Staggered overdose pattern and delay to hospital presentation are associated with adverse outcomes following paracetamol-induced hepatotoxicity

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WHAT IS ALREADY KNOWN ON THIS SUBJECT

- Paracetamol hepatotoxicity is the commonest cause of acute liver failure (ALF) in the UK.
- Relatively little is known regarding the impact of staggered overdose pattern or delayed hospital presentation upon subsequent mortality or need for emergency liver transplantation.

WHAT THIS STUDY ADDS

- Staggered paracetamol overdoses, frequently taken to relieve pain, are strongly associated with reduced survival compared with single time point overdose.
- Staggered paracetamol overdoses should be treated as high risk for the development of multiorgan failure, and should be considered for *N*-acetyl cysteine treatment irrespective of admission serum paracetamol concentrations.
- The King's College poor prognostic criteria may have reduced sensitivity in staggered overdose patients.

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AIMS

Paracetamol (acetaminophen) poisoning remains the major cause of severe acute hepatotoxicity in the UK. In this large single centre cohort study we examined the clinical impact of staggered overdoses and delayed presentation following paracetamol overdose.

RESULTS

Between 1992 and 2008, 663 patients were admitted with paracetamol-induced severe liver injury, of whom 161 (24.3%) had taken a staggered overdose. Staggered overdose patients were significantly older and more likely to abuse alcohol than single time point overdose patients. Relief of pain (58.2%) was the commonest rationale for repeated supratherapeutic ingestion. Despite lower total ingested paracetamol doses and lower admission serum alanine aminotransferase concentrations, staggered overdose patients were more likely to be encephalopathic on admission, require renal replacement therapy or mechanical ventilation and had higher mortality rates compared with single time point overdoses (37.3% vs. 27.8%, $P = 0.025$), although this overdose pattern did not independently predict death. The King's College poor prognostic criteria had reduced sensitivity (77.6, 95% CI 70.8, 81.5) for this pattern of overdose. Of the 396/450 (88.0%) single time point overdoses in whom accurate timings could be obtained, 178 (44.9%) presented to medical services >24 h following overdose. Delayed presentation beyond 24 h post overdose was independently associated with death/liver transplantation (OR 2.25, 95% CI 1.23, 4.12, $P = 0.009$).

CONCLUSIONS

Both delayed presentation and staggered overdose pattern are associated with adverse outcomes following paracetamol overdose. These patients are at increased risk of developing multi-organ failure and should be considered for early transfer to specialist liver centres.

Introduction

Paracetamol (acetaminophen) hepatotoxicity remains the leading cause of acute liver failure (ALF) in the UK, North America and Europe, and represents a significant health-care burden [1–3]. Management of early, non-staggered, paracetamol overdose using *N*-acetyl cysteine (NAC) as an antidote is based upon the use of the Prescott nomogram [4], but this nomogram cannot be used in patients who have taken repeated supratherapeutic ingestions of paracetamol (staggered overdoses), and there are too few data available to conclude that it is reliable in patients who present >15 h post overdose [5]. Such overdoses are considered to be at higher risk for developing hepatotoxicity [6, 7], but little is known regarding these overdose patterns and the development of hepatic encephalopathy (HE), multi-organ failure, and the need for emergency orthotopic liver transplantation (OLT). Furthermore, most ALF prognostic models in widespread clinical practice do not incorporate the mechanism of overdose, focusing instead upon clinical or laboratory parameters such as the presence of acidosis, degree of coagulopathy, renal impairment and presence of advanced HE [8].

The aims of this cohort study were to analyze the incidence, clinical course and outcome of staggered and delayed paracetamol overdoses compared with single time point overdoses utilizing prospectively defined data collected from 903 patients with acute severe liver injury admitted to the Scottish Liver Transplantation Unit (SLTU). We hypothesized that patients presenting with severe liver injury following staggered or delayed paracetamol overdose would have a greater degree of systemic dysfunction, and subsequently worse clinical outcomes, compared with single time point overdoses.

