

1 **Outcomes from massive paracetamol overdose: a retrospective**
2 **observational study**

3 **Daniel J B Marks^{1,2}, Paul I Dargan^{1,3}, John R H Archer^{1,3}, Charlotte L Davies²,**
4 **Alison M Dines¹, David M Wood^{1,3}, Shaun L Greene⁴**

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6 *¹Department of Clinical Toxicology, Guy's and St Thomas' NHS Foundation Trust*
7 *and King's Health Partners, London, UK, ²Department of Clinical Pharmacology,*
8 *University College London, London UK, ³Faculty of Life Sciences and Medicine,*
9 *King's College London, London, UK, ⁴Austin Toxicology Service and Victorian*
10 *Poisons Information Centre, Austin Hospital, Victoria, Australia*

11
12 **Submitting author** Dr Daniel J B Marks, Centre for Molecular Medicine,
13 University College London, UK; E-mail: d.marks@ucl.ac.uk

14
15 **Correspondence** Dr Shaun L Greene, Austin Toxicology Service and Victorian
16 Poisons Information Centre, Austin Hospital, Victoria, Australia; E-mail:
17 shaun.greene@austin.org.au

18
19 **Principal investigator** Dr Shaun L Greene

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24

25 **STRUCTURED SUMMARY**

26 **AIM**

27 Treatment of paracetamol (acetaminophen) overdose with acetylcysteine is
28 standardised, with dose determined only by patient weight. The validity of this
29 approach for massive overdoses has been questioned. We systematically
30 compared outcomes in massive and non-massive overdoses, to guide whether
31 alternative treatment strategies should be considered, and whether the ratio
32 between measured timed paracetamol concentrations ($APAP_{pl}$) and treatment
33 nomogram thresholds at those time points ($APAP_t$) provides a useful assessment
34 tool.

35 **METHODS**

36 Retrospective observational study of all patients (n=545) between 2005-2013
37 admitted to a tertiary care toxicology service with acute non-staggered
38 paracetamol overdose. Massive overdoses were defined as extrapolated 4-hour
39 plasma paracetamol concentrations $>250\text{mg/L}$, or reported ingestions $\geq 30\text{g}$.
40 Outcomes (liver injury, coagulopathy and kidney injury) were assessed in
41 relation to reported dose and $APAP_{pl}:APAP_t$ ratio (based on a treatment line
42 through 100mg/L at 4 hours), and time to acetylcysteine.

43 **RESULTS**

44 Ingestions of $\geq 30\text{g}$ paracetamol correlated with higher peak serum
45 aminotransferase ($r=0.212$, $P<0.0001$) and creatinine ($r=0.138$, $P=0.002$)
46 concentrations. Acute liver injury, hepatotoxicity and coagulopathy were more
47 frequent with $APAP_{pl}:APAP_t \geq 3$ with odds ratios (OR) and 95% confidence
48 intervals (CI) of 9.19 (5.04-16.68), 35.95 (8.80-158.1) and 8.34 (4.43-15.84),

49 respectively ($P < 0.0001$). Heightened risk persisted in patients receiving
50 acetylcysteine within 8 hours of overdose.

51 **CONCLUSION**

52 Patients presenting following massive paracetamol overdose are at higher risk of
53 organ injury, even when acetylcysteine is administered early. Enhanced
54 therapeutic strategies should be considered in those who have an $APAP_{pl}:APAP_t$
55 ≥ 3 . Novel biomarkers of incipient liver injury and abbreviated acetylcysteine
56 regimens require validation in this patient cohort.

57

58 **WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT**

- 59
- 60 • Acetylcysteine protocols in paracetamol overdose were initially
61 developed empirically, with subsequent validation using pharmacokinetic
62 studies of non-toxic doses in healthy individuals.
 - 63 • It is unclear whether these modelling assumptions are robust in massive
64 overdoses.
 - 65 • Case reports suggest that such patients may have worse outcomes, and
66 biochemical data hint at the need for supplemental acetylcysteine.

66

67 **WHAT THIS STUDY ADDS**

- 68
- 69 • Patients with an $APAP_{pl}:APAP_t \geq 3$ (based on a treatment line through
70 100mg/L at 4 hours) have higher rates of organ injury.
 - 71 • Excess risk persists even with acetylcysteine administration within 8
hours of overdose.

