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Comparison of assays for measuring plasma paracetamol. Possibility of calibration error needs evaluation

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Abstract
Egleston et al report a significant difference in plasma paracetamol concen trations assayed with the AcetaSite bench assay and a standard laboratory assay. Rapid and accurate determinations of plasma paracetamol concentrations are crucial in the expeditious and appropriate administration of antidotal treatment, which prevents severe liver damage if given sufficiently early in the course of poisoning.

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larisation service, supports the following observations. There is an increasing problem in the United States when randomised controlled trials are timed to follow on from lengthy uncontrolled non-randomised studies, often in the same centres. The reluctance of American doctors and patients to take part in a randomised controlled trial of transmyocardial revascularisation led to the crossover design and short term follow up, both features that were criticised by the Food and Drug Administration.[1 2]

To avoid such problems in Britain the health technology assessment process needs to be sufficiently responsive to ensure that randomised controlled trials of new technologies are conducted in a timely manner. There may also be a case for more cooperation between centres, a proposition arising from our second observation, which concerns recruitment to the British trial of transmyocardial revascularisation. We should have reported definitive results last autumn, but, because recruitment was slower than expected, a one year extension was agreed with the Medical Research Council, at additional cost. Although efforts have been made to publicise the trial widely, the uneven pattern of referral, with higher numbers from local regions, does not reflect the geographical distribution of coronary artery disease. Maybe an additional trial centre located in the north of the country would have resulted in more rapid recruitment. The NHS research and development health technology assessment programme, the Medical Research Council, and other major funders could play a part in encouraging grant applicants to work together to complete such trials as quickly and efficiently as possible. In the meantime, the jury in the trial of transmyocardial revascularisation is still out.

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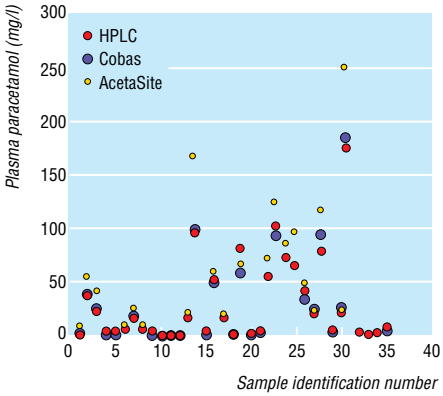
Comparison of assays for measuring plasma paracetamol

Possibility of calibration error needs evaluation

Editor—Egleston et al report a significant difference in plasma paracetamol concentrations assayed with the AcetaSite bench assay and a standard laboratory assay.[1] Rapid and accurate determinations of plasma paracetamol concentrations are crucial in the expeditious and appropriate administration of antidotal treatment, which prevents severe liver damage if given sufficiently early in the course of poisoning.[2]

We compared two methods for estimating plasma paracetamol (Cobas paracetamol assay kit (Cambridge Life Sciences, Ely) and AcetaSite blood acetaminophen (paracetamol) test (Cambridge Life Sciences)) with a standard high performance liquid chromatographic method.[3] We used the methods on 35 samples from 23 patients presenting between 5 and 50 hours after a paracetamol overdose who claimed to have taken a mean of 22.0 g (range 5-50 (SD 13.1) g) of paracetamol alone. Samples were taken and stored at −40°C, and all assays were performed in our laboratory.



Plasma paracetamol concentrations assayed by AcetaSite, Cobas, and standard high performance liquid chromatographic (HPLC) methods in 35 samples from 23 patients who admitted having taken paracetamol overdose

The figure shows the results obtained with the three methods. Compared with high performance liquid chromatography, the AcetaSite assay overestimated plasma paracetamol concentration in a considerable number of cases; the difference was significant ($P=0.002$, paired t test). There was no significant difference between the results obtained with the Cobas assay and high performance liquid chromatography ($P=0.81$, paired t test. The Pearson correlation coefficients of the AcetaSite and Cobas assays with standard high performance liquid chromatography were 0.97 and 0.97 respectively.

We believe that the most likely source of the discrepancy between the AcetaSite assay and the other methods in our study was a calibration error within the AcetaSite method. All assays were carried out in our laboratory by an experienced clinical chemist (by contrast, some of the assays in Egleston et al's study were done by emergency doctors). We therefore believe that operator error is an unlikely explanation for the results of our study or those of the study reported by Egleston et al. The possibility of a calibration error in the AcetaSite system requires further evaluation; external calibration is not possible with this assay.

Egleston et al do not make clear what results they obtained in the 100 patients who had apparently not taken paracetamol but from whom blood was taken for assay. These results should have been negative by both methods; this is an important point for exclusion of false positive results. In patients who admit to having taken paracetamol, interference in the assay by other drugs taken concurrently is a potential source of error.

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Training and education in use of assay are important

Editor—Egleston et al compared the accuracy of a standard laboratory paracetamol assay with that of a rapid bedside test (AcetaSite).[1] Egelston et al used a statistical method developed by Bland and Altman[2] to assess agreement between the two methods of clinical measurements. The limits of agreement were calculated to be 0.16 and 5.04. This translates into poor agreement between the two assays, with 95% of values obtained with AcetaSite being between 0.16 and 5.04 times the values obtained with the laboratory assay. The authors concluded that the AcetaSite test should not replace the established laboratory method.

We have also evaluated the AcetaSite test, recruiting 58 patients to our study. Four sets of results were excluded from the analysis because the Stat-Site meter recorded a maximum of >250 mg/l (by contrast, the laboratory gave a specific reading). At the lower end of the range (<20 mg/l) 15 sets were excluded for similar reasons. On the remaining 39 samples, using Bland and Altman's test, we found our limits of agreement to be 0.79 and 1.1. Our results therefore suggest good agreement between the two assays. The performance ($r=0.974$) matches closely that shown in the datasheet for AcetaSite compared with standard reagents ($r=0.97$ and $r=0.983$).

When evaluating a new technology, such a contrast between studies merits careful analysis. Egleston et al make some suggestions for the reason for the poor agreement between the two assays in their study. Although there may be other reasons, the most likely is training and education. Our study was carried out by the six middle grade doctors in the accident and emergency department and a small number of senior house officers after a one to one training programme. An algorithm card was used from the outset (modified after piloting). Particular attention should be paid to this much overlooked aspect of study design if accurate results are to be attained and valid conclusions drawn.

We believe that the AcetaSite test does provide a rapid and accurate bedside assay of paracetamol concentrations. Further analysis in our study, however, indicates that