Effect of the UK's revised paracetamol poisoning management guidelines on admissions, adverse reactions and costs of treatment

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Effect of the UK's revised paracetamol poisoning management guidelines on admissions, adverse reactions and costs of treatment

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Management of paracetamol poisoning is different in the UK from other countries following a decision by the Commission on Human Medicines (CHM) in 2012, including treatment at the '100 mg l^{-1}' nomogram line, stop risk assessment.
- The impact of this advice on patients is unclear.
- The CHM also advised change in the rate of initial infusion in an attempt to reduce adverse drug reactions (ADRs).

WHAT THIS STUDY ADDS

- The change has resulted in a highly significant increase in admissions and the proportion of patients treated for paracetamol poisoning (estimated UK effect: 31.1 thousand pre-change; 49.0 thousand post-change).
- The net effect is to treat many low risk patients and in the NHS cost per life saved is £17.4 million.
- The change in initial acetylcysteine infusion does not result in any reduction in ADR frequency.

AIMS

In September 2012 the UK's Commission on Human Medicines (CHM) recommended changes in the management of paracetamol poisoning: use of a single '100 mg l^{-1}' nomogram treatment line, ceasing risk assessment, treating all staggered/uncertain ingestions and increasing the duration of the initial acetylcysteine (NAC) infusion from 15 to 60 min. We evaluated the effect of this on presentation, admission, treatment, adverse reactions and costs of paracetamol poisoning.

METHODS

Data were prospectively collected from adult patients presenting to three large UK hospitals from 3 September 2011 to 3 September 2013 (year before and after change). Infusion duration effect on vomiting and anaphylactoid reactions was examined in one centre. A cost analysis from an NHS perspective was performed for 90 000 patients/annum with paracetamol overdose.

RESULTS

There were increases in the numbers presenting to hospital (before 1703, after 1854; increase 8.9% [95% CI 1.9, 16.2], $P = 0.011$); admitted (1060/1703 [62.2%] *vs.* 1285/1854 [69.3%]; increase 7.1% [4.0, 10.2], $P < 0.001$) and proportion treated (626/1703 [36.8%] *vs.* 926/1854 [50.0%]; increase: 13.2% [95% CI 10.0, 16.4], $P < 0.001$). Increasing initial NAC infusion did not change the proportion of treated patients developing adverse reactions (15 min 87/323 [26.9%], 60 min 145/514 [28.2%]; increase: 1.3% [95% CI –4.9, 7.5], $P = 0.682$). Across the UK the estimated cost impact is £8.3 million (6.4 million–10.2 million) annually, with a cost-per-life saved of £17.4 million (13.4 million–21.5 million).

CONCLUSIONS

The changes introduced by the CHM in September 2012 have increased the numbers of patients admitted to hospital and treated with acetylcysteine without reducing adverse reactions. A safety and cost-benefit review of the CHM guidance is warranted, including novel treatment protocols and biomarkers in the assessment of poisoning.

Introduction

Paracetamol poisoning is the most common acute overdose seen in industrialized countries [1, 2]. It is estimated that between 82 000 and 90 000 patients present in the UK each year with paracetamol overdose [3–5]. Between 150 and 250 deaths occur annually, the vast majority in patients who have presented late, after a staggered overdose or after unintentional therapeutic excess [6–9]. Deaths or episodes of liver failure in patients [10] who present and are treated within 8 h of a single acute ingestion are extremely rare [1, 5, 11].

The main reason for the relatively low number of deaths is the availability of a highly effective antidote, acetylcysteine (NAC) [12], which has been administered intravenously using the same complex regimen since the 1970s. This has involved three weight-related doses of NAC given intravenously in 5% dextrose over three different time frames: 150 mg kg^{-1} body weight over 15 min, followed by 50 mg kg^{-1}over 4 h and 100 mg kg^{-1}over 16 h. In other parts of the world, notably North America and Australia, the initial dose is given over 60 min rather than 15 min. In the UK, treatment has been recommended for most patients with acute overdose who have a timed plasma paracetamol concentration above the '200 mg l^{-1}' line on a nomogram (Figure 1) after a single acute ingestion or a dose of 150 mg kg^{-1} or more within 24 h of a staggered ingestion or where the time of ingestion was unknown [13]. Patients with risk factors for hepatotoxicity (poor nutrition, chronic alcohol excess, enzyme inducing drugs) were given NAC if their timed blood paracetamol concentration was above the '100' line, or they had ingested more than 75 mg kg^{-1} within 24 h [21].

