Assessment of a point-of-care test for paracetamol and salicylate in blood

C. DALE1, A.A.M. AULAQI2, J. BAKER3, R.C. HOBBSS1, M.E.L. TAN1, C. TOVEY4, I.A.L. WALKER2 and J.A. HENRY1

From the 1Academic Department of Accident and Emergency Medicine, Imperial College, London, 2Wexham Park Hospital, Slough, 3Charing Cross Hospital, London and 4Prince Charles Hospital, Merthyr Tydfil, UK

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Summary

Background: Paracetamol and salicylate are commonly taken in acute overdose. Clinicians have a low threshold for excluding the presence of these two drugs, by ordering laboratory tests in any patient suspected of ingesting an overdose or with an altered mental state.

Aim: To test the effectiveness of a new point of care test that qualitatively detects paracetamol and salicylate in blood and to examine the potential time saved by its use.

Design: Prospective multicentre trial.

Methods: The new test was compared with laboratory analysis in a routine blood sample taken from patients presenting to emergency departments with suspected overdose.

Results: The test had sensitivities of 98.5% and 88.5%, and specificities of 74.7% and 92%, for paracetamol and salicylate, respectively, at cut-off levels of 25 mg/l and 100 mg/l, respectively. The point of care test results were available 2 h before the laboratory result.

Discussion: This point-of-care test could be used to rule out an overdose with either of these two drugs, and could thus lead to earlier clinical decisions for suspected overdose patients. Recommendations have been made following this trial that the cut-off value for paracetamol should be reduced from 25 mg/l to 12.5 mg/l in order to increase its usefulness. To prevent the test being misread, we also suggest that each device should be embossed to remind users that the presence of a line indicates there is no drug present.

Introduction

Deliberate self-poisoning, usually in the form of drug overdose, is a common presentation in Emergency departments (EDs). In the UK, it constitutes up to 10% of the ED workload,1 and leads to 100 000 hospital attendances per year.2 Paracetamol is implicated in up to 48% of all overdoses,3 and is thought to cause about 200 deaths per year in England and Wales.4 This figure has subsequently reduced since legislation on restricting pack sizes of paracetamol and salicylate sold in the UK.5 It also accounts for over half of all cases of acute liver failure referred to liver units.3 Clinicians need to have a low threshold to screen for paracetamol in patients who present with suicidal ingestion, because of the initial lack of symptoms, the serious consequences of missing such an overdose, and the availability of a safe and effective antidote. A recent retrospective review showed that out of all drug overdose cases dealt with by an American regional poison control centre over a 6-month period who gave no history of paracetamol ingestion, 7.2% had paracetamol levels in excess...
of 10 mg/l and 2.2% had potentially toxic levels requiring treatment. This implies that although the overall risk of missing a potentially serious paracetamol overdose is small, it is clinically justifiable to universally screen for paracetamol exposure in patients presenting with suspected or actual self-poisoning.

Aspirin is commonly used in self-poisoning, and overdose with this drug accounts for approximately 2% of emergency enquiries to the National Poisons Information Service (London). Although there is less evidence to suggest that clinicians should universally screen for salicylate, levels of this drug are often checked following a possible or suspected overdose, or when a patient presents with tachypnoea and acid-base disturbances without any evident cause. Delay in diagnosis of aspirin poisoning has been shown to increase mortality and morbidity.

A survey of 28 UK Biochemistry departments showed that 67.8% and 86.2% of paracetamol and salicylate levels taken were negative (paracetamol <10 mg/l, salicylate <50 mg/l) (unpublished data). This means that the majority of patients tested for these drugs have not taken them. The patient with an actual or suspected overdose is made to wait until 4 h after ingestion of the overdose before blood is taken, followed by a further wait for the result from the laboratory. A quick and effective screening device could potentially improve the management of these patients in the ED. There have been three previous studies evaluating near-patient tests for paracetamol detection. Shannon et al. tested the accuracy of a newly developed meter that determined the serum paracetamol level. They found a sensitivity and specificity of 100%, but only included 31 specimens in the study. They did not measure the time saving involved, but estimated that at least 60–90 min could be saved, and concluded that the test could lead to a reduction of presumptive acetylcysteine administration. The meter was a preliminary design and was not available commercially. Two more recent studies compared the AcetaSite test (a point-of-care test which quantitatively determines paracetamol levels) with a laboratory method. One group found considerable discrepancies between the two assays, which the authors considered was partly due to operator error, and concluded that the test could not replace the standard laboratory method. The other group found strong concordance within the recommended operating range, but concluded that it did not offer economic benefit.