Methods

Patients

The cohort retrospectively analyzed were from 938 patients admitted to the SLTU between 1 November 1992 and 31 October 2008 with suspected severe acute liver injury. Severe acute liver injury was defined as sudden deterioration in liver function with associated coagulopathy in the absence of a history of chronic liver disease, whilst the term ALF (i.e. fulminant liver failure) was restricted to those patients developing HE [9]. Guidelines for accepting patients from referring hospitals were based on previously published criteria and have remained unchanged over the time course of the study [10]. Following admission a detailed clinical history, examination and laboratory investigations were performed, with imaging studies and transjugular liver biopsy undertaken where clinically indicated. Laboratory investigations were repeated at daily intervals or more frequently in patients with rapidly progressive liver failure. Patients admitted to

the SLTU are managed using a standard protocol as previously described, with patients with paracetamol poisoning treated with a continuous NAC infusion ($6.25 \text{ mg kg}^{-1} \text{ h}^{-1}$) until the international normalized ratio (INR) is less than 2 [11]. The main therapeutic goals of this protocol have remained similar over the 16 years of this cohort study. The modified King's College Hospital poor prognostic criteria (KCC) are used in this unit and throughout the UK to determine patients who will most likely die without OLT [12]. OLT was considered in all patients meeting KCC in conjunction with their medical condition and psychological assessment. If accepted as transplant candidates, patients are 'super-urgently' listed with United Kingdom Transplant and prioritized for the next available compatible organ.

Methods

Details of patient history, clinical examination and laboratory results along with therapeutic interventions, including intensive care admission, need for renal replacement therapy or inotropic support were prospectively recorded in the ALF database. The following variables were recorded at the time of admission: temperature, pulse, white cell count (WCC), platelet count, INR, serum electrolytes, serum bilirubin, alanine aminotransferase (ALT), serum albumin, arterial hydrogen ion, bicarbonate and arterial lactate. Where available, the paracetamol preparation, number of tablets, type and timing of overdose, delay to presentation and use of NAC were all recorded. Background information such as alcohol use and dependency, illicit drug use, pre-existing psychiatric history and employment was obtained by the admitting medical and psychiatric teams from a variety of sources including, where possible, the patient, the patient's family and the patient's general medical practitioner. Where available, further information was obtained from review of the medical and psychiatric notes from the referring hospital.

Definitions

Paracetamol overdose was prospectively assigned as the cause of acute severe liver injury if there was a clear history of ingestion of potentially toxic amounts of paracetamol ($>4 \text{ g day}^{-1}$) within 7 days of presentation, serum paracetamol concentrations were $>10 \text{ mg l}^{-1}$ or serum ALT concentration $>1000 \text{ IU l}^{-1}$ within 7 days of a history of paracetamol ingestion irrespective of the serum paracetamol concentration [2]. Paracetamol overdose was only accepted as the cause of acute severe liver injury after exclusion of other potential aetiologies, in particular hepatitis A and B, autoimmune hepatitis and Wilson's disease.

A *single time point overdose* referred to an overdose ($>4 \text{ g}$) of paracetamol taken at a single defined time point whilst a *staggered overdose* described ingestion of two or more supratherapeutic paracetamol doses over a time interval of greater than 8 h resulting in a cumulative dose of $>4 \text{ g day}^{-1}$. A *delayed presentation* referred to presentation $>24 \text{ h}$ following the last ingestion of paracetamol. Due

to potential confounding and difficulties with timings following staggered overdoses, this term was only used in conjunction with single time point overdoses. *Mixed overdose* described more than one type of tablet being taken concomitantly with the paracetamol overdose, whilst *compound overdose* described overdose of compound tablets which included paracetamol such as co-proxamol or co-dydramol. *Alcohol abuse* was defined as alcohol consumption >56 units week⁻¹ for men and >42 units week⁻¹ for women. Outcome was defined as spontaneous survival to discharge without transplant, death without transplant, survival with transplant and death with transplant. When undertaking survival analysis, death and OLT were considered equivalent.

Statistical analysis

All patient data were prospectively recorded in the SLTU ALF database. Statistical analysis was retrospectively performed using SPSS software (SPSS 16.0, Chicago IL, USA) and Graphpad Prism (GraphPad Software Inc., La Jolla, CA). Data values are presented as median and interquartile range (IQR) or percentages unless otherwise stated. Continuous data were compared using analysis of variance or the Kruskal-Wallis test for non-normally distributed variables. Categorical data were analyzed using Chi-squared tests. Stepwise logistic regression was used to determine factors predictive of death or OLT in paracetamol-induced acute severe liver injury patients. Actuarial probability curves were constructed using the Kaplan-Meier method and compared with log-rank testing. A two-sided *P* value of less than 0.05 was considered statistically significant.