The NAC regimen is associated with a high incidence of adverse effects, in particular vomiting and anaphylactoid reactions [8–10, 14]. Because these occur during or soon after infusion of the first 15 min bag [14, 15], this is given over 60 min in some countries in the hope of reducing adverse effects, although the one trial that assessed this question did not find a difference [16]. Importantly, anaphylactoid reactions are more frequent when NAC is administered to patients with relatively low concentrations of paracetamol [15, 17]. Anaphylactoid reactions are unpleasant for patients, result in temporary cessation of therapy, extend treatment and admission duration and sometimes cause doctors to withhold effective treatment from patients who need it [1, 18].

In September 2012, the UK's Commission on Human Medicines (CHM) reviewed the use of NAC in the management of paracetamol overdose. This followed the case of a patient who had not been treated with NAC at first presentation due to the timed paracetamol concentration being below recommended treatment thresholds, who subsequently developed fatal hepatotoxicity. The review identified nine further UK patients since 1991

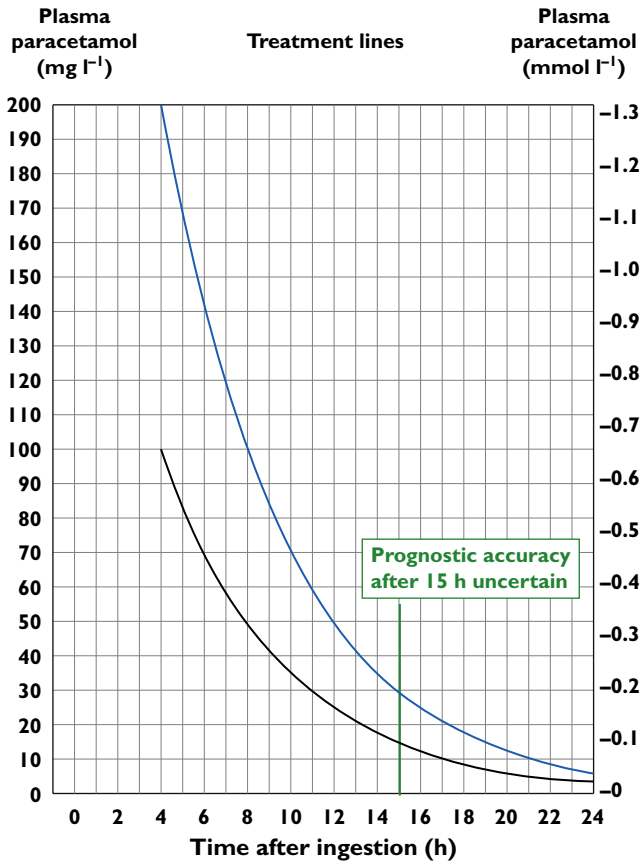

Figure 1

Paracetamol nomogram used in the UK until September 3 2012. ——, normal treatment line; ——, high risk treatment line

who had also died after being initially assessed as not requiring NAC. Three key recommendations arose from the CHM review. First to use a single lower '100 mg l^{-1}' line on the nomogram for all patients with acute overdose and to stop assessing risk factors in deciding their need for treatment, on the basis that use of risk factor assessment was poor and inconsistent, and that many of the risk factors were imprecise and difficult to determine with sufficient certainty in clinical practice [5]. Second to treat all patients with staggered overdose or unknown time of ingestion with NAC. Third to change the duration of the initial NAC infusion from 15 to 60 min, in an attempt to reduce the risk of adverse reactions [5]. These changes were subsequently endorsed by the UK Departments of Health, but not subjected to formal cost-benefit analysis.

These changes in management guidance resulted in a lower treatment threshold for paracetamol poisoning in the UK than in most other countries, including the USA, Canada, Australia and New Zealand, where a '150' (Rumack-Matthew) line is used [19]. An exception is Denmark, where all patients with a suspected overdose receive antidote [5]. Although Ireland has subsequently

also introduced the CHM changes, clinical toxicologists in other countries have thus far rejected it [20]. Of note, the change increases the number of patients with low blood paracetamol concentrations receiving NAC, potentially increasing the number of patients at risk of developing anaphylactoid reactions. An initial report for the first 6 months after the change in York showed substantial increases in admissions following the change in guidance [4].

We therefore evaluated the effect of the change (i) on the NHS by examining presentations, admissions, treatment and estimated national cost of treating paracetamol poisoned patients and (ii) on patients in terms of adverse reactions to the antidote, especially in those with low paracetamol concentrations. Costs were related to numbers of lives expected to be saved, according to CHM projections.

Methods

Data for audit of the management of paracetamol overdose are routinely and prospectively collected on databases held within the clinical toxicology units of the Royal Infirmary of Edinburgh, the Royal Victoria Infirmary, Newcastle upon Tyne and Guy's and St Thomas' NHS Foundation Trust, London. The use of these databases for audit has approval of the data protection officers/Caldicott Guardians of NHS Lothian Health Board and of the Newcastle Hospitals and Guy's and St Thomas' NHS Foundation Trusts.

