Sodium cromoglycate in childhood asthma

The review of placebo controlled trials of sodium cromoglycate (SCG) in childhood asthma by Tasche et al concludes that "there is insufficient evidence that SCG has a beneficial effect as maintenance treatment in children with asthma". We do not believe this conclusion is justified. The principal criteria for assessing the efficacy of inhaled SCG are the mean differences in the effect on the symptoms of cough and wheeze between SCG and placebo across all trials included in the review. The 95% confidence intervals for these differences are 0.12 to 0.27 for cough and 0.11 to 0.26 for wheeze. As the differences are in favour of SCG and the confidence intervals do not include zero, the only conclusion that can be drawn is that there is strong statistical evidence for a beneficial effect of SCG in children with asthma—the reverse conclusion to that presented.

The review identified 24 randomised controlled trials and is claimed to include "all published randomised, placebo controlled trials". Two published trials are not included (those by Berman et al and Mikawa et al) and the trial by Silverman et al, which is included, does not meet the author's criteria. Both excluded trials, which involved 472 children, were subjectively statistically significant differences in favour of SCG compared with placebo. The study by Silverman et al compared the combination of inhaled SCG and isoprenaline with isoprenaline alone and did not include a placebo comparison.

The authors have calculated a tolerance distribution for study effects and we believe it is this distribution which has been fundamentally misinterpreted. They provide a tolerance interval for the results of future studies based on the between study variation seen. The fact that this interval contains zero does not mean that there is no evidence of a difference between treatments, as the authors imply, but rather just that all future studies can be predicted to mean giving a difference numerically in favour of SCG. The tolerance interval quoted suggests that perhaps 90% of future trials will have an outcome in favour of SCG, a really positive finding. This is, of course, entirely consistent with the strong indication of publication bias, the tolerance interval including zero, the small treatment effect. The analysis as presented provides very strong evidence of statistically significant benefits in favour of SCG for the key symptoms of cough and wheeze which would be strengthened further by the inclusion of all published studies and further still if only those studies which identified a clear asthmatic population were included. Despite the fact that we consider this paper in a general practice setting in children with asthma, they doubt whether the evidence for a beneficial effect of SCG in childhood asthma studies were generally low due to dilution by symptom-free days. In these circumstances the estimated size of effect may well have clinical relevance.

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maintenance treatment with SCG in children with asthma. We think that Dr Edwards and colleagues have misunderstood this conclusion as they only address the issue of the tolerance interval. We agree that, from the interval as we found it, one would predict some 90% of future studies to have a positive outcome (though not all significant). However, because of the strong suggestion of publication bias, with negative studies being underrepresented, the overall small effect size and the corresponding confidence intervals are probably biased—that is, overestimating the true effect size.

The pooled point estimates were found to be 0.19 both for cough and wheeze. This method, compared with the placebo group, the children who used SCG had, on average, a 0.19 lower symptom score on a scale of 0–3 during the period they were studied. These are small effects indeed, of which the clinical relevance is questionable, especially as the bias caused by selective publication by pharmaceutical companies.

Instead of evidence based, and authors of this published in the past were positive is not unequivocal. Some studies found a positive effect as maintenance treatment in children with asthma. We think that Dr Edwards and colleagues are insufficient to modify this conclusion.

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Tuberculin reactivity

We read with interest the paper by Oomenas and colleagues on the relationship between tuberculin reactivity and atopy in BCG vaccinated young adults. Thorax 2000;55:145–8.

We appreciate the help of the authors in completing the three stages of publication bias. We excluded the studies performed by Oomenas, since this study is not designed to do so. For this purpose a prospective randomised trial in young children is required.

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AUTHORS’ REPLY

We thank Drs Steenhuis and Hoekstra for their comments on our cross sectional study indicating that modulation of the immune response by BCG vaccination at the age of 14 does not result in a reduction of atopy in adults. As pointed out in the paper, a long time elapsed between the BCG vaccination and tuberculin testing. Knowledge of the relationship between intraindividual immediate tuberculin reactivity after BCG vaccination and later reactivity is limited. However, our clinical experience tends to support the view that a person with a strongly positive response due to BCG vaccination will later show reactions that are weaker but of corresponding rank within the same cohort. We are not aware of data to support this view; there is, however, a possibility that the tuberculin negative group at follow up contained a high fraction of initial responders to the BCG vaccination (with subsequent low IG E levels), thus minimising the difference between tuberculin positive and negative subjects. As pointed out by Drs Steenhuis and Hoekstra, this question can best be answered in a prospective randomised trial in young children.

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Respiratory Medicine

A conference on Respiratory Medicine will be held at the Royal College of Physicians of Edinburgh on 26 October 2001. For further information contact Ms Eileen Straw, Symposium Coordinator. Telephone 0131 225 7324. Fax 0131 220 4393. Email: e.straw@rcpe.ac.uk. Website: www.rcpe.ac.uk.
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