- 72 • Patients with massive overdoses may benefit from higher or protracted
73 doses of acetylcysteine, or approaches to enhance gastrointestinal drug
74 elimination.

75

76 **TABLE OF LINKS**

LIGANDS
paracetamol This Table lists key ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org , the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1].

77

78

79 **Introduction**

80 Paracetamol overdose remains the commonest drug overdose, and cause of
81 acute liver failure, in Europe, Australia and North America [2, 3] Intravenous
82 acetylcysteine is the mainstay of treatment and an effective antidote if used early
83 in the course of poisoning [3, 4]. The decision to treat acute, non-staggered,
84 paracetamol overdose is principally based on measured plasma paracetamol
85 concentrations, taken at least 4 hours after ingestion [3]. International guidelines
86 differ in their recommendations as to threshold paracetamol concentrations for
87 treatment on nomograms, but once these have been exceeded acetylcysteine
88 dosing regimens are very similar throughout the world [5]. The dose of
89 acetylcysteine is determined only by patient weight, and does not vary according
90 to other factors including the dose of paracetamol taken, plasma paracetamol
91 concentration, time to presentation, and/or co-ingestion of other drugs.

92 Acetylcysteine regimens have never been subject to definitive dose-
93 ranging studies in humans, nor have different regimens been compared in
94 randomised controlled trials sufficiently powered to inform on the optimal
95 strategy for preventing hepatotoxicity. As a result, current guidelines still
96 advocate treatment principally based on the dose calculated in the 1970s for the
97 initial studies of acetylcysteine in paracetamol toxicity [4]. At this time, there
98 were few data to inform on appropriate dosing, and much of the initial work was
99 empirical. It had, however, been established that hepatic and renal toxicity were
100 mediated through formation of N-acetyl-p-benzoquinone imine (NAPQI), once
101 paracetamol conjugation through glucuronidation and sulphation had been
102 saturated [6]. NAPQI can be detoxified to cysteine and mercapturate conjugates
103 by glutathione, with organ injury resulting once stores of the latter become

104 deplete [7]. Consequently, pharmacokinetic studies were performed in healthy
105 individuals to determine the level of glutathione depletion over a range of
106 paracetamol concentrations, and a dose of acetylcysteine selected that would
107 match this on a stoichiometric basis [5, 7].

108 Whilst this standard treatment regimen has proven extremely successful,
109 the “one size fits all” approach has been criticized [5, 8, 9]. In particular, it is not
110 clear whether the modelling assumptions underlying the initial acetylcysteine
111 dose calculations hold true with very large overdoses, and whether therapy
112 could be better tailored to individual cases in these situations [10, 11]. Several
113 case reports, and one recent observational study, highlight adverse outcomes in
114 patients with massive paracetamol overdoses despite early acetylcysteine [12-
115 16]. Such patients have higher cysteine and mercapturate to glucuronide
116 conjugate ratios, implying increased proportions of paracetamol undergoing
117 conversion to NAPQI and consistent with the need for supplemental
118 acetylcysteine beyond that suggested by the original models [6]. The aims of this
119 study were to evaluate the development of organ injury in massive overdoses in
120 a systematic manner, compare this to non-massive ingestions, and assess
121 whether reported ingested dose or the ratio of the measured plasma
122 paracetamol concentration ($APAP_{pl}$) to the corresponding treatment nomogram
123 paracetamol concentration threshold at that time ($APAP_t$) provided superior
124 prediction of outcome. We assessed all patients presenting to a specialist
125 toxicology service with acute paracetamol overdose meeting criteria for
126 treatment with acetylcysteine, and determined outcomes for those taking
127 massive overdoses.

128

129 **Methods**

130 *Patients and clinical data*

131 Clinical data on all patients presenting to our large inner-city hospital with
132 toxicology-related problems are prospectively entered into a purpose-designed
133 clinical database, with follow-up to the end of the acute inpatient admission
134 episode [17]. Data were extracted for all individuals who had taken an acute,
135 single (non-staggered) overdose of paracetamol in whom the time of ingestion
136 was recorded, and who received treatment with acetylcysteine, between May
137 2005 and May 2013. There are no universally agreed criteria of what constitutes
138 a massive paracetamol overdose; we therefore defined this pragmatically as an
139 extrapolated 4-hour plasma paracetamol concentration $>250\text{mg/L}$ (2.5-fold the
140 current UK threshold requiring treatment with acetylcysteine), or (where
141 plasma paracetamol concentrations were not available) if a patient reported
142 ingestion of $\geq 30\text{g}$ paracetamol. Caldicott and Ethical Approval are in place for the
143 database; data for this study were analysed anonymously and therefore no
144 further ethical approval was required. This manuscript is written in compliance
145 with STROBE guidelines.

