ORIGINAL ARTICLE

Measuring plasma paracetamol concentrations in all patients with drug overdoses; development of a clinical decision rule and clinicians willingness to use it

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Objectives: The study proposed a clinical decision rule: In patients who have taken a deliberate overdose, but deny taking paracetamol or paracetamol containing compounds, who have a GCS of 15, understand English well, and have not taken excessive alcohol, there is no need to take blood for paracetamol estimation.

Methods: 307 consecutive emergency department patients were followed up, and the history of their overdose was correlated to blood paracetamol concentrations. In addition, clinicians were asked what level of confidence they required from such a clinical decision rule before they would use it.

Results: 152 admitted paracetamol and 155 denied it. Of the 155 that denied it, 13 had concentrations detected in the blood, but needed no treatment with antidote. Eighty three per cent of clinicians require a false negative rate of less than 1%.

Conclusions: Using this decision rule, only 46 of 307 patients would not have required paracetamol concentrations to be measured. To show a negative rate of less than 1% a sample size of 20 000 patients would be needed.

Bottom line: All patients who allege taking an overdose need paracetamol concentrations checking.

The use of paracetamol in deliberate overdose is very common in the United Kingdom. Approximately 48% of all overdoses are attributable to this drug and potentially 300 deaths per year.[1] It is standard practice in many emergency departments in the UK to screen all patients suspected of an overdose for paracetamol ingestion, as paracetamol poisoning does not have any early signs, but if toxic doses are detected early enough there is an effective treatment.[2]

However, this policy does result in many screenings being negative. There have been studies in the USA and Hong Kong showing that the number of patients with a history negative for paracetamol ingestion and positive blood results on screening is low. The exact results are analysed in table 1.

Looking at the figures and mitigating features from these studies, we formulated a clinical decision rule (CDR):

In patients who have taken a deliberate overdose, but deny taking paracetamol or paracetamol containing compounds, and who have a GCS of 15, understand English well, and have not taken excessive alcohol, there is no need to take blood for paracetamol estimation.

We designed a study to test this CDR, and also discover what level of confidence clinicians require from such a rule.

METHODS

A prospective study was set up to include all consecutive adult patients (over the age of 16 years) presenting to the emergency department of Southampton General Hospital between February and May 2000.

For all patients with suspected overdose, doctors were asked when they first saw the patient to fill in the following details with "yes" or "no" answers; paracetamol taken, other non-paracetamol containing drugs taken, alcohol taken or obvious intake, previous overdose attempts, comprehends English, and GCS of 15. This was facilitated with the use of a table in the notes, and the notes collected immediately the patients had left the department (table 2).

The department computer was also used to cross check that all the patients presenting with diagnoses of poisoning or deliberate self harm were included, and the hospital records of all these patients were traced and reviewed.

Paracetamol concentrations were measured after four hours or on presentation, whichever was the later, according to current policy. The Southampton laboratory uses a modified Shield diagnostic enzyme assay with colormetric analysis. The lower limit set is <0.07 mmol/l. In our study we used this level as negative for paracetamol.

Table 1

Study	Sporer *et al* 1996[3]	Ashbourne *et al* 1988[4]	Chan *et al* 1996[5]	Yaron *et al* 1992[6]	Dargan *et al* 2001‡[7]
Total number of patients	1820	476	294	70	440
History of paracetamol ingestion negative and levels negative	50	365	204	26	136
History of paracetamol ingestion negative and levels positive, not requiring treatment	5*	7	4	4	0
History of paracetamol ingestion negative and levels requiring treatment, with antidote	0	1†	0	Not stated	0

*Mitigating features: two patients had low GCS, one patient had excess alcohol, two patients had taken "many drugs"; †patient did not speak English well; ‡this paper was not used to formulate the rule as it was published afterwards, but is shown for comparison.

Table 2

Risk factors	Yes	No
Admitted paracetamol intake		
Admitted to other drugs		
Alcohol admitted or obvious intake		
GCS =15		
Previous overdoses		
Comprehends English		

To test the level of confidence clinicians would require before being prepared not to take paracetamol concentrations on history negative patients, we formulated a questionnaire. It was given to senior house officers, specialist registrars, and consultants in five emergency departments.