Data on patients presenting to the Emergency Departments and discharged, without admission to the toxicology units, were also recorded. Data on treatment indication and adverse events were collected by specialist toxicology nurses, database scientists, senior medical trainees and consultant clinical toxicologists. In addition, in Edinburgh, use and timing of administration of treatments for anaphylactoid reactions and vomiting following commencement of NAC was routinely extracted from the medication administration record (drug kardex) in combination with the medical notes.

The data collected included: patient demographics; nature of the overdose (acute or staggered [i.e. repeated excess therapeutic ingestion or repeat overdose, i.e. over more than 60 min]), time from ingestion to presentation for single acute ingestions (0–8 h, >8–24 h, >24 h, and unknown time), plasma paracetamol concentration at time of presentation, history of paracetamol dose, use of NAC, nomogram treatment line [21] and need for additional NAC beyond the original 21 h infusion.

Patients

All patients presenting to the Emergency Departments of the three hospitals with paracetamol overdose for 2 calendar years, from 3 September 2011 until and including 3 September 2013 were eligible for inclusion in this study, except those seen or admitted on 3 September 2012, who were excluded as the CHM recommendations were published and implemented that day. Eligible patients were those reporting ingestion of (i) >4 g of paracetamol, alone or in combination with other drugs, as a single ingestion or over any 24 h period, (ii) <4 g where the blood results indicated the need for NAC or (iii) an unknown amount of paracetamol.

In Edinburgh, 150 patients requiring NAC were recruited to the SNAP randomized clinical trial (RCT) of anti-emetics and a novel regimen of NAC during the study period (starting September 2010, terminating 31 December 2012) [18]. These patients were excluded from the adverse reaction analysis since they were included in the RCT. The CHM change in management was introduced on 3 September 2012. Prior to this date, all patients received an initial NAC infusion over 15 min. All patients admitted on or after this date, except for those recruited to the RCT, were treated with an initial acetylcysteine infusion over 60 min.

Cost estimation

Building on the work of McQuade and colleagues [3], we estimated costs from an NHS perspective using NHS financial year 2011–12 reference costs (HRG4) for three different diagnostic groups (https://www.gov.uk/government/publications/nhs-reference-costs-financial-year-2011-to-2012). For those discharged home from the emergency department, we used VB08Z [Emergency Medicine, Category 2 Investigation with Category 1 Treatment (Toxicology investigation other treatment)] to give £137 per case. For admitted patients not treated we used VB08Z [Emergency Medicine, Category 2 Investigation with Category 1 Treatment (Toxicology investigation other treatment)] cost (£137) and PA50Z [Ingestion poisoning] in-patient episode cost (£572), giving a total of £709. For those admitted and treated with NAC, we used VB04Z [Emergency Medicine, Category 2 Investigation with Category 4 Treatment (Toxicology investigation with i.v. drug treatment)] cost (£196) and PA50Z [Ingestion poisoning] in-patient episode cost (£572), giving an overall cost of £768 per case. We applied these costs equally across the 2 calendar year periods before and after the change to ensure comparability between time frames.

The number of patients admitted to hospital in the UK can be taken from hospital activity statistics, but there are no good sources to measure accurately all hospital attendances with paracetamol overdose, as many are discharged and admission rates vary. The MHRA estimated that there are 68–70 000 presentations in England and Wales, and including Scottish data, an estimated 82–90 000 patients are seen per annum with deliberate or accidental paracetamol overdose [5].

Table 1

Presentations, admissions and use of NAC across three UK hospitals

	Pre	Post	+/–	Change 95% CI	*P*
Presentations (*n*)					
Centre 1	990	1111	12.2%	3.0, 22.3	0.008
Centre 2	378	386	2.1%	–11.4, 17.6	0.772
Centre 3	335	357	6.6%	–8.2, 23.7	0.403
Overall	1703	1854	8.9%	1.9, 16.2	0.01
Admitted (%)					
Centre 1	54.7 (541/990)	63.1 (701/1111)	8.5%	4.2, 12.7	<0.001
Centre 2	79.1 (299/378)	86.8 (335/386)	7.7%	2.4, 13.0	0.005
Centre 3	65.7 (220/335)	69.8 (249/357)	4.1%	–2.9, 11.0	0.251
Overall	62.2 (1060/1703)	69.3 (1285/1854)	7.1%	4.0, 10.2	<0.001
Treated with NAC (%)					
Centre 1	39.0 (386/990)	49.6 (551/1111)	10.6%	6.4, 14.8	<0.001
Centre 2	30.4 (115/378)	50.3 (194/386)	19.8%	13, 26.7	<0.001
Centre 3	37.3 (125/335)	50.7 (181/357)	13.4%	6.2, 20.7	<0.001
Overall	36.8 (626/1703)	50 (926/1854)	13.2%	10.0, 16.4	<0.001

Centre 1 = Royal Infirmary of Edinburgh; centre 2 = Guy's and St Thomas' NHS Foundation Trust, London; centre 3 = Royal Victoria Infirmary, Newcastle upon Tyne.