146 The following information was extracted from the database: basic
147 demographic data; time of presentation to the emergency department; reported
148 quantity and time of paracetamol ingested; plasma paracetamol concentration
149 (APAP_{pl}) and time (t) this blood test was performed relative to exposure; time to
150 initiation of acetylcysteine; and peak serum aminotransferase concentration,
151 international normalized ratio (INR) and serum creatinine occurring on
152 admission or during the course of treatment. Calculated 4-hour plasma
153 paracetamol concentrations were back-extrapolated from measured values using

154 the formula used in previous studies: $APAP_{pl}/2e^{-(0.693/4)t}$ [18]. We also calculated
155 the ratio between $APAP_{pl}$ and the threshold concentration at that time point on
156 the treatment nomogram (based on a line through 100mg/L at 4 hours) above
157 which acetylcysteine would be administered ($APAP_t$).

158

159 *Treatment regimens during study period*

160 In the UK prior to 2012, single (non-staggered) paracetamol overdoses were
161 treated with acetylcysteine if measured plasma paracetamol concentrations
162 were above a nomogram line starting at 200mg/L at 4 hours if deemed standard
163 risk, or 100mg/L at 4 hours if high risk (for example, patients with chronic
164 alcohol misuse, medical conditions associated with glutathione depletion, and/or
165 taking cytochrome P450-2E1 inducing medication). The standard acetylcysteine
166 protocol was 150mg/kg over 15 minutes, followed by 50mg/kg over 4 hours,
167 and finally 100mg/kg over 16 hours. From 2012, UK guidelines changed such
168 that everyone was treated according to the 100mg/L at 4 hours nomogram
169 threshold line, with the duration of the first dose of acetylcysteine extended to 1
170 hour [19]. With both of these regimens, after completion of the third infusion,
171 renal function, liver function and coagulation parameters are rechecked, and a
172 further 16 hour acetylcysteine infusion instituted in the event of any significant
173 derangement [20].

174

175 *Assessment of organ injury*

176 There are a number of different working definitions for liver injury based on
177 rises in serum alanine or aspartate aminotransferase concentrations, and data
178 for all of the following were considered: 1. paracetamol-related liver injury,

179 defined by a rise ≥ 2 -fold the upper limit of normal (ULN; the threshold above
180 which UK guidelines recommend extending the acetylcysteine course) [8]; 2.
181 drug-induced acute liver injury, defined as ≥ 3 -fold ULN [16, 21]; and 3.
182 paracetamol-related hepatotoxicity, with aminotransferase concentrations
183 $> 1,000$ IU/L [4, 15, 22]. Coagulopathy was defined as an INR rising above 1.3 (the
184 threshold that would prompt extension of acetylcysteine therapy) [23], and
185 significant acute kidney injury as a serum creatinine > 150 μ mol/L (in the absence
186 of pre-existing chronic kidney disease) [24]. In addition, current UK guidelines
187 advocate consideration for liver transplantation in paracetamol overdoses with
188 an INR > 6.5 or serum creatinine > 300 μ mol/L [23].

189

190 *Statistical analysis*

191 Data are expressed as median (interquartile range), unless otherwise stated, and
192 were analysed using GraphPad Prism (version 7.0; GraphPad Software, CA,
193 2016). All eligible patients within the specified time frame were included in the
194 study, and no formal power calculation was performed. Continuous variables
195 were compared using the Mann-Whitney U-test, correlation by Spearman rank
196 coefficient, and event frequencies by Fisher's exact test. A P value ≤ 0.05 was
197 considered significant. Analyses did not impute missing data.