Results

Overall study population

Over a 16 year period (November 12 1992–November 11 2008) 938 patients were admitted to the SLTU with severe acute liver injury, of whom 663 (70.7%) were prospectively classified as having paracetamol-induced hepatotoxicity. A total of 344 (51.9%) of paracetamol-induced acute liver injury patients went on to develop HE, and thus ALF, at some point during their illness. Of the 663 paracetamol cases, 520 (78.4%) had been transferred to the SLTU from a total of 14 separate health authorities, with the remaining 143 patients transferred from local hospitals or from wards within the Royal Infirmary of Edinburgh. In those patients (396/663, 59.7%) in whom accurate timings could be obtained, presentation to emergency services occurred at a median of 23 h post overdose (range 1–130 h). Five hundred and fifty-nine/644 (86.8%) patients had received intravenous NAC in the referring hospital, at a median time from overdose of 23.75 (IQR 10–44) h. Further baseline demographic, psychiatric and clinical characteristics of the paracetamol study group are outlined in Table 1.

Table 1

Admission characteristics of 663 subjects with paracetamol-induced acute severe liver injury

Admission characteristic (n = 663 unless otherwise stated)	Value
Gender (male/female)	315/348 (47.5/52.5%)
Age (years)	34 (26–44)
Time course of overdose	
Single	450 (67.9%)
Staggered	161 (24.3%)
Unknown	52 (7.8%)
Number of tablets (n = 538)	50 (35–90)
Paracetamol concentration (mg l ⁻¹) (n = 561)	60.5 (20–130)
Mixed overdose (n = 620)	316 (51.0%)
Associated alcohol with overdose (n = 590)	264 (44.7%)
Alcohol abuse† (n = 581)	263 (45.3%)
Previous psychiatric history (n = 577)	244 (42.3%)
Active drug abuse (n = 623)	96 (15.4%)
Previous overdose (n = 619)	242 (39.1%)
Unemployed at time of overdose (n = 606)	289 (47.7%)
Time from overdose to SLTU admission (h) (n = 414)	52 (40–67)
Received NAC in referring hospital (n = 644)	559 (86.8%)
Admission laboratory parameters	
WCC (×10 ⁹ l ⁻¹)	10.7 (7.6–14.5)
Platelets (×10 ⁹ l ⁻¹)	125 (73–174)
Creatinine (μmol l ⁻¹)	134 (84–234)
ALT (IU l ⁻¹)	7 291 (4 250–10 130)
Bilirubin (μmol l ⁻¹)	83 (58–113)
Albumin (g l ⁻¹)	35 (31–39)
PT (s)	48 (34–67)
Ever encephalopathic	344 (51.9%)
Never encephalopathic	319 (48.1%)
Not encephalopathic on admission	387 (58.4%)
Developed encephalopathy during admission (n = 387)	43 (11.1%)
Overall outcome	
Survived without transplant	446 (67.3%)
Died without transplant	165 (24.9%)
Survived with transplantation (to hospital discharge)	37 (5.6%)
Died with transplantation	15 (2.2%)

Data are presented as median (IQR) or numbers (%) as appropriate. †>56 units week⁻¹ (male); >42 units week⁻¹ (female). WCC, white cell count; ALT, alanine aminotransferase; PT, prothrombin time.

Single time point vs. staggered overdoses

Information regarding the time course of the paracetamol overdose was available in 611 (92.2%) of cases; 450 (73.6%) of subjects were classified as have taken a single time point overdose and 161 (26.4%) as having taken a staggered overdose (Table 2). Staggered overdose subjects were significantly older (median 39 (29–46) years) compared with single overdose patients (32 (24–43) years, *P* < 0.001), were more likely to have a history of alcohol abuse (48.9% vs. 29.2%, *P* < 0.001) and to have taken alcohol concomitantly with their overdose (53.5% vs. 38.5%, *P* = 0.001). Staggered overdose patients were significantly less likely to receive NAC in the referring hospital (80.4% vs. 89.6%, *P* = 0.036). Staggered overdose patients had significantly lower

Table 2

Admission clinical and laboratory data in patients with single time point or staggered paracetamol overdose