Point-of-care tests, bedside tests or near-patient tests have been in use in medicine for many years now. It is generally accepted that the benefits of such tests depends on the clinical problem and how the result will affect the patient’s management. There are difficulties as well as benefits when introducing a point-of-care test. These include training individuals to use the tests properly, and creating systems to enable good record keeping and monitoring of the results. Point-of-care testing, as with any test, is only effective if action is taken on the result. Although these tests are often more expensive than central laboratory testing, if used appropriately, they can produce wider economic benefits. ED clinicians need to make decisions quickly so that the patient can be managed rapidly and appropriately. Point of care testing reduces the time taken to make decisions on patient management, as well as bringing about faster treatment.

A new qualitative point-of-care test (PoCT), SureStep™ (Applied Biotech, San Diego), has been developed to detect paracetamol and salicylate in the blood. It is a lateral-flow, one-step immunoassay, with manufacturer cut-offs of 25 mg/l and 100 mg/l, respectively. The plate requires four drops of whole blood and three drops of buffer, and gives a result in between 5 and 8 min. Its performance under laboratory conditions has been examined using spiked whole blood, plasma and serum to determine its sensitivity, accuracy, specificity and potential interference from chemicals found in human blood. We wanted to evaluate the test’s effectiveness in a clinical setting, and to see whether it has the potential to reduce the number of laboratory tests and shorten the time to discharge or referral.

We carried out a multicentre trial to determine the sensitivity and specificity of the test, and also to calculate any time saving over laboratory testing when using the test in the ED.

Methods

Local Research Ethics Committee approval was obtained for a prospective, multicentre clinical trial. The emergency departments involved were St Mary’s and Charing Cross Hospitals in London, Wexham Park Hospital, Slough, and Prince Charles Hospital, Merthyr Tydfil, Wales. Between March 2001 and March 2003, any patient presenting to the ED with a clinical indication for measurement of plasma paracetamol or salicylate, i.e. a history of self-poisoning or patients with altered consciousness and suspicion of possible overdose, was included. We excluded patients who had taken the overdose >12 h before arrival. When the 4-h post-ingestion blood sample was collected, four drops of blood were analysed using the PoCT, and the remainder was sent to the
laboratory for standard automated laboratory procedures. The cut-offs for paracetamol at the four centres were all 10 mg/l, except one which had a cut-off of 25 mg/l, and the cut-offs for salicylate ranged from 4 mg/l to 25 mg/l. The investigators (clinicians within the ED) documented the results and timings of the overdose, arrival to department, when blood was taken and when results were available.

Results

The trial included 367 patients, mean age 34.1 years, with a male to female ratio of 1:1.5. Twelve patients had presented ≥12 h after the overdose and were therefore excluded. Tables 1 and 2 show how the PoCT performed compared with the laboratory levels. The prevalences of paracetamol and salicylate overdose in our study population were 0.39 and 0.07, respectively. The PoCT had sensitivities of 98.5% and 88.5% and specificities of 74.7% and 92% for paracetamol and salicylate, respectively (Table 3). There were two false negative results for paracetamol at the cut-off of 25 mg/l. These were at 28 mg/l and 56 mg/l. There were three false negatives for salicylate at the cut-off of 100 mg/l. These were at 110 mg/l, 113 mg/l and 229 mg/l.

The PoCT results were available within a mean of 107 min of arrival, and a mean of 118 min (95%CI 109–126 min) before the laboratory results (Table 4). Some 14% of cases had no time entered for when the clinician received the results and these were defaulted to 30 min after the time the laboratory received the blood sample, an earlier result than this being highly unlikely.

Time of overdose was documented for 285 patients; mean time from overdose to presentation was 193 min (range 15–720 min; 95%CI 173–213). The patients spent a mean time of 372 min (range 15–1318 min; 95%CI 341–402) in the ED.