198

199 **Results**

200 **Patient and overdose characteristics**

201 A total of 545 patients fulfilled the inclusion criteria. Median age was 31 (22-43)
202 years, and 341 (62.6%) patients were female. Median time from overdose to
203 presentation was 3h25min (1h44min-6h47min). Plasma paracetamol

204 concentrations were available in 529 (97%) patients; in four individuals the
205 samples had haemolysed and were not repeated, and in twelve individuals they
206 were not performed. Median plasma paracetamol concentration was 119mg/L
207 (66-182), and time from exposure to measurement was 5h47min (4h36min-
208 9h5min). The median extrapolated 4-hour concentration was 190.0 (126.8-
209 273.5) mg/L.

210

211 *Reported ingested dose of paracetamol*

212 The reported ingested dose was recorded in 520 (95.4%) cases, with a median of
213 16 (12.5-25) grams. One hundred and four patients (20.0%) took a dose \geq 30g,
214 and the maximum ingested dose was 141g. Reported ingested doses correlated
215 with extrapolated 4-hour plasma concentrations ($r=0.367$, $P<0.0001$; Figure 1a).

216

217 *APAP_{pl}:APAP_t ratios*

218 Ratios were calculated in 527 (96.7%) patients; in the remainder this was not
219 possible either due to lack of a measured plasma paracetamol concentration
220 (n=4) or due to late presentation beyond the time limits of treatment
221 nomograms (n=14). The median ratio was 1.94 (1.30-2.77). This measure
222 correlated strongly with 4-hour extrapolated plasma concentrations ($r=0.999$,
223 $P<0.0001$), and moderately with reported dose ($r=0.368$, $P<0.0001$; Figure 1b).

224

225 **Prevalence of organ injury**

226 Peak serum aminotransferase concentrations, INR and creatinine results were
227 available in 538, 540 and 542 patients, respectively. One hundred and seventeen
228 (21.5%) patients had peak serum aminotransferase concentrations >2 -fold ULN;

229 69 (12.8%) >3-fold ULN; and 20 (3.7%) >1,000 IU/L. Forty-nine (9.1%) had a
230 peak INR >1.3; and 2 (3.7%) >6.5. Nine (1.7%) had significant acute kidney
231 injury with a creatinine >150 μ mol/L, and 4 (0.7%) >300 μ mol/L. Fifty-three
232 (9.7%) patients received additional acetylcysteine beyond the standard regimen.
233 All patients recovered from the acute episode of poisoning, except for one
234 individual who presented 13h8min after reported ingestion of 24g paracetamol
235 and ethanol, and developed chronic renal impairment requiring long-term renal
236 replacement therapy. This patient also had acute liver failure with a serum
237 aminotransferase concentration of 8,509 IU/L and INR of 3.32, although hepatic
238 function subsequently recovered and was normal at the time of hospital
239 discharge. No patients died as a result of the acute episode of poisoning.

240

241 **Relationship between estimates of overdose and development of organ** 242 **injury**

243 Patient demographics described by nomogram group (according to extrapolated
244 4-hour plasma paracetamol concentrations) are shown in Table 1. Correlations
245 between reported ingested dose, 4-hour extrapolated plasma paracetamol
246 concentrations, $APAP_{pl}:APAP_t$, and the various outcome measures were assessed
247 (Table 2). Sensitivities, specificities, positive predictive values, and odds ratios
248 for different $APAP_{pl}:APAP_t$ thresholds for identifying serum aminotransferase
249 rises >2-fold ULN (promoting extended acetylcysteine infusion) are reported in
250 Table 3.

251

252 *Relationship to reported ingested dose of paracetamol*

253 Reported ingested dose correlated with peak serum aminotransferase
254 concentrations ($r=0.212$, $P<0.0001$; Figure 2a) and creatinine ($r=0.138$, $P=0.002$;
255 Figure 2b), but not INR ($r=0.034$, $p=ns$; Figure 2c). Median peak serum
256 aminotransferase concentration was 23IU/L (16.75-39.25) in patients reporting
257 overdoses under 30g, and 29IU/L (22-73) in those who had taken $\geq 30g$
258 ($P=0.001$). Reported dose did not reliably differentiate the different grades of
259 liver injury (Figure 2d). Median INR was 1.1 in both patients taking $\geq 30g$
260 paracetamol and also those reporting non-massive overdoses (IQR 1.02-1.18 and
261 1.03-1.19, respectively). Median serum creatinine was 65 μ mol/L (57-75) in
262 patients reporting ingestions $<30g$ and 72.5 μ mol/L (63.25-82.75) in those who
263 reported ingestion of $\geq 30g$ ($P<0.0001$), but there was no difference in the
264 frequency of creatinine rises over 150 μ mol/L ($<30g$, $n=5$; $\geq 30g$, $n=3$) or
265 300 μ mol/L ($<30g$, $n=1$; $\geq 30g$, $n=2$) between these groups.

