care and determining targets for intervention. Renal failure is a feature of severe paracetamol poisoning. The aim of this study was to investigate the relationship between renal function (serum creatinine, Cr) at first hospital presentation and time of tertiary referral to outcomes in severe paracetamol poisoning.

Methods This was a retrospective cohort analysis of patients referred to the Scottish Liver Transplant Unit due to paracetamol poisoning between 1992 and 2004. The relation between degree of renal injury and outcomes, including worst prothrombin time, Kings College Hospital Criteria (KCHC) and death were examined. The effects of age, nature (single or multiple) and stated size of overdose, hepatic enzyme induction (gamma-glutamyl transpeptidase, GGT), degree of liver injury (aspartate aminotransferase, prothrombin time), blood pressure and renal injury were assessed.

Results Data from 522 patients were included. Renal impairment (Cr >120 mmol/l) was present in 48.8% of patients with

liver injury at time of first presentation. Creatinine at first admission predicted poorer outcome in terms of worse prothrombin time, KCHC and death ($p < 0.001$). Associated risk factors for renal dysfunction included later presentation, staggered ingestion, increased age, hypotension and elevated GGT at first admission.

Conclusions Creatinine at first admission appears to be a predictor of poor outcome in paracetamol overdose. A better understanding of mechanisms involved in causing renal dysfunction may offer potential therapeutic targets for improving outcome in this common poisoning.

Keywords First presentation · Paracetamol poisoning · Predictors of outcome · Renal dysfunction · Risk factors

Introduction

Paracetamol is one of the commonest medications used in overdose in developed countries [1, 2]. Intravenous acetylcysteine is an effective antidote if administered sufficiently early after ingestion. A variety of treatment guidelines are in existence worldwide, but in the UK patients are grouped as “normal” or “high risk” depending on their history of risk factors and paracetamol concentrations [3]. Despite this, paracetamol poisoning is responsible for around 200 deaths annually in the UK alone [1, 4, 5]. Early markers of poor outcome are important both for acute physicians and liver units. Of particular interest is that while high doses of paracetamol are capable of causing both hepatic necrosis and renal tubular necrosis [6–9], renal failure is less common than liver failure after paracetamol overdose and has been reported in less than 1% of all patients [6]. The occurrence of renal failure is greater in more severely poisoned patients and is often observed in those that develop major liver injury

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[7, 10]. Less commonly, renal failure is seen as an isolated manifestation of paracetamol toxicity [8, 9, 11].

The King's College Hospital Criteria (KCHC) for liver transplantation [12] are widely used to predict outcome in more severely poisoned patients in liver units. Despite this, comparatively little is known about the prognostic value of investigations performed at first admission to hospital after severe poisoning. We hypothesised that since renal failure is an important component of the syndrome of severe paracetamol toxicity, elevated creatinine concentrations at the time of first admission or at the time of tertiary referral might indicate more severe paracetamol poisoning and poorer prognosis in those transferred to a liver unit. We also wished to explore the relationship between other known risk factors for liver injury and renal injury in this context.

Methods

Data collection

The Scottish Liver Transplant Unit (SLTU) is a tertiary referral centre for Scotland and part of Northern Ireland, providing clinical management of patients with severe liver disease and patients that require liver transplantation. Patients referred with liver damage due to paracetamol overdose were identified from a database maintained within the SLTU that contains information on clinical and laboratory variables and outcomes for patients referred to the Unit. Approval for this retrospective anonymised case study was received from the Local Ethics Committee. Referrals to the Unit from other hospitals between 1992 and 2004, including those due to severe paracetamol-induced liver damage, were accounted for, with the vast majority coming from Scotland. Available data at the time of initial referral to SLTU included age, gender, stated dose ingested, interval between ingestion and presentation to hospital, plasma paracetamol concentration, the presence of hypotension (systolic blood pressure <100 mmHg), serum creatinine (Cr), alanine transaminase (ALT) activity, gamma-glutamyl transpeptidase (GGT) activity and prothrombin time (PT) at time of admission to referring hospital and to SLTU. Additional data were worst recorded PT and clinically relevant outcome data: liver transplant, requirement for haemodialysis, intensive care unit (ITU) admission and death. Admission to ITU was determined by necessity for ventilation.