It asked them to consider several scenarios describing the performance of the CDR, understanding that any savings made by implementing the rule would be available to treat other emergency department patients. Each question was on a different page and the next could not be read before completing the one before (see box 1).

RESULTS

A total of 316 patients attended with the above diagnoses and their notes were reviewed. Nine sets of notes could not be traced leaving 307 patients included in the study. None of the patients lost to follow up, (with notes missing, results missing or those that self discharged), were subsequently admitted for treatment. They are noted on the flow chart (fig 1) with an asterisk. From a total of 316 patients, full results were available for 288 patients (91.1%).

The patient characteristics are shown in table 3.

Of the 155 patients who denied taking paracetamol, none required treatment with the antidote. The characteristics of the identifiable risk factors for each group are shown in table 4.

Thirteen patients who denied taking paracetamol had detectable but not toxic consentrations in the blood. Their exact risk profiles are shown in table 5.

Box 1

1 For every 5000 patients who deny they have taken paracetamol, 100 (2%) have. Of these 100, one will die who could have been successfully treated with n-acetylcysteine. The cost of detecting this patient is £35 000. Would you use this rule? YES/NO.
2 For every 10 000 patients who deny they have taken paracetamol, 100 (1%) have. Of these 100, one will die who could have been successfully treated with n-acetylcysteine. The cost of detecting this patient is £70 000. Would you use this rule? YES/NO
3 For every 100 000 patients who deny they have taken paracetamol, 100 (0.1%) have. Of these 100, one will die who could have been successfully treated with n-acetylcysteine. The cost of detecting this patient is £700 000. Would you use this rule? YES/NO.
4 Now imagine that further research has shown the true false negative rate of the test is 1% (scenario 2) and the NHS Trust you work for has endorsed the rule. They state they will support staff who follow this rule and any medicolegal consequences that may follow. Would you now use this rule? YES/NO
5 Finally imagine that further research has shown the true false negative rate of the test is 0.1% (scenario 3) and the NHS Trust you work for has endorsed the rule. The state they will support staff who follow this rule and any medicolegal consequences that may follow. Would you now use this rule? YES/NO

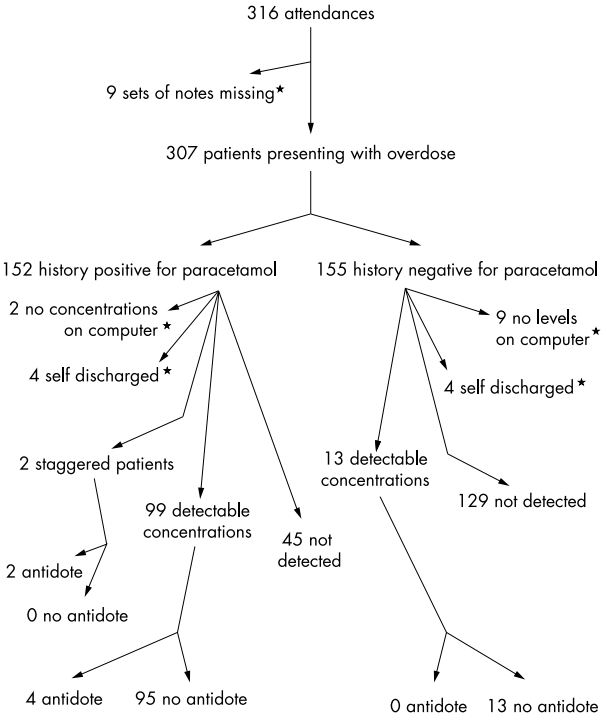

Figure 1 Flow chart of all patients in the study.

Validation of the clinical decision rule

In the subset of 13 patients with a history negative for paracetamol but concentrations present in their blood only six had a GCS less than 15. This means the seven other patients would not have been identified if GCS was the only risk factor considered.