266

267 *Relationship to APAP_{pl}:APAP_t*

268 APAP_{pl}:APAP_t ratio correlated with peak serum aminotransferase concentration
269 ($r=0.286$, $P<0.0001$; Figure 3a), INR ($r=0.314$, $P<0.0001$; Figure 3b) and
270 creatinine concentration ($r=0.090$, $P=0.04$; Figure 3c). There were associations
271 between increasing APAP_{pl}:APAP_t and liver injury (Figure 4a-c), coagulopathy
272 (Figure 4d) and acute kidney injury. A ratio ≥ 3 was associated with an OR of 7.15
273 (4.20-12.06; $P<0.0001$) for peak serum aminotransferase concentrations >2 -fold
274 ULN; 9.19 (5.04-16.68; $P<0.0001$) for acute liver injury; 35.95 (8.80-158.1;
275 $P<0.0001$) for hepatotoxicity; 8.34 (4.43-15.85; $P<0.0001$) for coagulopathy; and
276 4.69 (1.38-15.44; $P=0.03$) for acute kidney injury.

277 Correspondingly, values for $APAP_{pl}:APAP_t$ ratios ≥ 6 were 13.93 (6.24-
278 31.79; $P < 0.0001$) for aminotransferase rises > 2 -fold ULN; 15.94 (6.97-35.32;
279 $P < 0.0001$) for acute liver injury; 44.64 (15.0-121.5; $P < 0.0001$) for
280 hepatotoxicity; 13.59 (5.84-32.33; $P < 0.0001$) for coagulopathy; and 10.65 (2.75-
281 39.12; $P = 0.008$) for acute kidney injury.

282

283 **Time to acetylcysteine and outcomes**

284 Median time to acetylcysteine was 8h30min (6h24min-12h36) in male patients
285 and 7h42min (6h0min-10h18min) in female patients ($P = 0.03$). Time to
286 treatment correlated with serum aminotransferase concentration ($r = 0.168$
287 $P = 0.0002$), INR ($r = 0.153$, $P = 0.0006$) and serum creatinine ($r = 0.087$, $P = 0.05$).

288 We subsequently restricted analyses to the 248 patients who received
289 acetylcysteine within 8 hours of reported paracetamol ingestion (Table 4). The
290 association between reported ingested dose and serum aminotransferase
291 concentration persisted ($r = 0.153$, $P = 0.02$), as did those between $APAP_{pl}:APAP_t$
292 and serum aminotransferases or INR. An $APAP_{pl}:APAP_t \geq 3$ remained predictive
293 of organ injury with an OR of 5.25 (1.98-13.13; $P = 0.002$) for aminotransferase
294 rise > 2 -fold ULN; 4.70 (1.66-14.48; $P = 0.02$) for acute liver injury; ∞ (3.56- ∞ ;
295 $P = 0.01$) for hepatotoxicity; and 5.21 (1.60-18.3; $P = 0.02$) for coagulopathy.

296 By comparison, in patients who received acetylcysteine later than 8 hours
297 from reported ingestion, $APAP_{pl}:APAP_t \geq 3$ had an OR of 8.61 (3.90-18.23;
298 $P < 0.0001$) for aminotransferase rises > 2 -fold ULN; 11.38 (4.91-25.36; $P < 0.0001$)
299 for acute liver injury; 18.88 (4.73-84.67; $P < 0.0001$) for hepatotoxicity; and 9.46
300 (4.00-21.29; $P < 0.0001$) for coagulopathy.