Statistical analysis

Demographic details of patients included in the analysis were illustrated by simple descriptive statistics. Continuous variables were presented as medians and ranges. Categorical variables were compared using chi-squared tests. Differences between proportions were compared by testing for their equality.

In order to assess as objectively as possible the rates of adverse reactions, the analysis concentrated on the use of medication to treat adverse events normally associated with acetylcysteine use, vomiting or anaphylactoid reactions. Medications were either anti-emetics such as ondansetron or cyclizine, antihistamines (generally chlorphenamine) or bronchodilators such as salbutamol.

Rates of treatments for adverse reactions were calculated overall for all patients, and then by the 15 or 60 min treatment groups. Patients were then grouped by both treatment regimens and initial paracetamol concentration (below or above 100 mg l^{-1}) and the rates of medication use in these groups compared.

Results are expressed as totals or proportions (%) of patients who had therapy for adverse effects following therapy. Statistical analysis was conducted using Wilcoxon rank-sum test and measurement of odds ratios (OR) and 95% CIs. Multivariable logistic regression was used to investigate the odds of reaction by infusion type and paracetamol concentration.

Results

Presentation, admissions, and NAC treatment

For the calendar year before and after the change, 3 September 2011 to 3 September 2013, and ignoring the day of the change, 3557 patients with paracetamol poisoning presented to the three participating hospitals (Table 1). A total of 1703 presented in the year before (03/09/11–02/09/12), and 1854 in the year after (04/09/12–03/09/13), a relative increase of 8.9% (95% CI 1.9, 16.2, $P = 0.011$) (Table 1). This increase remained consistent throughout the following year (Figure 2).

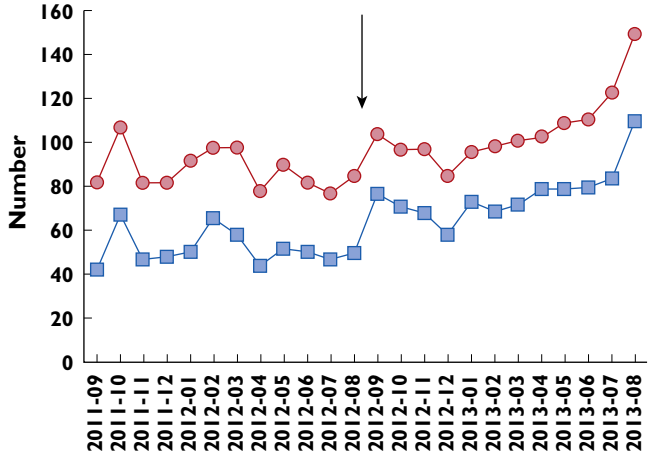

Figure 2

Patients admitted (—●—) and treated (—■—) for paracetamol poisoning with acetylcysteine in the index hospitals during 2011–2013. Vertical arrow indicates new MHRA guidance

Comparing the year after the change with the year before, a greater proportion of patients were admitted to hospital (before 1060/1703 [62.2%], after 1285/1854 [69.3%]; absolute increase 7.1%, 95% CI 4.0, 10.2, $P < 0.001$) and more patients were treated with NAC (before 626/1703 [36.8%], after 926/1854 [50.0%]; absolute increase 13.2%, 95% CI 10.0, 16.4, $P < 0.001$) (Table 2, Figure 2).