Data analyses

Ingestions at a single time-point, or within a 2-h period, were considered to be an acute ingestion, whereas ingestion at multiple related time-points or during an interval of more than 2 h was considered a staggered overdose. Acute

ingestions were grouped by interval between overdose and first presentation to hospital: ≤ 24 , >24 –48 and >48 h. Renal function was categorised in a clinical manner as normal ($\text{Cr} \leq 120 \mu\text{mol/l}$), mild impairment ($120 < \text{Cr} \leq 180 \mu\text{mol/l}$), moderate impairment ($180 < \text{Cr} < 300 \mu\text{mol/l}$) and severe impairment ($\text{Cr} \geq 300 \mu\text{mol/l}$). Severe liver injury was determined by PT, and a PT of >25 s was used as an arbitrary clinically relevant cut off.

A receiver operator characteristic was used to examine the relationship between serum Cr concentration at the time of referral to SLTU and the subsequent need for haemodialysis (or other outcome measure).

In a dataset of this type, in which clinical sampling was not pre-determined by protocol, it was not surprising that some data were absent. Data for analysis were therefore included for all patients in whom these were available for each time period. The data are presented as mean \pm standard error of the mean (SEM), with proportions where appropriate. Between-group comparisons were made using Student's *t* test for independent samples and Pearson's Chi square tests. Multiple comparisons analysis for continuous data was made by one-way analysis of variance (ANOVA) with Post-Hoc Bonferroni correction.

Results

In the period of this study, 522 patients with paracetamol overdose were admitted to the SLTU from referring hospitals. There were approximately equal numbers of men (49.2%) and women (50.8%), and the median age of the patients was 34.0 [interquartile range (IQR) 26.0–53.0] years. Full biochemical data for analysis were available at admission for 444 patients at the referral hospital and for 507 patients in the SLTU. Overall mortality was 28.2% (147/522), and 34.2% of patients required dialysis.

At first presentation to the referring hospital, 69.1% (320/463) of patients for whom data were available had significant impairment of liver function, as reflected by the PT (Table 1). Of this group with liver injury, 156 (48.8%) had a serum Cr suggesting some degree of renal injury ($\text{Cr} > 120 \mu\text{mol/l}$). At first presentation, 39.4% (182/463) of all patients, with and without PT elevation, had data compatible with renal injury (18.6% mild, 11.9% moderate and 8.9% severe renal impairment).

Abnormalities in liver function occurred more rapidly than those in renal function, thus ALT and PT were generally abnormal at initial presentation (Table 2). By the time patients were admitted to the SLTU, 90% had developed significant liver injury, while 16.8% had mild, 20.9% moderate and 16.2% severe renal injury (Table 1). Overall, 96.6% of patients developed significant liver injury (worst PT ≥ 25 s).

Table 1 Severity of liver and renal impairment at presentation to the referring hospital and to the Scottish Liver Transplant Unit tertiary centre

Groups according to renal and liver function	Referring hospital (<i>n</i> =463)				SLTU (<i>n</i> =507)			
	PT \geq 25 s (with liver injury)		PT<25 s (no liver injury)		PT \geq 25 s (with liver injury)		PT<25 s (no liver injury)	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Normal renal function, Cr \leq 120 μ mol/l	164	35.4	117	25.3	209	41.2	26	5.1
Mild renal dysfunction, 120 < Cr \leq 180 μ mol/l	69	14.9	17	3.7	81	16.0	3	0.6
Moderate renal dysfunction, 180 < Cr < 300 μ mol/l	48	10.4	7	1.5	97	19.1	9	1.8
Severe renal dysfunction, Cr \geq 300 μ mol/l	39	8.4	2	0.4	70	13.8	12	2.4
Total	320	69.1	143	30.9	457	90.1	50	9.9

SLTU, Scottish Liver Transplant Unit; PT, prothrombin time (s); Cr, creatinine; *n*, number of subjects with available data.