301

302 **Discussion**

303 Although the current regimen of acetylcysteine for treating paracetamol
304 overdose has been extremely successful, the continued use of a standard
305 protocol for every case has been questioned [5, 8, 9]. In particular, it has been
306 suggested that patients who have taken very large overdoses may require higher
307 doses of acetylcysteine, or protracted infusions. Intravenous doses up to
308 980mg/kg acetylcysteine over 48 hours have previously been used safely [25],
309 notwithstanding evidence from one animal model that suggested prolonged
310 therapy might delay recovery from hepatotoxicity [26]. It is known that NAPQI
311 generation rises with increasing paracetamol dose, and also that hepatic injury
312 prolongs paracetamol half-life. Furthermore, there are several case reports, and
313 one observational study, of patients developing hepatotoxicity despite receiving
314 acetylcysteine within 8 hours of reported overdose [12-16].

315 Our study systematically assessed outcomes of massive paracetamol
316 overdose. Key findings were that, despite receiving standard therapy with
317 acetylcysteine, patients with massive overdoses were more likely to develop
318 significant liver and kidney injury, and coagulopathy. $APAP_{pl}:APAP_t$ ratio was a
319 better predictor of organ toxicity than the reported dose ingested. Although
320 overall correlations with outcomes were modest in magnitude, and differences in
321 medians (while statistically significant) were of limited clinical relevance, this
322 did provide a tool for distinguishing higher and lower risk groups. This persisted
323 even when acetylcysteine was administered within 8 hours of reported
324 ingestion, demonstrating that while time to treatment was a strong predictor of
325 organ injury it was not the sole determining factor in early presenting poisoning.
326 These findings validate and extend, in an independent cohort, those recently

327 published by a specialist toxicology unit in Edinburgh [16]. The case features in
328 our patients were broadly similar, except that liver injury and hepatotoxicity
329 were more frequent in the highest concentration subgroups in our study; this
330 may relate to the higher measured paracetamol concentrations at the times of
331 presentation.

332 The original acetylcysteine treatment regimen was constructed based on
333 empirical considerations [4, 7]. Although effective for the majority of patients, it
334 is not clear that the implicit assumptions necessarily hold true in massive
335 overdose. In such patients, absorption of paracetamol may be delayed: this could
336 be due to direct effects of paracetamol on gastric motility [27]; co-ingestion of
337 other drugs such as opiates or anticholinergics that delay gastric emptying [28];
338 insufficient volume of gastric secretions to solubilize large quantities of
339 paracetamol [29]; or formation of a pharmacological bezoar [13]. The half-life of
340 paracetamol can progressively extend as hepatotoxicity develops, such that
341 significant quantities of NAPQI could be generated after the 16-hour
342 acetylcysteine infusion has finished [30]. Finally, there is evidence from animal
343 models that paracetamol may undergo enterohepatic recirculation, with
344 hydrolysis of non-toxic conjugates by gut flora and reabsorption of the parent
345 drug [31]. These factors likely explain, alone or in combination, the double peaks
346 of plasma paracetamol reported following large overdoses [13]. In some of these
347 patients, the second peak can occur in excess of 30 hours after ingestion, and
348 these individuals are more likely to develop hepatotoxicity despite early
349 acetylcysteine therapy.

350 While there has been considerable recent interest in the development of
351 novel early biomarkers, such as miRNA-122, to further stratify those at high risk

352 of tissue injury and guide management, there is a possibility these might fail to
353 identify cases if a major contributor to adverse outcomes in massive paracetamol
354 overdose is a delay in the pharmacokinetic profile [32]. This is also relevant
355 when considering adoption of an abbreviated acetylcysteine protocol [33], and
356 might mandate protracted observation in people who have taken massive doses.
357 It is important that this patient cohort is specifically considered when evaluating
358 proposed changes to practice.

359 There are a few limitations to the current study. Principal among these is
360 the reliance on an accurate patient history and medical documentation at the
361 time of clinical review, particularly as regards paracetamol dose and time of
362 ingestion. As the database is clinical, there is a risk of misclassification since data
363 are not validated at the time of entry, although one strength of this approach is
364 that data entry is blinded to the study question. The correlations between
365 reported doses, extrapolated 4-hour plasma paracetamol concentrations and
366 $APAP_{pl}:APAP_t$ provide some reassurance that these possess a reasonable degree
367 of reliability, although concordance was lower than in previously reported series
368 [34] and there were a number of outliers. These could result from errors in
369 patient estimation of dose or calculation by the admitting physician, or by an in
370 increase in the half-life of paracetamol as has been previously documented in
371 patients with significant paracetamol toxicity, thus introducing inaccuracies into
372 extrapolation of paracetamol concentrations. Secondly, blood tests for
373 paracetamol, liver, coagulation and renal function were performed routinely
374 during clinical practice at presentation to the Emergency Department, as well as
375 on completion of the standard acetylcysteine regimen, and were thus not
376 completely systematic. In the absence of more frequent testing it is possible that