Discussion

This test was devised with the aim of saving time in the ED by ruling out paracetamol and salicylate overdose rapidly and accurately. The National Academy of Clinical Biochemistry have published guidelines\(^\text{14}\) stating that screening for the presence of salicylates is not necessary routinely, unless there is a clinical indication such as altered mental status, tinnitus, tachypnoea or metabolic disturbances. They did however endorse screening for paracetamol in all ED patients who present with intentional drug ingestion. It was suggested that a qualitative assay could be used if the majority of samples were negative and an appropriate cut-off was used. In the case of paracetamol, the sensitivity of the test was 98.5%. It should be made clear that this is only out of a total of 137 patients (as this was the number who had a laboratory concentration ≥25 mg/l). However the negative predictive value was 0.988, and the likelihood ratio for a negative result was 0.019 (95%CI 0.005–0.07). These are acceptable results for a PoCT, but when clinicians were asked what level of confidence they would require before being prepared to not take formal paracetamol concentrations, 83% required a false negative rate of <1%.\(^\text{15}\) This could be achieved by limiting the time post ingestion that the PoCT is used. The highest recorded false negative for paracetamol was 56 mg/l. When plotted on the nomogram, a level >60 mg/l is considered potentially hepatotoxic if

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**Table 4** Comparison of laboratory paracetamol levels with point-of-care test (PoCT) results

**Table 5** Comparison of laboratory salicylate levels with near patient test results

**Table 3** Performance of PoCT when compared with laboratory results at cut-offs of 25 mg/l and 100 mg/l for paracetamol and salicylate, respectively
the ingestion took place >7 h previously in high-risk patients, or >11 h previously in ‘normal’-risk patients. Therefore, the PoCT would have a sensitivity of 100% if used between 4 and 11 h post ingestion in a patient who is considered not to be at high risk. In high-risk patients, the PoCT would need to be used at between 4 and 7 h for such a sensitivity to apply.

The specificity of the test for paracetamol at the cut-off of 25 mg/l was 74.7%. In this case, 44.4% of the false positives were actually true results, in that the paracetamol level was between 10 and 25 mg/l. It could be argued that this is a reasonable price to pay in order to maximize the sensitivity of the PoCT. As the test is qualitative, any patient with a positive result will need a quantitative test performed by the laboratory, but with a high proportion of paracetamol results being negative, the potential clinical value of this test to reliably rule out a paracetamol overdose, even with a specificity of 74.7%, is apparent.

Although, it has been advised that screening for the presence of salicylate should not be carried out routinely, as mentioned earlier, we have included these results here. Salicylate toxicity seems to be less frequent than for paracetamol, and the likelihood of clinical evidence for such an overdose and the fact that there is no antidote, means a more selective approach can be used. However, we feel the results have shown that the PoCT is accurate for detecting salicylate presence, even though the numbers of patients who had taken salicylate were very small. A false negative result for salicylate occurred in three cases, each <230 mg/l. For this drug, overdose is considered mild up to a level of 350 mg/l, and treatment would not be considered necessary at these levels. Of the 363 results, only 4 (1.1%) were >350 mg/l. The likelihood ratio (LR) is independent of the prevalence of the condition being tested; in the present case, the LR for a positive test is 11 (95%CI 7.4–16.2) and for a negative test is 0.13 (95%CI 0.04–0.32).

The test is designed so that a line becomes visible when there is no drug present. This could be considered counter-intuitive and may confuse people, especially if they have not been trained adequately, or are familiar with bedside tests which are read as positive when a line is seen. It is conceivable that the false negatives were due to the tests being misread rather than a failure of the test itself. As there is often a high turnover of staff within an ED, which is itself often a busy environment, it can be difficult to ensure that all are trained; this needs to be taken into consideration when introducing any new PoCT. It was noticed during the course of the trial that considerable emphasis was needed to remind those who used the test, that a line indicated a negative result. Systems need to be in place to be sure that those who use the test have been trained and are confident to read the test accurately. It was felt that this potential problem of misreading undermined the safety of the SureStep test, and may have been responsible for some of the false negatives. It was therefore recommended to the manufacturers to have embossed on each device wording that indicated the presence of a test line meant there was no drug present. This, of course, should not substitute training, but would act as a reminder each time the test was used.