Table 2

Demographics of patients with paracetamol poisoning

	Pre-change $n = 1703$	Post-change $n = 1844$	Total $n = 3547$
Age (years) median (range)	32 (1–95)	31 (1–98)	2 (1–98)
Blood paracetamol (mg l^{-1}) median (range)*	37 (0–587)	30 (0–660)	32 (0–660)
Admitted *n* (%)	1060 (62.2)	1285 (69.3)	2345 (65.9)
Median age (years) (% F)	34 (57.4)	33 (60.2)	34 (58.9)
Discharged *n* (%)	643 (37.8)	569 (30.7)	1212 (34.1)
Median age (years) (% F)	30 (59.4)	29 (58.0)	30 (58.7)
Presentation times			
0–8 h *n* (%)	1071 (62.9)	1077 (58.1)	2148 (60.4)
Median age (years) (% F)	32 (59.7)	30 (61.5)	31 (60.6)
>8–24 h *n* (%)	177 (10.4)	188 (10.1)	365 (10.3)
Median age (years) (% F)	28 (62.1)	30 (62.2)	29 (62.2)
>24 h *n* (%)	92 (5.4)	92 (5.0)	184 (5.2)
Median age (years) (% F)	32 (57.6)	35 (56.5)	34 (57.1)
Staggered *n* (%)	309 (18.1)	435 (23.5)	744 (20.9)
Median age (years) (% F)	36 (50.8)	34 (54.7)	36 (53.1)
Unknown *n* (%)	54 (3.2)	62 (3.3)	116 (3.3)
Median age (years) (% F)	37 (57.4)	42 (54.8)	40 (56.0)
Deliberate self-harm *n* (%)	1483 (88.2)	1535 (83.8)	3018 (85.9)
Median age (years) (% F)	32 (59.7)	31 (61.9)	31 (60.8)
Accidental *n* (%)	198 (11.8)	296 (16.2)	494 (14.1)
Median age (years) (% F)	34 (47.5)	38 (47.4)	36 (47.6)

Figures in brackets are 95% CIs or % in the patient group. *For statistical analysis paracetamol concentrations below the level of detection for the laboratory have been treated as zero.

Table 3

Patient demographics and reactions to treatment by infusion rate

	15 min infusion rate ($n = 323$)	60 min infusion rate ($n = 514$)
Age (years) median (range)	36 (13–90)	33 (13–98)
Female	184 (57.0)	325 (63.2)
Blood paracetamol (mg l^{-1})		
Median (range)	80 (0–424)	76.5 (3–660)
Adverse reactions *n* (%)		
1. Vomiting only	58 (18.0)	90 (17.5)
2. Anaphylactoid only	13 (4.0)	38 (7.4)
3. Both vomiting and anaphylactoid	16 (5.0)	17 (3.3)
4. All vomiting (1 + 3)	74 (22.9)	107 (20.8)
5. All anaphylactoid (2 + 3)	29 (9.0)	55 (10.7)
6. No reaction	236 (73.1)	369 (71.8)

Figures in brackets are 95% CIs or % in the patient group.

There was some evidence to suggest differences in the patterns of poisoning before and after the change (Chi-squared = 15.3, $P = 0.003$), with fewer presentations 0–8 h after overdose and more staggered presentations. There were also more accidental presentations after the change (Chi-squared = 14.0, $P < 0.001$) (Table 2). None of the patients in this study was referred for liver unit care.

There were 1340 (78.7%) acute ingestions before the change and 1357 (73.2%) afterwards, of these 822 were admitted before and 917 afterwards, representing 61.3% and 61.7% of these presentations, respectively, (absolute increase 6.2% (95% CI 2.6, 9.8, $P < 0.001$). A lower proportion of single ingestions were treated with NAC before the change (32.4%, 435/1340) than afterwards (43.7%, 593/1357) absolute increase 11.2% (95% CI 7.6, 14.9, $P < 0.001$). For staggered overdoses (including therapeutic excess) there were 309 before the change and 435 afterwards, representing 18.1% and 23.5% of presentations, respectively. Comparing before and after the change, there was no statistical evidence of a difference in the proportion of such cases admitted (215/309 [69.6%] *vs.* 327/435 [75.2%]; absolute increase 5.6%, 95% CI 0.1, 12.1, $P = 0.091$). However, the proportion treated with NAC increased (178/309 [57.6%] *vs.* 300/435 [69.5%]; absolute increase 11.4%, 95% CI 4.3, 18.4, $P = 0.001$).

There was no reduction after the change in the number of patients who required extended treatment with NAC on review of the blood results taken around the end of bag three. Based on data from Edinburgh, 43 patients (4.3%, 43/990) required additional NAC before the change compared with 43 (3.9%, 43/1111) after the change (absolute change –0.5%, 95% CI –2.2, 1.2, $P = 0.587$).

Incidence and timing of adverse drug reactions to acetylcysteine

The number of recorded ADRs increased substantially following the change in guidance. However, the proportion of treated patients experiencing ADRs was unchanged (before 87/323 [26.9%], after 145/514 [28.2%]; absolute increase 1.3%, 95% CI –4.9, 7.5, $P = 0.682$). This was also the case for anaphylactoid reactions (before 29/323 [9.0%], after 55/514 [10.7%]; absolute increase 1.7%, 95% CI –2.4, 5.8, $P = 0.426$) (Table 3). The time of onset of these reactions following initiation of NAC was later after the change (83.2 min, IQR 50 to 95) compared with before (47.5 min, IQR 20 to 50, Wilcoxon rank-sum, $P < 0.001$, Tables 4 and 5).