Mortality rates were highest in patients that first presented to hospital more than 24 h after ingestion ($p<0.01$). Delay in presentation was also associated with an increase in poor prognosis according to the KCHC. Thus, in the group who presented after 24 h, 33.6% (49/146) developed poor prognosis according to the KCHC as compared to 17.6% (31/176) of patients presenting within 24 h ($p<0.01$) (Table 2). Mortality in the group with staggered overdose was significantly worse (34.4%, 44/128) than in those with a single overdose (21.5%, 76/354). There was also no significant difference in the stated dose of ingested paracetamol in the group with single and staggered overdose (staggered overdose: 30 \pm 2.3 g, single overdose: 33.5 \pm 5 g).

Creatinine concentration at first admission (referral Cr) was significantly higher in patients presenting more than 24 h after ingestion (155.8 \pm 7.9 μ mol/l) than in those presenting within 24 h (98.3 \pm 3.7 μ mol/l) ($p<0.0001$; Table 2), which is in keeping with deteriorating renal function. There was no age difference between groups who presented within (32.5 \pm

0.9 years) or after 24 h (34.6 \pm 1.0 years). Referral Cr following staggered overdose (177.9 \pm 12.0 μ mol/l, $n=116$) was significantly higher ($p<0.0001$) than that in acute overdose patients who presented within 24 h of ingestion (98.3 \pm 3.7 μ mol/l, $n=161$), but was similar to that in those presenting more than 24 h (Table 2). Patients with staggered overdose were significantly older (38.2 \pm 1.0 years) than those with a single overdose (33.7 \pm 0.6 years).

Data on the highest Cr during inpatient stay was not available to us, however 38.4% of patients developed moderate and severe renal injury (worst Cr > 180 μ mol/l) as judged on samples available at admission to either the referring hospital or the SLTU. Stated paracetamol dose in acute ingestions did not correlate with risk of renal impairment as judged by Cr at time of referral to SLTU (Cr \leq 120 μ mol/l: 34 \pm 2 g; 120 < Cr \leq 180 μ mol/l: 28 \pm 2 g; 80 < Cr < 300 μ mol/l: 39 \pm 3 g; \geq 300 μ mol/l: 27 \pm 3 g).

Factors associated with more severe renal impairment at the time of transfer to SLTU were increased age ($p<0.0001$),

Table 2 Laboratory and clinical variables with respect to the interval between single acute paracetamol ingestion and first presentation to hospital in paracetamol overdose

Time from ingestion to presentation	\leq 24 h (<i>n</i>)	>24, \leq 8 h (<i>n</i>)	>48 h (<i>n</i>)	Significance level (<i>p</i>)
Interval (h)	15.2 \pm 0.5 (176)	37.4 \pm 0.8 (104)	66.6 \pm 2.8 (42)	
Referral Cr (μ mol/l)	98.3 \pm 3.7(161)	140.6 \pm 7.9 (94)	192.6 \pm 18.2 (39)	<0.0001 ^a
Referral PT (s)	29.9 \pm 1.7 (166)	45.4 \pm 2.1 (101)	65.0 \pm 6.0 (39)	<0.0001 ^a
Referral ALT (IU/l)	1960 \pm 264 (147)	5524 \pm 520 (75)	7887 \pm 875 (30)	<0.0001 ^b
Worst PT (s)	62.8 \pm 2.9 (173)	67.3 \pm 3.4 (104)	77.1 \pm 6.4 (42)	NS
Dialysis (%)	19.5 (34/174)	44.2 (46/104)	34.1 (14/41)	<0.0001 ^c
KCHC poor prognosis (%)	17.6 (31/176)	36.5 (38/104)	26.2 (11/42)	<0.01 ^d
Mortality (%)	15.3 (27/176)	28.3 (30/104)	23.8 (10/42)	<0.05 ^d

n, Number of subjects with available data; KCHC, King's College Hospital Criteria; ALT, alanine aminotransferase; NS, non-significant. Values are presented as the mean \pm standard error of the mean (SEM)

^a Serum Cr and PT higher in patients presenting > 24 h ($p<0.0001$). Cr and PT were also higher in >48 h group compared to >24–48 h ($p<0.0001$).