	Single time point	<i>n</i>	Staggered	<i>n</i>	<i>P</i>
Gender (male/female)	217/233 (48.2/51.8%)	450	81/80 (50.3/49.7%)	161	0.649
Age (years)	32 (24–43)	450	39 (29–46)	161	<0.001
DepCat score*	4 (3–6)	450	5 (4–6)	161	0.420
Paracetamol concentration (mg l ⁻¹)	75.6 (24–149.6)	390	37.8 (16.6–77)	131	<0.001
Paracetamol only	216 (48.8%)	443	67 (45.0%)	149	0.423
Compound narcotic/paracetamol use	114 (25.7%)		48 (32.2%)		
Mixed overdose	113 (25.5%)		34 (22.8%)		
Total paracetamol dose consumed (g)	27 (20–45)	426	24 (10–45)	100	0.017
Overdose taken with suicidal intent	440 (98.0%)	449	46 (34.3%)	134	<0.001
Associated alcohol†	171 (38.5%)	444	83 (53.5%)	155	0.001
Alcohol abuse†	115 (29.2%)	394	69 (48.9%)	141	<0.001
Previous psychiatric history	178 (44.7%)	398	48 (34.0%)	141	0.023
Active drug use	75 (17.5%)	429	16 (10.5%)	153	0.040
Received NAC in referring hospital	395 (89.2%)	443	129 (82.7%)	156	0.036
Admission laboratory parameters					
Platelets (×10 ⁹ l ⁻¹)	130 (83–180)	450	113 (62–163)	161	0.006
Sodium (mmol l ⁻¹)	136 (133–138)		134 (130–138)		0.001
Creatinine (μmol l ⁻¹)	114 (81–208)		172 (98–296)		<0.001
ALT (IU l ⁻¹)	8 415 (5 335–11 078)		4622 (2809–8754)		<0.001
Bilirubin (μmol l ⁻¹)	84 (57–108)		81 (58–127)		0.207
Albumin (g l ⁻¹)	37 (33–41)		33 (26–37)		<0.001
PT (s)	49 (35–67)		45 (34–64)		0.292
Encephalopathic on admission	154 (34.5%)		70 (43.5%)		0.036
Developed encephalopathy during admission	57 (19.3%)	296	20 (22%)	91	0.570
Met King's College criteria	119 (26.4%)	450	51 (31.7%)	161	0.204
CVVH	127 (28.2%)		63 (39.1%)		0.010
Mechanical ventilation	172 (38.2%)		77 (47.8%)		0.033
Transplanted	39 (8.7%)		10 (6.2%)		0.325
Spontaneously survived	326 (72.4%)		101 (62.7%)		0.025

Data are on admission to the SLTU unless otherwise stated and are presented as median (IQR) or numbers (%) as appropriate. *DepCat (deprivation category) score is a seven point measure of relative socioeconomic deprivation in Scotland, with DepCat 1 being the most affluent and DepCat 7 the most deprived. †>56 units week⁻¹ (male); >42 units week⁻¹ (female). ‡Alcohol taken with paracetamol overdose.

admission serum paracetamol concentrations (staggered 37.8 (16.6–77) mg l⁻¹, single time point 75.6 (24–149.6) mg l⁻¹, *P* < 0.001) and had ingested significantly lower total amounts of paracetamol (staggered 24 (10–45) g, single time point 27 (20–45) g, *P* = 0.017). Within the staggered overdose group, patients who died had consumed a similar total paracetamol dose to spontaneous survivors (24 (12–45) g vs. 22.5 (6.5–50) g respectively, *P* = 0.511).

Repeated supratherapeutic overdoses and pain

Information regarding the reasons for overdose was available for 134/161 (83.2%) of staggered overdoses. The most common (58.2%) rationale for overdose was for relief of pain, including abdominal pain (*n* = 29), musculoskeletal pain (*n* = 23), headache (*n* = 16), toothache (*n* = 7), chest pain (*n* = 2) and dysmenorrhoea (*n* = 1). A total of 46/134 (34.3%) of staggered overdoses were taken deliberately as a suicide attempt. Other causes for staggered overdose included accidental overdose during chemical intoxication (*n* = 6), non-specific systemic illness (*n* = 2), iatrogenic overdose (*n* = 1) and one overdose taken

unintentionally by a patient with cognitive impairment. Of the 48 subjects who had consumed an overdose of compound analgesics, the majority (21/48, 43.8%) had used codeine phosphate/paracetamol compounds (co-codamol), an analgesic available over the counter (OTC) in pharmacies in the UK at a dose of 8/500 mg, and only by prescription at higher doses. A total of 14 subjects had overdosed on prescribed compound analgesics, namely dextropropoxyphene/paracetamol (co-proxamol, *n* = 7) and dihydrocodeine tartrate/paracetamol (co-dydramol, *n* = 7). A total of four cases had overdosed on both co-codamol and co-proxamol. The remaining compound overdose cases had used aspirin/paracetamol OTC compounds (*n* = 9). Of the mixed overdoses, seven cases had taken non-steroidal anti-inflammatories and paracetamol, six had used aspirin and paracetamol, six had taken a mixed antidepressant and paracetamol overdose, whilst a further three cases had taken paracetamol with benzodiazepines. A further four patients had taken concomitant illegal substances, whilst the remaining eight cases had taken mixed overdoses of other prescription medications and paracetamol.