Association of adverse reactions with infusion duration

To determine whether changing the duration of infusion had affected the incidence of adverse reactions, we performed a multivariable analysis, while controlling for the paracetamol concentration, gender and age. The analysis included a total of 837 patients, 323 (215 acute, 105 staggered, three unknown) treated using an initial 15 min infusion of NAC and 514 (325 acute, 177 staggered, 12 unknown) treated using a 60 min initial infusion. The median age and gender ratios did not differ between patients treated at the different infusion rates (Table 4).

Rates of use of anti-emetic therapies did not differ between patients receiving 15 min or 60 min infusions of NAC (Table 3). After controlling for age, gender and presenting paracetamol concentration, the odds of being treated with anti-emetics did not differ in patients receiving a 60 min infusion compared with those treated with a

Table 4

Odds ratios of adverse events to treatment by infusion rate and presenting blood paracetamol

		All vomiting				All anaphylactoid			
		Events / *n*	OR	95% CI	*P*	Events / *n*	OR	95% CI	*P*
Infusion rate[1]									
All patients (*n* = 835[3])	15 min	73/321	1	–	–	29/321	1	–	–
	1 h	107/514	0.85	0.61, 1.20	0.368	55/514	1.22	0.75, 1.98	0.414
<100 mg l^{-1} patients (*n* = 495)	15 min	46/185	1	–	–	26/185	1	–	–
	1 h	56/310	0.67	0.43, 1.05	0.084	47/310	1.10	0.66, 1.86	0.707
>100 mg l^{-1} patients (*n* = 340)	15 min	27/136	1	–	–	3/136	1	–	–
	1 h	51/204	1.19	0.69, 2.04	0.527	8/204	2.15	0.54, 8.55	0.256
Paracetamol concentration[2]									
All patients (*n* = 835[3])	>100	78/340	1.09	0.78, 1.53	0.618	11/340	0.19	0.10, 0.37	<0.001
	<=100	102/495	1	–	–	73/495	1	–	–
15 min infusion (*n* = 321)	>100	27/136	0.77	0.45, 1.33	0.354	3/136	0.14	0.04, 0.48	<0.001
	<=100	46/185	1	–	–	26/185	1	–	–
1 h infusion (*n* = 514)	>100	51/204	1.37	0.88, 2.12	0.163	8/204	0.21	0.10, 0.47	<0.001
	<=100	56/310	1	–	–	47/310	1	–	–
Age[4]									
All patients (*n* = 835[3])	<35	111/412	1	–	–	45/423	1	–	–
	>=35	69/413	0.58	0.42, 0.82	0.002	39/414	0.82	0.51, 1.30	0.391
Gender[5]									
All patients (*n* = 835[3])	Female	125/507	1	–	–	51/507	1	–	–
	Male	55/328	0.66	0.46, 0.95	0.025	33/328	0.91	0.60, 1.51	0.688

1. Controlling for age, gender and presenting paracetamol concentration. 2. Controlling for age, gender and infusion rate. 3. one patient who had no data on blood paracetamol concentration was excluded. 4. Controlling for gender, infusion rate and presenting paracetamol concentration. 5. Controlling for gender, infusion rate and presenting blood paracetamol concentration.

Table 5

Total number of adverse reactions by time of reaction

Time from start infusion	Pre-change group n (%) n = 87	Post-change group n (%) n = 145
0–29 min	29 (33.3)	11 (7.6)
30–59 min	32 (36.8)	34 (23.5)
1–1 h 29 min	9 (10.3)	45 (31)
1 h 30 min–2 h	4 (4.6)	27 (18.6)
>2 h	5 (5.8)	19 (13.1)
Unknown time	8 (9.2)	9 (6.2)

15 min infusion (OR 0.85, 95% CI 0.61, 1.20, $P = 0.367$). In the 495 patients presenting with blood paracetamol concentrations below 100 mg l^{-1}, the longer infusion duration was not associated with less use of anti-emetic therapy (15 min 46/185 [24.9%] *vs.* 60 min 56/310 [17.1%}; OR 0.67, 95% CI 0.43, 1.05, $P = 0.084$).

The odds of an anaphylactoid reaction did not differ according to the infusion duration, when controlled for age, gender and presenting paracetamol concentration: 60 min 55/514 (10.7%) *vs.* 15 min 29/321 (9.0%, OR 1.22, 95% CI 0.75, 1.98, $P = 0.414$).

As seen in previous studies, we did find an excess of anaphylactoid reactions in patients with lower paracetamol concentrations. Patients with presenting blood paracetamol concentrations >100 mg l^{-1} (11/340) were 80% less likely to experience an anaphylactoid reaction than those with blood paracetamol <100 mg l^{-1} (73/495; OR 0.19, 95% CI 0.10, 0.37, $P < 0.001$). This association was replicated in both the 15 min (OR 0.14, 95% CI 0.04, 0.48, $P < 0.001$) and 60 min (OR 0.21, 95% CI 0.10, 0.47, $P < 0.001$) treatment groups (Table 4).