^b ALT was higher in patients presenting >24 h ($p<0.0001$) compared to those presenting \leq 24 h. The ALT was also higher in >48 h group compared to >24–48 h group ($p<0.05$).

^c Dialysis requirement was significantly higher in patients presenting >24 h ($p<0.0001$).

^d KCHC poor prognosis and mortality were significantly higher in patients presenting >24 h ($p<0.01$ for KCHC poor prognosis, $p<0.05$ for mortality).

hypotension at admission to referral hospital or at transfer ($p < 0.0001$) and interval between ingestion and delay to first presentation to hospital ($p < 0.0001$) (Table 3). Patients with more severe renal injury also had a higher GGT at first presentation, and acidosis was also more common in renal injury ($p < 0.0001$). A higher proportion of patients with severe renal impairment had taken a staggered overdose (Table 3).

Discussion

Paracetamol poisoning is a common clinical problem, and early identification of patients with more severe poisoning is key to improving outcomes. Present tools for risk-stratification are predominantly based on paracetamol concentration timed after ingestion and are targeted at reducing liver injury, usually as rises in hepatic transami-

nase [6, 13]. This approach is dependant on an accurate history and a single ingestion time point. Accuracy beyond 15 h after ingestion is less certain. Thus, research that is aimed at improving outcome prediction based on paracetamol concentration [14] may not be applicable to many in this cohort of more severe poisoning, where patients present late or with staggered ingestion. In addition to the factors we report here, previous work has identified hypophosphataemia and phosphaturia as potential early markers of more severe toxicity at first presentation [15]. We have not studied these, as these measurements were not routinely carried out.

Although renal failure is a recognised complication of paracetamol toxicity, the underlying mechanisms are poorly understood. Toxic metabolites of paracetamol are generated by local metabolism in the kidney and may cause acute tubular necrosis, particularly in conditions associated with glutathione depletion [16]. Even in the absence of acute

Table 3 Clinical characteristics at first admission and outcomes in patients with paracetamol overdose grouped by renal function at the time of tertiary admission

Renal impairment Cr ($\mu\text{mol/l}$)	Normal: Cr ≤ 120	Mild: 120 < Cr ≤ 180	Moderate: 180 < Cr < 300	Severe: Cr ≥ 300	Significance level (p)
n (%)	239 (46.8%)	84 (16.4%)	106 (20.7%)	82 (16.0%)	
Male/female	102/137	45/39	62/44	42/40	
Age (years)	32 \pm 1	38 \pm 2	39 \pm 1	39 \pm 1	<0.0001 ^a
Staggered overdose (%)	18.5% ($n=43/2333$)	28.5% ($n=22/78$)	26.9% ($n=25/93$)	50.7% ($n=36/71$)	<0.0001 ^b
Hypotension at first admission (%)	3.9% ($n=9/239$)	18.1% ($n=15/83$)	32.0% ($n=33/103$)	32.1% ($n=25/78$)	<0.0001 ^c
Delay to first admission (h)	25 \pm 1 ($n=179$)	28 \pm 2 ($n=56$)	36 \pm 3 ($n=65$)	43 \pm 5 ($n=37$)	<0.0001 ^d
First PT (s)	37 \pm 9 ($n=211$)	42 \pm 2.8 ($n=77$)	51 \pm 3.2 ($n=92$)	59 \pm 4 ($n=75$)	<0.0001 ^e
First GGT (u/l)	82 \pm 8 ($n=144$)	155 \pm 19 ($n=57$)	164 \pm 18 ($n=57$)	238 \pm 24 ($n=51$)	<0.0001 ^f
First [H ⁺] (mmol/l)	42 \pm 1 ($n=149$)	53 \pm 3 ($n=58$)	61 \pm 4 ($n=64$)	54 \pm 3 ($n=54$)	<0.0001 ^g
First K (mmol/l)	3.9 \pm 0.05 ($n=222$)	4.2 \pm 1.0 ($n=75$)	4.5 \pm 1.0 ($n=100$)	4.8 \pm 0.1 ($n=73$)	<0.0001 ^h
Worst PT (s)	59 \pm 2 ($n=235$)	73 \pm 5 ($n=84$)	82 \pm 5 ($n=106$)	75 \pm 5 ($n=81$)	<0.0001 ^k
ITU stay (days)	1.4 \pm 0.2 ($n=237$)	2.5 \pm 0.4 ($n=83$)	4.7 \pm 1.0 ($n=104$)	4.1 \pm 0.6 ($n=80$)	<0.0001 ^m
Mortality (%)	8.8 ($n=21/239$)	32.1 ($n=27/84$)	47.2 ($n=50/106$)	51.2 ($n=42/82$)	<0.0001 ⁿ