By reviewing other risk factors documented at the time, we tried to identify all 13 patients. In addition to the 6 of 13 who had a GCS less than 15, 10 of 13 had taken significant alcohol. Three of 13 patients had neither of these risk factors but had either taken previous overdoses or multiple drugs in overdose.

Unfortunately even applying our CDR, these three patients would still not have been identified as high risk. However, it is still important to note that none of these patients had paracetamol concentrations that required treatment.

Importance of a clinical decision rule

Does it matter that if we decide not to test the patients with a negative history for paracetamol a few of them will have paracetamol concentrations present but below the treatment line?

Table 3

	Admitted taking paracetamol	Denied taking paracetamol
Total number of patients	152	155
Male	52	59
Female	100	96
Age		
16–19	23	19
20–29	55	34
30–39	35	50
40–49	24	34
50–59	13	12
60–69	0	2
>70	2	4
Self discharged before levels taken	4	4
Unable to find levels on computer	2	9
Staggered overdoses	2	0

Table 4

	Admitted taking paracetamol (n=152)	Denied taking paracetamol (n=155)
Paracetamol levels detectable	99	13
Paracetamol levels requiring antidote	6	0
Admitted or detectable alcohol	77	81
GCS <15	21	41
Admitted previous overdoses	63	76
Taken other drugs	71	137
Did not understand English	1	0
No risk factors	20	0

We took a sample of 307 patients. The 95% confidence intervals for a false negative for our sample were 0% to 2%. This means that there is between a 0% and 2% chance that using this rule a patient has an adverse event—that is, 2 in 100 patients could have toxic concentrations.

Forty seven practising emergency physicians were asked what false negative rate they would be prepared to accept. Only 9 of 47 (19%) of doctors would accept a level of 2%, 16 of 47 (35%) would accept a level of 1%, and 39 of 47 (83%) of doctors required a false negative rate of 0.1% (table 6).

To show that a CDR has a false negative rate of less than 1%, we would need a sample in excess of 20 000 patients. Eighty three per cent of clinicians require a false negative rate of 0.1% before being happy to use the clinical decision rule.

It is interesting to note, that when the emergency physicians were given trust endorsement and protection of the CDR the numbers rose to 39 of 47 at the 1% level and almost all 45 of 47 at the 0.1% level.

Application of the clinical decision rule

If the CDR was applied to all the 142 patients with a history negative for paracetamol, (not including those with notes missing or self discharged), 96 had one or both significant risk factors of lowered GCS or significant alcohol. This leaves 46 patients who could fall into the category of not requiring paracetamol concentrations to be analysed. This is 15% (46 of 307) of the total patients entering the department with alleged overdose.

CONCLUSIONS

Paracetamol is the commonest drug taken in overdose in the UK. Despite this there have been few studies about emergency department management in the UK, most of the research is from the USA where paracetamol poisoning is less of a problem. Our results reflect other studies in the UK, just under 50% (49.5%) of patients with suspected deliberate overdose admitted using paracetamol and we found concentrations in 36.5 % of our patients.

In our study none of the patients who denied paracetamol needed treatment. However, 13 patients with a history negative for paracetamol ingestion had non-significant paracetamol levels, implying that they had taken some despite denying it. Their reasons for not telling the truth were not known, it may have been that the patient was unaware of what they had taken, forgotten they had taken it, taken paracetamol prior to the overdose or that they were lying.

Our results concur with those in the Hong Kong study,[5] where 4 of 204 had detectable but non-toxic conentrations, and also with the USA study[4] where 7 of 365 patients with a negative history had detectable but non-toxic conentrations. Worryingly though in the USA study 1 of 365 had a potentially toxic result.

The Southampton results do vary from those in the study by Dargan *et al*.[7] They had no patients in their study with detectable levels after having taken paracetamol. They would have identified the 6 of 13 of our patients that had an obtunded GCS but not the other 7 of 13.