Cost effects of the change

Before the change, an estimated 90 000 patients presented to hospitals across the UK and 45 000 were admitted to hospital [5]. We observed an 8.9% (95% CI 1.9, 16.2) increase in presentations over the study period, a 7.1% (95% CI 4.0, 10.2) increase in the proportion of patients admitted, and a 13.2% (95% CI 10.0, 16.4) increase in use of antidote in admitted patients. We estimated the cost implications of each aspect of patient care, including patients not treated with NAC and discharged from the emergency department or admitted, and those admitted for NAC. We calculate that the full annual cost of managing paracetamol overdose was £40.0 million before the change and £48.3 million afterwards, an absolute annual increase of £8.3 million (95% CI 6.4, 10.2 million) (Table 6).

The CHM estimated that the reduction in treatment thresholds would save a life every 2.1 years [5]. On the basis of this estimate and the data collected in the current study, the cost-per-life saved for this change was

Table 6
Estimating the impact on the cost of estimated change in practice in the UK (with 95% CI)

	Cost	Before i) National presentations and costs			ii) Estimated change (from data in Table 1)			iii) Estimated % impact of estimated change nationally			After iv) Estimated numbers of patients nationally			v) Overall estimated costs		
	£/patient	Number	Original %*	Cost £	Change	Lower CI	Upper CI	New %	Lower CI	Upper CI	Number	Lower CI	Upper CI	Cost £	Lower CI	Upper CI
Overall		90 000	–	–	8.9%	1.9%	16.2%	–	–	–	98 010	91 710	104 580	–	–	–
Discharged from ED	137	45 000	50.0%	6 165 000	–7.1%	–4.0%	–10.2%	42.9%	46.0%	39.8%	42 046	45 085	39 008	5 760 302	6 176 645	5 344 096
Admitted and treated	768	33 120	36.8%	25 436 160	13.2%	10.0%	16.4%	50.0%	46.8%	53.2%	49 005	45 869	52 141	37 635 840	35 227 392	40 044 288
Admitted and not treated	709	11 880	13.2%	8 422 920	–	–	–	7.1%	7.0%	7.2%	6 959	6 861	7 057	4 933 931	5 003 413	4 864 449
Total costs £				**40 024 080**										**48 330 073**	**46 407 450**	**50 252 833**
Increase in costs £														**8 305 993**	**6 383 370**	**10 228 753**

Notes: First column costs per episodes (see Methods). Before: (i) Costs applied to national estimates before change. After: (ii) illustrates impact of the changes found in this study as %; (iii) application of these data to the national data in (i) as % change; (iv) impact of estimated changes on total number of presentations, discharged, treated and patients nationally; (v) Total estimated costs post change on patients discharged, treated and untreated.

estimated to be £17.4 million (95% CI 13.4, 21.5 million) (Table 6).

Discussion

This study provides evidence that the 2012 CHM guidance for the management of paracetamol poisoning has resulted in substantial increases in hospital presentations, hospital admissions and NAC treatment courses, but an apparent improved consistency in the proportion of patients treated (with almost identical rates of 50% treatment in the three participating hospitals compared with a previous range of 31 to 39%). In spite of the slower initial infusion rate, there has been no decrease in the proportion of people developing the more severe adverse reactions to acetylcysteine that require treatment.

The increase in presentation rate is, at least in part, in patients with chronic therapeutic or staggered paracetamol overdose. The CHM guidance has resulted in a significant increase in calls from NHS public telephone advice services (NHS Direct, NHS111 and NHS24) for advice on suspected paracetamol overdose and hospital referrals [22]. Although the CHM guidance defined staggered overdose in terms of duration of consumption, the amount of paracetamol required to constitute an overdose needing acetylcysteine was not defined and this may have increased hospital referrals and treatment for patients with modest overdoses.

Modelling of the national impact of the CHM advice relies on the assumption that changes seen in these three hospitals are representative of changes that have occurred across the UK. This seems a reasonable approach, particularly as there was consistency in the proportion of patients treated with acetylcysteine across the three centres. A shorter study elsewhere also found an increase in admissions following the change in advice [4]. The increases in hospital activity as a result of the change in guidance are expensive, costing the NHS an estimated £8.3 million every year, with a cost per life saved of £17.4 million.

The study found that the rates of vomiting requiring anti-emetic therapy and of anaphylactoid reactions were little different with a 60 min infusion as compared with a 15 min infusion, even in patients with low paracetamol concentrations, although they were delayed in patients receiving the 60 min infusion (Table 5). It also confirmed a much higher rate of anaphylactoid reactions in those with lower paracetamol concentrations. The changes to the initial acetylcysteine infusion rate recommended by the CHM have therefore not reduced the rates of adverse reactions. However, the patients affected by the change who have lower paracetamol concentrations and a low risk of hepatic injury and who are now being treated with NAC, have the highest risk of anaphylactoid reactions.