n , Number of subjects with available data; ITU, Intensive Care Unit

^a Patients with any renal dysfunction were older ($p < 0.0001$). Those with moderate and severe dysfunction were older than those with mild dysfunction ($p < 0.0001$)

^b Staggered overdose was more common in those with severe renal dysfunction than in those with normal renal function ($p < 0.0001$) and mild or moderate renal dysfunction ($p < 0.01$)

^c Renal dysfunction at first admission was more common in those with hypotension ($p < 0.0001$). Severe dysfunction was more common than normal ($p < 0.0001$) or mild dysfunction ($p < 0.01$)

^d Patients with moderate and severe renal dysfunction presented later than those with normal renal function ($p < 0.0001$). Patients with severe renal dysfunction presented later than mild dysfunction ($p < 0.01$)

^e Significant intergroup difference in referral PT ($p < 0.01$). Referral PT was higher in patients with moderate and severe renal function than in those with normal ($p < 0.01$). Referral PT was less in mild than severe renal function ($p < 0.01$)

^f GGT was lower in patients with normal renal function ($p < 0.0001$). GGT was higher in severe than mild ($p < 0.01$) or moderate renal function ($p < 0.05$)

^g Referral [H⁺] in group with normal renal function was significantly lower than that in mild ($p < 0.01$), moderate ($p < 0.0001$) and severe ($p < 0.01$) renal dysfunction

^h Referral K in the group with normal function was significantly lower than that in moderate and severe renal dysfunction ($p < 0.0001$). Referral K in the group with mild dysfunction was significantly lower than that in severe renal dysfunction ($p < 0.0001$)

^k Worst PT in normal group was significantly lower than mild ($p < 0.05$), moderate ($p < 0.0001$), or severe renal dysfunction ($p < 0.05$)

^m Patients with moderate and severe renal dysfunction stayed longer in the intensive care unit (ITU) than those with normal renal function ($p < 0.0001$ and $p < 0.01$, respectively)

ⁿ Mortality in the group with normal renal function was significantly lower than those with mild, moderate and severe renal dysfunction ($p < 0.0001$). Those with mild renal dysfunction had lower mortality than those with moderate or severe renal dysfunction ($p < 0.05$)

renal failure, paracetamol ingestion is associated with dose-dependent changes in electrolyte transport, suggesting a direct pharmacological action of paracetamol on renal tubular function [17, 18]. Risk factors, such as glutathione depletion in the kidney, concomitant ingestion of nephrotoxic substances, dehydration at presentation, chronic excessive overdose of paracetamol and pre-existing liver and renal insufficiency may all increase the risk of renal injury after paracetamol overdose [19].

As expected, most patients in the current series requiring tertiary referral after paracetamol overdose had evidence of acute liver dysfunction defined by $PT \geq 25$ s (96.6%). Our study found that within this patient population, there was a higher prevalence of renal impairment (38.4%; $Cr > 180 \mu\text{mol/l}$ at admission to either hospital) than has been previously described in severe paracetamol poisoning [6, 20]. This is almost certainly due to the highly selected patient population. Importantly, these data indicate that Cr at the time of first admission in this cohort was an important predictor of developing poor prognosis according to the KCHC. The data also show that groups with more severe renal injury, both at first presentation and tertiary transfer, had other markers of worse outcome, as indicated by higher PT, longer stay in ITU, greater need for dialysis and higher mortality (Tables 1 and 3). The vast majority of patients stated they had taken doses regarded as potentially hepatotoxic, although we could not find a dose-response relationship between stated dose and nephrotoxicity. We have previously reported on a very small number in this case series in whom paracetamol dose appeared to be below the standard plasma concentration–time curves [21].