Figure 1

Survival curves of patients with paracetamol-induced acute severe liver injury according to the pattern of overdose. Survival curves were significantly different when compared using log-rank testing ($\chi^2 = 5.75$, $P = 0.017$). OLT was considered equivalent to death

Laboratory values, hepatic encephalopathy, and clinical outcomes

Staggered overdose patients had significantly lower admission ALT concentrations compared with single time point overdoses, but had significantly more deranged admission serum sodium, creatinine and albumin concentrations. Thrombocytopenia was also significantly worse in the staggered overdose subjects compared with single time point overdoses, but admission prothrombin times were not significantly different between the two groups (Table 2). Staggered overdose patients were more likely to be encephalopathic on admission, develop encephalopathy at any stage (90/161, 55.9% vs. 211/450, 46.9%, $P = 0.050$), require renal replacement therapy or mechanical ventilation, compared with single time point overdose patients. Although there was no significant difference between the two overdose types in fulfillment of the KCC (31.7% vs. 26.4%, $P = 0.204$), spontaneous survival was significantly reduced in the staggered overdose group (62.7% vs. 72.4%, $P = 0.025$) (Figure 1).

Multivariate logistic regression of the staggered overdose cohort (Table 3) revealed that the presence of HE on admission, increased PT, leucocytosis, renal impairment and hypoalbuminaemia were independent predictors of death/OLT, whereas demographic factors or the lack of NAC treatment in the referring hospital did not predict death.

Delayed presentation amongst single time point overdoses

Of the 396/450 (88%) single time point patients in whom accurate timings could be obtained, 78 (19.7%) presented to emergency services within 12 h of the last ingestion of paracetamol, 140 (35.4%) presented 12–24 h after the last ingestion, with the remaining patients (178, 44.9%) presenting after a period of at least 24 h post ingestion had elapsed (maximum 130 h) (Table 4). These three overdose subgroups were similar in terms of gender distribution, subject age range and type of overdose (whether paracetamol alone, overdose with paracetamol/narcotic compounds or mixed overdoses). The three subgroups also showed no significant differences in the proportions of subjects with a previous psychiatric history, active drug use, and the numbers with a history of chronic alcohol abuse or alcohol taken concomitantly with their overdose. Patients presenting at >24 h following their last ingestion of paracetamol had significantly lower serum paracetamol concentrations (37 (IQR 13–89) mg l⁻¹) compared with either patients presenting at 12–24 h (89 (42–150) mg l⁻¹) or those presenting within 12 h (139 (80–261) mg l⁻¹, $P < 0.001$). Patients presenting at the three time points had similar serum concentrations of ALT, bilirubin, albumin and sodium, and similar prothrombin times and platelet counts. However, patients presenting

Table 3

Factors predictive of mortality on multivariate analysis of admission parameters in patients with paracetamol-induced acute severe liver injury. OLT was considered equivalent to death

Variable	Staggered overdose (n = 161) Multivariate OR (95% CI)	P value	Single time point overdose (n = 450) Multivariate OR (95% CI)	P value	All paracetamol overdoses (n = 663) Multivariate OR (95% CI)	P value
Staggered overdose	N/A (constant)		N/A		1.25 (0.73, 2.16)	0.416
Presentation >24 h	N/A		2.25 (1.23, 4.12)	0.009	1.59 (0.94, 2.69)	0.085
No NAC treatment in referring hospital	1.70 (0.40, 7.19)	0.470	0.77 (0.30, 1.98)	0.587	0.80 (0.41, 1.54)	0.494
Gender	1.20 (0.39, 3.70)	0.745	1.23 (0.68, 2.23)	0.490	1.31 (0.82, 2.10)	0.265
Age	1.05 (0.99, 1.10)	0.072	1.04 (1.01, 1.07)	0.002	1.04 (1.02, 1.06)	<0.001
Encephalopathy on admission	15.77 (4.79, 51.96)	<0.001	2.72 (1.44, 5.12)	0.002	4.13 (2.56, 6.68)	<0.001
Admission WCC	1.13 (1.03, 1.24)	0.011	1.11 (1.05, 1.17)	<0.001	1.10 (1.06, 1.15)	<0.001
Admission PT	1.04 (1.01, 1.06)	0.002	1.03 (1.02, 1.04)	<0.001	1.03 (1.02, 1.04)	<0.001
Admission albumin	0.91 (0.84, 0.99)	0.022	0.98 (0.94, 1.03)	0.529	0.97 (0.94, 1.01)	0.125
Admission creatinine	1.01 (1.00, 1.01)	0.001	1.00 (1.00, 1.04)	0.080	1.00 (1.00, 1.01)	<0.001

