Paracetamol-codeine combinations versus paracetamol alone

EDITOR,—In their systematic review Anton J M de Craen and colleagues conclude, on the basis of a range of outcome measures, that the combination of paracetamol and codeine is a more effective analgesic than paracetamol alone.¹ They find the increase in efficacy to be small but significant and suggest that future studies should report the proportion of patients in whom good or moderate pain relief is achieved. Such data would enable us to relate statistical significance to clinical importance.

In a similar overview we also concluded that codeine added to the analgesic efficacy of paracetamol, using derived outcome measures of pain such as the sum of the pain intensity difference (as defined in de Craen and colleagues' paper).² In the meta-analysis of six head to head comparison trials, however, a significant pooled estimate of a 6.7 point difference in the sum of the pain intensity difference (95% confidence interval 3.2 to 10.3) between the paracetamol-codeine combination and paracetamol was not translated into a significant increase in the proportion of patients obtaining moderate to excellent pain relief (response rate ratio 1.14 (0.97 to 1.34)). More head to head comparisons will of course improve our ability to estimate additive effects.^{3,4}

Deciding what change is clinically important is often difficult. Better reporting of patients' assessment of how their treatments have affected their symptom or condition, as advocated by de Craen and colleagues, would ease the interpretation of data from clinical trials and facilitate evidence based practice. We would go one step further and request that the time at which this response is assessed should be defined consistently to take account of the drugs' pharmacokinetics and pharmacodynamics.

In our meta-analysis, caffeine (another additive in many products that combine analgesics) did not add to the efficacy of paracetamol, as measured by either the sum of the pain intensity difference or the response rate ratio.

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Intention to treat approach is not popular

EDITOR,—Anton J M de Craen and colleagues address the question of the added analgesic effect and safety of codeine combined with paracetamol through a literature review with meta-analysis and an assessment of the methodological quality of the published trials.¹ Their paper is a long overdue contribution to evidence based pharmacotherapy. Their recommendations to improve the quality of clinical trials, however, deserve attention.

The authors criticise several of the papers for not using the intention to treat approach. The justification for using this approach is its

supposed relation to actual clinical practice.² Furthermore, the authors recommend the use of larger treatment groups ($n > 100$) to ensure that baseline pain intensities are similar.

Contrary to the view still held by many people, the efficacy of oral analgesics in relieving pain is not universal. Their efficacy is highly dependent on the quality³ and quantity⁴ of the pain against which they are intended to be used. Oral surgery, which is possibly the best characterised model of postoperative pain in use today, shows these relations well.⁴ Thus the purpose of controlled trials of analgesics should be to show potency, relative potencies, or equivalence in particular pain intensities (for example, mild, moderate, or severe pain) with the minimum necessary number of patients.

As a consequence, the intention to treat approach is not particularly popular because the outcome measures are believed to be diluted. Having a large number of patients (> 100) in each treatment group is avoided whenever possible because it raises questions of ethics, cost, and benefit. The way in which many traditional epidemiologists and statisticians look on trials of analgesics supports and reinforces the tradition of non-discriminatory use of oral analgesics in clinical practice without the necessary assessments of patients.

One of the authors' two most useful recommendations is that baseline pain should be stratified.¹ Doing this and using a fixed minimum level of pain for entry would greatly reduce the need for large numbers of patients in each treatment group, depending on the type of analgesic study performed. The second recommendation, that proportions of patients achieving various states of pain relief should be included, is also useful. Differences found in clinical trials of oral non-steroidal anti-inflammatory drugs have, more than once, been caused by different ratios of responders (those in whom the drugs have an analgesic effect) to non-responders (those in which they have no effect) rather than differences in pain relieving effects.

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Actual size of increase needs to be measured

EDITOR,—Underlying Anton J M de Craen and colleagues' conclusion that adding codeine 60 mg to paracetamol can result in a small but significant increase in analgesia is the crucial question "How big is small?"¹ The benefit of adding 60 mg codeine to paracetamol in studies of single doses can be quantified.² Thirteen of the 19 reports from de Craen and colleagues' search met our inclusion criteria of comparisons of single doses of oral paracetamol with single doses of paracetamol plus codeine 60 mg, double blind treatment with random allocation, baseline pain of moderate to severe intensity, and total pain relief as a derived outcome. Two studies used paracetamol doses of 1000 mg and the rest used 600 mg or 650 mg. We calculated the

risk ratio and number needed to treat for paracetamol versus paracetamol with codeine 60 mg, using the criterion of pain relief of at least 50%.²

Only one of the 13 reports had a significantly increased risk ratio (the 95% confidence interval did not include 1 (fig 1)). The combined risk ratio (fixed effects model) for this homogeneous dataset was significant (1.25 (1.09 to 1.43)). Adding 60 mg codeine to paracetamol for single dose pain relief produced a number needed to treat of 9.1 (5.8 to 24). This means that one of every nine patients with pain of moderate to severe intensity will get at least 50% pain relief with paracetamol plus 60 mg codeine who would not have done had they been given the same dose of paracetamol alone.

Fig 1—Risk ratios for individual trials of paracetamol plus codeine 60 mg compared with same dose of paracetamol alone

We, like others, find the number needed to treat to be a clinically useful finding of quantitative systematic reviews of treatments. To get credible numbers, however, attention must be paid to the validity of the trials that are included in the review. We had to omit two of the trials in de Craen and colleagues' analysis because of their failure to ensure adequate sensitivity by requiring at least moderate or severe pain at baseline.³ They also used the mean descriptors from the trials. Means of asymmetrically distributed data (summed difference in pain intensity) can produce incorrect conclusions.⁴

Paracetamol-codeine combinations are often used in multiple doses. Assessing the additional benefit of the codeine in trials of single doses may underestimate the effect after multiple doses.

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