Renal dysfunction was more severe with later presentation, in patients with hypotension at admission, those who were older and those who had a high initial GGT. Renal dysfunction was also worse in those who had taken a staggered overdose. Our findings are similar to those reported in children who present to hospital after paracetamol overdose: a prolonged interval between ingestion and presentation to hospital and renal impairment were both associated with poorer prognosis [22].

To explore this data further, a receiver operating characteristic (ROC) curve was constructed for referral Cr concentration as a predictor of poor prognosis according to the KCHC (Fig. 1). The area under the curve was 74.3% [95% confidence interval (CI) 70.1–78.1%, $p=0.0001$ compared to the 50% line by the z test]. This plot indicated that in this cohort a $Cr > 123 \mu\text{mol/l}$ at presentation to the referring hospital had a sensitivity of 71.3% (95% CI 62.7–78.9%) and specificity of 73.3% (95% CI 68.3–77.9%) for a poor prognosis according to the KCHC during the hospital stay. A serum Cr of $123 \mu\text{mol/l}$ is very close to the upper limit of normal, and while this potential tool needs validation in other similar large cohorts, it has the

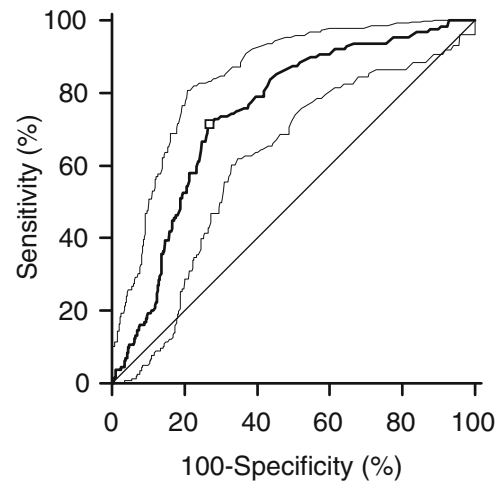


Fig. 1 The receiver operating characteristic (ROC) curve for referral creatinine versus "King's College poor outcome" area under the ROC curve (AUC)=74.3% [95% confidence interval (CI) 70.1–78.1%, significance level $p=0.0001$ (versus 0.5 line by z test)]. The most "accurate predictor" is referral creatinine $>123 \mu\text{mol/l}$, sensitivity=71.3% (95% CI 62.7–78.9%) and specificity=73.3% (95% CI 68.3–77.9%)

attraction of simplicity as a clinical marker for the early detection of patients at greatest risk.

These data come from a large single UK centre and may therefore not be representative of other liver units. Other factors not tested in this study include deprivation, which has also been found to be associated with poor outcomes in Scotland [23] and might be a confounder not generally applicable in other patient groups.

The use of serum Cr as a risk factor thus needs to be tested independently by others. Nevertheless, the present data underpin the importance of prompt hospital referral and the administration of acetylcysteine, which has been shown to be most effective when given within the first 8–12 h after paracetamol ingestion [13]. It is increasingly recognised that patients presenting to hospital after staggered overdose are at substantially increased risk than those after acute single ingestion. This is reflected in the present data, where staggered overdoses comprise a high proportion of patients referred to the SLTU. Thus, a careful history in which close attention is paid to Cr concentration, the presence of hypotension and GGT activity should allow earlier identification of patients who are at greater risk of poor outcome. Better public information on the need for urgent therapy and avoidance of excess therapeutic doses may also be warranted.

In conclusion, while renal impairment is relatively uncommon after mild to moderate paracetamol overdose, it was a common complication in the patients of our study cohort who were referred to a tertiary centre with severe paracetamol toxicity, and it was identifiable in a majority of high-risk patients in this cohort at first

presentation. Important clinical factors predicting poor outcome were: presentation to hospital >24 h after ingestion, elevated Cr concentration at the time of first presentation, hypotension, staggered overdose and raised GGT. Renal dysfunction at first presentation appears to be an important predictor of subsequent liver toxicity and death in this group. Further work is required to explore whether more subtle markers of renal impairment might allow better risk-stratification in patients that present to hospital after paracetamol overdose.

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