Table 4

Admission clinical and laboratory data in patients with single time point paracetamol overdose according to time of presentation to hospital

	Time (h) between last paracetamol ingestion and presentation to medical services		
	<12 (n = 78)	12–24 (n = 140)	>24 (n = 178)
Gender (male/female)	34/44 (43.6%/56.4%)	67/73 (47.9%/52.1%)	91/87 (51.1%/48.9%)
Age (years)	30 (24–42)	30 (24–40)	34 (25–43)
Paracetamol concentration (mg l ⁻¹)	139 (80–261)	89 (42–150)	37 (13–89)*
Paracetamol only	36 (46.2%)	73 (52.5%)	96 (54.6%)
Compound narcotic/paracetamol use	24 (30.8%)	35 (25.2%)	40 (22.7%)
Mixed overdose	18 (23.0%)	31 (22.3%)	40 (22.7%)
Associated alcohol†	28/72 (38.9%)	63/136 (46.3%)	59/162 (36.4%)
Alcohol abuse‡	16/73 (21.9%)	29/134 (21.6%)	39/168 (23.2%)
Previous psychiatric history	28/63 (44.4%)	56/122 (45.9%)	59/162 (36.4%)
Active drug use	12/74 (16.2%)	27/135 (20%)	25/176 (14.2%)
Received NAC in referring hospital	68/76 (89.5%)	136/139 (97.8%)	119/148 (80.4%)*
Admission laboratory parameters			
Platelets (×10 ⁹ l ⁻¹)	115 (79–174)	142 (100–192)	126 (69–171)
Sodium (mmol l ⁻¹)	136 (132–138)	136 (134–139)	135 (132–137)
Creatinine (μmol l ⁻¹)	94 (71–175)	94 (74–156)	162 (91–251)*
ALT (IU l ⁻¹)	8 697 (6 500–11 390)	8 112 (4 949–10 890)	8 406 (5 383–10 490)
Bilirubin (μmol l ⁻¹)	93 (66–116)	78 (55–104)	86 (58–112)
Albumin (g l ⁻¹)	36 (34–41)	37 (34–41)	37 (33–41)
PT (s)	47 (33–65)	44 (34–67)	51 (36–67)
Developed encephalopathy	22 (28.2%)	58 (41.4%)	102 (57.3%)*
Met King's College criteria	8 (10.3%)	27 (19.3%)	60 (33.7%)*
CVVH	10 (12.8%)	32 (22.9%)	71 (39.9%)*
Mechanical ventilation	16 (20.5%)	46 (32.9%)	84 (47.2%)*
Transplanted	4 (5.1%)	10 (7.1%)	19 (10.7%)
Spontaneously survived	69 (88.5%)	107 (76.4%)	114 (64.0%)*

*P < 0.05 Compared with earlier time points; †>56 units week⁻¹ (male); >42 units week⁻¹ (female); ‡Alcohol taken with paracetamol overdose.

at >24 h had significantly higher serum creatinine concentrations (162 (91–251) μmol l⁻¹) compared with either patients presenting at 12–24 h (94 (74–156) μmol l⁻¹) or those presenting within 12 h (94 (71–175) μmol l⁻¹, P < 0.001). Patients presenting at >24 h following overdose were significantly more likely to develop HE during their illness (102/178, 57.3%) compared with patients present-

ing at earlier time points (P < 0.0001). Of those patients presenting at >24 h, 47.2% required mechanical ventilation compared with 32.9% and 20.5% of subjects presenting at 12–24 h and <12 h respectively (P = 0.0001). Likewise, 39.9% of those patients presenting at >24 h required renal replacement therapy compared with 22.9% and 12.8% of subjects presenting at 12–24 h and

Figure 2

Survival curves of patients with paracetamol-induced acute severe liver injury according to time of presentation to hospital following overdose. Survival curves were significantly different when compared using log-rank testing for trend ($\chi^2 = 16.97$, $P < 0.001$). OLT was considered equivalent to death

<12 h respectively ($P < 0.0001$). Patients presenting at >24 h were also more likely to fulfil the KCC (33.7%), compared with 19.3% and 10.3% of subjects presenting at 12–24 h and <12 h respectively ($P < 0.0001$). Spontaneous survival occurred in 88.5% of patients presenting <12 h, 76.4% of patients presenting at 12–24 h, and 64.0% of patients presenting at >24 h ($P = 0.0001$, Figure 2). Within the single time point cohort, presentation at >24 h was independently associated with death/OLT (Table 3). Other independent risk factors included the presence of HE on admission, older age, leucocytosis and PT. Further analysis of the entire paracetamol overdose cohort ($n = 663$) revealed that neither staggered overdose nor delayed presentation >24 h were independently predictive of death/OLT (Table 3).