The time difference of 2 h from when the PoCT result was available and when the laboratory result was obtained is potentially of value to the patient. Patients have to wait under the present protocol until 4 h post ingestion followed by a further 2 h for the results. Although a formal trial looking at the difference in clinical outcomes would need to be performed, it is possible to see a potential benefit in this particular group of patients. If the SureStep was introduced, those with a positive result would still need to wait for laboratory results, but the high proportion with a negative result could be deemed medically fit on the basis of that result and discharged home or to the care of the psychiatric liaison team. In the current political climate of EDs having to see, investigate, treat and refer patients in just 4 h, this time saving could make a difference between achieving targets and not, especially as the
average time the patients in this trial spent in the department was 6 h. Point-of-care testing has not been previously shown to reduce time in the emergency department, but has been shown to expedite decision making and treatment. The evidence to date is that other factors (such as lack of available beds) are thought to be limiting the benefits of point-of-care testing. Unfortunately this study did not specifically examine what proportion of patients were admitted. From the forms that had documented the time of ingestion, it was possible to establish using the nomogram that only 4.6% would have required treatment for paracetamol ingestion if they were all considered at normal risk (10.7% if all were ‘high risk’), while only 1.1% had levels of salicylate >350 mg/l. This did not take into account the patients who were tested following multi-drug ingestions and those with altered consciousness, who would require hospital admission regardless of their paracetamol and salicylate concentrations. From this study we can only estimate that a considerable number could be discharged from the care of the Emergency Physicians on the basis of a negative result.

Another group of patients are children with suspected accidental poisoning. Since parents usually bring their child to hospital at great speed, there is often a long wait before blood can be taken, followed by a further wait for the result. It would clearly be preferable to reduce the time that children and their parents have to wait, and using the PoCT would also mean a less traumatic procedure. Further studies need to be performed to see whether the PoCT can be used any earlier than 4 h for the true benefit of such a screening device.

Evidence has shown that it is clinically justifiable to check for paracetamol levels in the collapsed patient, since there is the potential for missing a significant overdose. This test could rapidly screen for such an overdose to facilitate decisions on treatment. It should also be remembered that there is a time pressure on the effectiveness of acetylcysteine. Current practice dictates that a patient who presents with an overdose ≥8 h previously should be treated immediately for overdose with acetylcysteine, pending a result from the laboratory. This may lead to some patients receiving the antidote when there is no drug present. However, a PoCT has the potential of avoiding this unnecessary intervention, so that only patients with drug present and who have presented between 8 and 12 h post ingestion would need treatment whilst waiting for the quantitative test result. Although the results in this trial showed an overall delay of 106 min (95%CI 97–115 min) between arrival and the PoCT result, this includes patients who arrived before 4 h post ingestion, and had to wait as part of the protocol. For those who attend 4 h post ingestion, it is possible that a result could be available within 4 min once intravenous access is obtained and a sample is taken.

Unfortunately we did not collect data as to whether the overdose had been staggered over a number of hours. When this has happened, it renders the laboratory level meaningless, and plotting it on the nomogram is unreliable. As a consequence, current practice is to treat a staggered overdose regardless of the level. We do not have any data on how the PoCT performs in this situation, but feel that there should be no change in the current management of these patients.

Conclusions

Screening for paracetamol overdose is clinically justifiable in the overdosed or unconscious patient. Clinicians will continue to have a low threshold for checking for its presence, as it is potentially fatal and has an effective antidote if given within 8 h post-ingestion. A PoCT which tests for the presence of both drugs could be of value in the ED, if it is considered reliable as well as quick and easy to use. The PoCT studied performed well overall in the ED. There were no problems reported with its use during the study. Although a total of 354 patients were included, the numbers to calculate the sensitivity of the PoCT were small, but it had a negative predictive value of 0.99 for both paracetamol and salicylate. It did, however, show the potential to shorten the ED stay by 2 h, which could lead to earlier clinical decisions for this group of patients.

Although the results found were encouraging, it is possible that the test was occasionally being misread, affecting its sensitivity and therefore safety. As a consequence of the findings in this study, a new version of the test is to be produced, with embossing on each device indicating that a line means there is no drug present. We have also advised a decrease in the cut-off for paracetamol from 25 mg/l to 12.5 mg/l, so as to ensure that even late-presenting cases or those requiring measurement against the high-risk treatment line can be detected. Following these changes, a further study will examine how the revised version performs from 1 h post ingestion, thereby enhancing the potential time saving when using the test.

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References