Newer approaches that might reduce rates of anaphylactoid reactions are clinically needed, and this

might include the use of different acetylcysteine infusion schedules such as we have recently described [18].

Limitations

The data come from three specialist centres, in London, Northern England and Scotland, and may not precisely reflect the whole of the UK. The London centre treated proportionally fewer patients in the pre-change year, and if this is representative of southern England as a whole the cost impact of change is even greater than we show. However, the centres see many paracetamol poisoned patients. Indeed, data from Edinburgh were used by the CHM in its risk assessment. We therefore consider that the changes we have found are likely to reflect national activity. While statistics in England as reflected in hospital activity analysis (available from http://www.hscic.gov.uk/hes) to March 2013 do not show an immediate change, there are several factors that may explain this, particularly coding methodologies, and time delays in actual coding. Coding has previously been shown weak in other types of poisoning [23], and importantly these data sets also do not provide information on proportions treated. In contrast, an 18% increase in annual hospital admissions with paracetamol poisoning (ICD10 T39.1) has been seen in Scotland, comparing the years before and after October 2012, which is similar to the increase reported in this paper (source NSD Scotland 2014).

We have not accounted for any reduced costs as a result of fewer cases of severe hepatic injury in patients who would have been untreated using the previous management guidelines. However we foresee few savings, as, although costs of hepatic intensive care are very high, serious hepatic injury and death are very rare in this patient group, and mortality in patients not treated with NAC is estimated at one death every 2.1–2.2 years [5]. The small increase in the rate of anaphylactoid reactions would have resulted in more treatment interruptions and therefore longer stays in hospital. Since neither of these is reflected in the Healthcare Resource Group costs, they are not included in this cost analysis.

It should be noted that some deaths previously occurring in patients presenting between the '100' and '200' lines may not be known to the MHRA. If this is the case, the numbers of lives that might be saved by the change in guidance would be underestimated and the costs per life saved overestimated. However, treatment at these lower paracetamol concentration thresholds is unlikely to reach conventional thresholds for cost effectiveness unless the actual numbers of deaths had been underestimated many fold. It is also likely that not all fatal adverse reactions to acetylcysteine have been reported to the MHRA and this would have the opposite effect. As the MHRA is only aware of one death occurring in a patient presenting with a paracetamol concentration between the '100' and '150' lines, treatment of this less severely poisoned subgroup would carry a much higher cost-per-life saved. We acknowledge, however, that considerations of cost-effectiveness of treatments are outside the remit of the CHM and the MHRA.

In the adverse reactions analysis, we only analyzed cases from one unit (the busiest) that received rescue treatments such as anti-emetics or antihistamines. This will underestimate true adverse reaction rates, as less severe symptoms may not be reported or treated. Of note, adverse reaction rates in the control arm of our prospective clinical trial were significantly greater, with 78% of patients suffering nausea or vomiting, and 30% suffering an anaphylactoid reaction severe enough to require interruption of acetylcysteine infusion or rescue therapy [18].

In conclusion, we have shown that the CHM changes have resulted in significant increases in rates of hospital presentation and admission, in use of acetylcysteine and in adverse reactions, at substantial cost. None of this cohort of over 3500 patients required liver unit referral before or after the CHM change, emphasizing the rarity of serious liver injury with either management strategy. As we, and others, have previously reported, most episodes of hepatotoxicity occur as a result of late presentation to hospital, and this should be a target for public health intervention [6, 11]. We believe a full safety/efficacy review of the new CHM recommendations is now needed, together with a detailed cost-effectiveness analysis. In view of the substantial increases in hospital presentations and use of acetylcysteine in patients with staggered overdose or therapeutic excess, this should include better definitions of the amount of paracetamol required to constitute an overdose needing acetylcysteine, potential for use of novel biomarkers [24] and alternative regimens for delivering acetylcysteine that have lower rates of adverse effects [18].

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work and no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; DJW has been a member of the Agency Board at MHRA since 1 September 2013. SHLT is a member of the UK Commission on Human Medicines and was a member of the CHM Paracetamol Expert Group. DNB presented evidence to the CHM Paracetamol Expert Group. SHLT, JD and ME were members of the MHRA *ad hoc* sub-groups to advise on the implementation of changes to the management of paracetamol overdose and on necessary research. RC is funded by a National Institute of Health Research (NIHR) Doctoral Research Fellowship. ME is a Scottish Senior Clinical Fellow, funded by CSO and

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