Prognostic accuracy of the KCC in different patterns of paracetamol overdose

The prognostic accuracy of the KCC was determined for the entire paracetamol ALF cohort ($n = 344$), then separately for ALF patients with single time point ($n = 211$) and staggered ($n = 90$) overdoses (Table 5). Although the KCC had high specificity for both overdose patterns, the sensitivity in predicting outcome was considerably better for single time point overdoses (89.9%, 95% confidence intervals (CI) 85.8, 92.7) compared with staggered overdoses (77.6%, 95% CI 70.8, 94.7).

Discussion

In this large, single centre cohort study of severe paracetamol-induced acute liver injury, we have analyzed the impact upon outcome of both staggered overdose pattern and delay to hospital presentation. Patients with staggered paracetamol overdoses had reduced survival compared with single intentional overdoses, despite ingestion of significantly lower total amounts of paracetamol. The KCC were less sensitive in predicting outcome in this cohort. We have further demonstrated that delay to hospital presentation at >24 h following overdose is independently associated with increased mortality or requirement for OLT following single time point overdose.

This study builds upon earlier data from our unit which indirectly found that staggered overdoses are associated with adverse outcomes [13], but this is the first cohort study to examine specifically the impact of staggered overdoses upon patients requiring tertiary level care, as previous studies of staggered paracetamol overdose have largely been based upon poison centre data [7, 14]. Further strengths of this study include the large number of patients, the single centre nature of the study and the prospectively defined criteria of overdose. The SLTU represents a single referral and management facility for all patients in Scotland with ALF irrespective of their suitability for liver transplantation, and the Scottish

Table 5
Predictive accuracy of the King's College poor prognostic criteria (KCC) according to the pattern of overdose

	KCC+ve/ deaths	Total deaths	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	LR- (95% CI)	DOR (95% CI)
Paracetamol ALF cases (n = 344)	197/180	213	84.5 (81.3, 87.0)	87.0 (81.8, 91.1)	91.4 (87.9, 94.1)	77.6 (72.9, 81.2)	6.5 (4.5, 9.8)	0.18 (0.14, 0.23)	36.6 (19.5, 68.4)
Single time point (n = 211)	115/107	119	89.9 (85.8, 92.7)	91.3 (86.0, 94.9)	93.0 (88.8, 95.9)	87.5 (82.4, 91.0)	10.3 (6.1, 18.2)	0.11 (0.08, 0.17)	93.6 (37.0, 236.9)
Staggered (n = 90)	49/45	58	77.6 (70.8, 81.5)	87.5 (75.3, 94.7)	91.8 (83.9, 96.5)	68.3 (58.8, 73.9)	6.21 (2.9, 15.3)	0.26 (0.20, 0.39)	24.2 (7.4, 78.2)

PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio; DOR, diagnostic odds ratio.

population has remained relatively stable at 5.1 million over the period of the study. However, we recognize that not all ALF cases occurring in Scotland will have been transferred to the SLTU during the course of the study due to medical instability precluding safe patient transfer [15]. Criteria for patient admission have remained largely unchanged during the time course of the study, further reducing patient heterogeneity, a recognized problem in previous cohort studies of paracetamol hepatotoxicity [16, 17].