377 in some cases peak values may have been missed. In addition, at our hospital at
378 the time of this study, paracetamol concentrations were not repeated during or
379 after treatment, so it is not possible to comment on alterations in plasma half-
380 life. It was also not possible to formally grade kidney injury using RIFLE/AKIN
381 criteria, due to the lack of baseline blood tests and limited longitudinal follow-up
382 in this patient cohort. Third, prior to 2012, the acetylcysteine protocol required
383 calculations to be performed by both the prescribing physician, as well as the
384 administering nurses. This process is error prone [35], and hence it is possible
385 that some patients nominally receiving early treatment were in fact under-
386 dosed. Finally, the assumptions underlying extrapolation of 4-hour paracetamol
387 concentrations may break down if paracetamol metabolism changes in a non-
388 liner fashion or becomes saturated at very high doses, or should a double peak
389 phenomenon exist widely.

390 These findings are clinically important, as they suggest that under current
391 protocols patients taking massive paracetamol overdoses may be undertreated,
392 and that either an increase in the dose intensity and/or duration of
393 acetylcysteine therapy could be beneficial. A high $APAP_{pl}:APAP_t$ ratio is
394 associated with increased risk and therefore further consideration should be
395 given to alternative acetylcysteine treatment strategies in these patients. Risks of
396 organ injury rose with an $APAP_{pl}:APAP_t$ (based on a treatment line through
397 100mg/L at 4 hours) ≥ 3 , and a ratio ≥ 6 was strongly predictive. Based on
398 analysis of the sensitivities and positive predictive values of different threshold
399 ratios, we believe on balance that the former cut-off should be used to define a
400 higher risk group. The optimum strategy is not clear at present, and would
401 require a more detailed understanding of the mechanisms responsible for the

402 excess in organ injury despite early acetylcysteine. This could be informed by
403 performing serial plasma paracetamol measurements in at-risk individuals to
404 determine whether this relates to delayed absorption, second peaks or
405 prolonged half-life. In the event of a significant contribution from the former, or
406 substantial enterohepatic recirculation of the parent drug, there may also be a
407 role for multiple doses of activated charcoal to augment gastrointestinal
408 elimination. Novel biomarkers of liver injury, and abbreviated treatment
409 protocols, should be specifically validated in this patient cohort.

410

411 **Competing Interests**

412 All authors have completed the Unified Competing Interest form at
413 http://www.icmje.org/coi_disclosure.pdf (available on request from the
414 corresponding author) and declare that PID is a member of the MHRA CHM 2016
415 Paracetamol Expert Working Group, and DJBM is a consultant for GSK. There are
416 no other relationships or activities that could appear to have influenced the
417 submitted work.

418

419 **Contributors**

420 PID, DMW and SLG conceived the study; DJBM, CLD and AMD collected data; and
421 DJBM performed statistical analyses. All authors were involved in data
422 interpretation, drafting and critical revision of the manuscript, and have
423 approved the final version submitted for publication.

424

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428

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544

545 **FIGURE LEGENDS**

546 **Figure 1** Correlations between reported dose of paracetamol and ingested and
547 **a)** extrapolated 4-hour plasma paracetamol concentrations and **b)** $APAP_{pl}:APAP_t$.

548

549 **Figure 2** Relationship between reported dose of paracetamol ingested and **a)**
550 serum aminotransferase concentration, **b)** INR and **c)** serum creatinine. **d)**
551 Cumulative frequency of different grades of liver injury with reported dose.

552

553 **Figure 3** Relationship between $APAP_{pl}:APAP_t$ and **a)** serum aminotransferase
554 concentration, **b)** INR and **c)** serum creatinine.

555

556 **Figure 4** Percentage of patients in each $APAP_{pl}:APAP_t$ group with **a)** no liver
557 injury (serum aminotransferase concentrations $<50IU/L$), **b)** acute liver injury,
558 **c)** hepatotoxicity and **d)** coagulopathy.

559