It is difficult to explain the variation in results of the British studies. There are differences in the study design, they recruited patients in retrospect from the pathology computer, and collected 440 patients in 12 months; we used a prospective cohort of patients coming through the department and collected 307 patients in three months, perhaps we were seeing slightly different patient populations. There is also a

Table 5 Patients with negative history and detectable levels

	History	Alcohol	Other drugs	Previous overdoses	GCS 15	Comprehends English
3	No	No	Yes*	Yes*	Yes	Yes
21	No	Yes*	Yes*	Yes*	Yes	Yes
28	No	Yes*	Yes*	No	Yes	Yes
38	No	Yes*	Yes*	Yes*	No*	Yes
75	No	Yes*	No	Yes*	No*	Yes
97	No	No	Yes*	Yes*	Yes	Yes
130	No	Yes*	Yes*	Not recorded	No*	Yes
132	No	Yes*	Yes*	Yes*	No*	Yes
153	No	No	Yes*	No	Yes	Yes
154	No	Yes*	Yes*	Yes*	Yes	Yes
259	No	Yes*	Yes*	No	No*	Yes
292	No	Yes*	Yes*	Yes*	No*	Yes
296	No	Yes*	Yes*	No	Yes	Yes

*Indicates presence of risk factor.

Table 6

	Question 1	Question 2	Question 3	Question 4	Question 5
Acceptable false negative rate	2%	1%	0.1%	1% with hospital endorsement	0.1% with hospital endorsement
Number of clinicians (%) Total 47	9 (19%)	16 (35%)	39 (83%)	39 (83%)	45 (95%)

disparity in the number of patients with lowered GCS: London 30% and Southampton 20%, we may have missed patients with a lowered GCS where the diagnosis of overdose was not coded as such.

This still does not explain why all the history negative patients in Dargon's study told the truth; perhaps the real truth is that overdose patients are an unpredictable group.

What all studies seem to show is that in history negative patients the chance of them having a clinically significant paracetamol concentration is low. However, the power of each of these studies is weak and the confidence intervals are wide. When the potential cost to the patient is death, evidence from our questionnaire shows that 83% of clinicians required a false negative rate of 0.1% before being happy to use a clinical decision rule. This would need a sample size in excess of 20 000 patients to rule out the possibility of missing one patient with a significant level—look at the USA study. There is no current study that shows this.

We tried to increase the sensitivity of the screening process by identifying certain risk factors that might make the patients history less accurate. Dargon *et al* recommended testing all the patients with a history negative for paracetamol and an abnormal GCS or history of collapse. This identified 6 of 13 patients with levels present. Our CDR also included alcohol as another risk factor and then 10 of 13 patients were identified. Three patients with detectable levels were still not identified.

By including more and more risk factors fewer patient tests will be avoided. For example, if we were to use our CDR in practice, then only 15% of the total patients entering the department with alleged overdose could fall into the category of not requiring paracetamol concentrations to be analysed. We estimate the cost of the screening policy in our hospital to be on average £10 per test (the approximation includes the increased cost of out of hours testing). We see about 100 overdose patients a month giving an average cost of £1000 per month. This would equate to a saving of approximately £150 per month.

This is a very small proportion of patients to be suggesting change in practice. We feel that when dealing with such small savings, the value of any CDR is rather pointless, when virtually all patients are going to have to be included anyway. This is of particular consideration when compared with the potential costs to both the patient; of late diagnosis, leading to liver damage or failure, possible transplantation or death, or to the hospital; incurring those medical charges and possible medicolegal costs.

In conclusion, from this work our clinical bottom line is that we cannot recommend changing the current practice of routinely checking all overdoses for paracetamol, even if they give a negative history for paracetamol ingestion.[8] Even if we did clinicians are unlikely to accept the advice. This may be explained by the fact that paracetamol testing is easy and relatively cheap, the antidote treatment is effective, and one of the consequences of failing to detect paracetamol poisoning is death.

Contributors

Dr Katharine Hartington initiated the idea, design of the protocol, data collection, analysis and writing of the paper. Dr Joanna Hartley initiated the design, data collection, analysis and writing the paper. Mr Mike Clancy discussed the core ideas and interpretation of the data. All three authors are guarantors.

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