This retrospective analysis of prospectively collected data has several limitations. The study accuracy is dependent upon the reliability and validity of patient recall regarding the time of last ingestion, total paracetamol dose and suicidal intent, although previous studies suggest that the patient history is often accurate following paracetamol overdose [18]. The distinction between a staggered overdose and a delayed single time point overdose is occasionally a blurred one, and some overdose types may have been wrongly classified. However, the association of both overdose patterns with adverse outcomes in this study suggests that patients presenting with either overdose pattern should be treated as high risk. There was also limited information available regarding the use of concomitant P450 enzyme inducers or recent fasting, both of which increase the risk of hepatotoxicity following repeated ingestion [19]. Our overall mortality rate of 32.7% represents selection bias for the more severe paracetamol cases in Scotland, since admissions to the SLTU are determined by severity of liver dysfunction, rather than on the basis of a history of paracetamol consumption or number of tablets consumed. As a result, our findings may not be directly applicable in the setting of an emergency department, where the vast majority of paracetamol overdoses will suffer no long-term physical sequelae. We cannot comment upon the overall epidemiology of staggered paracetamol overdoses, since these patients usually present to medical services as a result of physical, rather than psychiatric, morbidity, and therefore a number of sub-clinical overdoses may go undetected in the community. However, these data suggest that the pattern of overdose should be taken into account when assessing patients with paracetamol-induced hepatotoxicity, and that staggered overdose patients should be managed as high risk cases due to their significantly increased mortality.

This study emphasises the adverse effects of delayed presentation, and therefore treatment with NAC, following a single time point paracetamol overdose. Several previous studies have shown that delay in NAC treatment, caused through either late patient presentation or failure to initiate treatment in a timely manner, is associated with poor outcome in paracetamol-induced ALF. A retrospective cohort study from King's College between 1987 and 1993 demonstrated significantly reduced survival in those patients who did not receive NAC treatment in their referring hospital (71%), or were not treated with NAC until at

least 24 h post overdose (72%), compared with earlier NAC treatment (80%) [20]. A study of 161 single time point overdoses identified 'time to NAC' as an independent predictor of the development of HE. [21], whilst a study of 645 single time point overdoses in Denmark between 1994 and 2000 confirmed the adverse effects of delayed NAC treatment upon survival [22]. This study demonstrates that presentation >24 h following single time point overdose is an independent risk factor for death, and we therefore suggest that all patients with hepatotoxicity and delayed presentation following paracetamol overdose receive NAC treatment at their admitting hospital, irrespective of serum paracetamol concentrations, and should be closely observed due to the high risk of progression to further organ injury.

This study also strongly suggests that patients with severe liver injury following a staggered overdose are at significantly increased risk of adverse outcomes. There is limited published data to guide management of these cases, with previous reviews suggesting that total ingested paracetamol dose and time to presentation were the most important prognostic factors [5]. These data suggest that the former factor has a limited impact upon outcome, given that there was no significant difference in total paracetamol dose between spontaneous survivors and patients who died within the staggered overdose group, and single time point overdoses had significantly better clinical outcomes than staggered overdoses despite ingestion of a higher total paracetamol dose. Repeated low dose paracetamol administration has recently been shown to potentiate hepatic microsomal enzyme induction in a rat model [23], a study with implications for the mechanism of hepatotoxicity following staggered overdoses in humans. An alternative explanation is that the adverse outcomes in the staggered overdose group relate to delay in initiation of NAC treatment, given that only synthetic hepatic failure markers were independently predictive of outcome, suggesting that hepatic failure was imminent or had already occurred in some patients prior to NAC treatment. A third explanation is that staggered overdoses act as a surrogate marker for other risk factors for adverse outcomes following paracetamol overdose, such as older age and chronic alcohol abuse [22, 24], both of which were more common in the staggered overdose group. Whilst acute alcohol consumption has an inhibitory effect on the oxidative metabolism of paracetamol and may be hepatoprotective [25], this protective effect is probably lost in the context of chronic alcohol abuse or where there is a delay between alcohol and paracetamol intake [26], perhaps explaining why staggered overdose patients had worse clinical outcomes despite the increased incidence of acute alcohol consumption at the time of overdose (54% vs. 39%) in this subgroup.

The KCC are widely used in the UK to predict those patients who will require emergency OLT, but this study suggests that the KCC may perform poorly in cases of

staggered overdose, with reduced sensitivity compared with single time point overdoses. Alternative triage and prognostic markers may therefore be required to accommodate this important subgroup, perhaps incorporating features of systemic inflammation or multi-organ injury such as the systemic inflammatory response syndrome or Sequential Organ Failure Assessment scoring systems [27].

In conclusion, this large cohort study demonstrates the deleterious effects of delayed presentation and staggered overdose pattern upon outcome following paracetamol-induced acute liver injury. Both delayed presentation >24 h and staggered overdoses are strongly associated with multi-organ injury and the need for OLT. Patients presenting with these overdose patterns should be treated as high risk for progression to ALF, and should receive NAC in their presenting hospital whilst awaiting serial ALT and PT concentrations. Existing prognostic markers may require adaptation to reflect the pattern of overdose.

Competing Interests

There are no competing interests to declare.

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