

Correspondence

Calculation of the minimal effective dose for fluticasone propionate and budesonide in children

To the Editor:

The recent study by Agertoft and Pederson (J Allergy Clin Immunol 1997;99:773-80) does not support the strength of the conclusions made in the article because of limitations in both study design and statistical methods.

The study design can be criticized because the lowest dose of fluticasone propionate that could be achieved was 100 µg once daily when using commercially available Diskhaler inhalers. Therefore the minimal effective dose (MED) was artificially limited through lack of lower-dose inhalers rather than lack of efficacy with lower doses of fluticasone propionate. This artificial limitation is seen when considering those patients who were satisfactorily controlled on a dose of 100 µg (i.e., had not reached their MED). There was a trend for more patients receiving fluticasone propionate than budesonide to be controlled with this dose, although the difference did not reach statistical significance (35 of 107 [33%] vs 23 of 107 [22%] patients, $p = 0.065$ as determined by chi-square test). The method of analyzing patients with a MED less than 100 µg is an important consideration and introduced an element of bias in addition to reducing the power of the study.

The power of the study was also reduced by using statistical methods relevant to continuous variables for the analysis of MED when in fact it is a categorical variable. A retrospective power calculation of the study reveals that the power to detect a difference between fluticasone propionate and budesonide is reduced from the 80% stated in the publication to a value of 60% when the statistical methods and the artificial truncation of the data at 100 µg is taken into account.

It is important to note that all the trends in efficacy (i.e., morning and evening peak expiratory flow rates ($p = 0.06$), patients controlled on 100 µg, MED, and number of dose reductions) were consistently in favor of fluticasone propionate over budesonide. Another important consideration is the funding of the study, which, somewhat surprisingly, was not evident from reading the article. This could mean that there may be a conflict of interest between the results and the funding (presumably Astra Draco), which the reader should be alerted to. Therefore the element of bias introduced by the study design and the statistical methods means that this study cannot exclude the possibility that fluticasone propionate is more effective than budesonide. Although this is contrary to the authors' conclusions, it has been shown consistently in a number of other studies in both children and adults.^{1,2}

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2. Barnes NC, Hallett C, Harris TAJ. Clinical experience with fluticasone propionate in asthma: a meta-analysis of efficacy and systemic activity compared with budesonide and beclomethasone dipropionate at half the microgram dose or less. Respir Med 1998. In press.

Reply

To the Editor:

Rick Fuller and Pauline Martin from Glaxo had four concerns about our recent article.

First, they suggested that the minimal effective dose (MED) was artificially limited through the lack of lower-dose inhalers rather than through a lack of efficacy with lower doses of fluticasone propionate. However, the same was true for budesonide. Because both fluticasone and budesonide were given at the lowest dose possible through their commercially available inhalers, any bias towards one or the other of the two drug-inhaler combinations was, in fact, avoided. As Dr. Fuller and Ms. Martin are certainly aware, the 27% fully-controlled patients were poorly suited for the study, because even when receiving a daily dose as low as 100 µg they still failed to reach the steep part of the dose-response curve. Suggestions or conclusions about the superiority of one drug-inhaler combination over another based on this subgroup of children alone is therefore scientifically unsound. The most appropriate group on which to focus any subgroup analysis would be the 156 children shown by asthma deterioration to have reached the steep portion of the dose-response curve. As we stated in our paper, the conclusions were the same for these children.

Second, Dr. Fuller and Ms. Martin suggested that there were problems with the use of statistical methods relevant to continuous variables for the analysis of MED. Although analysis of variance of ordered categorical data is an approximate method, it is nonetheless known to be suitable in many situations such as this one. Further verification that our results did not depend critically on the method of analysis has been corroborated by stratified Wilcoxon tests. Probability (p) values from these analyses are equal to, or slightly higher than, the corresponding p values from analysis of variance reported in the article. The retrospective power calculation reported by Dr. Fuller and Ms. Martin is unsubstantiated in their letter and is in disagreement with our own calculations.

Third, we disagree with the comments about a trend in all efficacy variables. The p values in our study seemed to be evenly distributed and not clustered around either of the ends of the confidence variables.

Fourth, we are genuinely surprised by the question and critique contained in Dr. Fuller's letter about funding and elements of bias in study design and statistical methods because the protocol was finalized with Dr. Fuller's active participation. In cooperation with Astra, Glaxo and Dr. Fuller made valuable contributions and changes to both the study design and protocol before their finalization. In fact, delivery of fluticasone and placebo Diskhalers from Glaxo were contingent on incorporation of the changes suggested by Dr. Fuller to both study design and protocol. Moreover, results and their initial analysis were discussed with Dr. Fuller, and additional analyses were made on the basis of his suggestions.

Dr. Fuller and Ms. Martin cite an open study in the *British Journal of Clinical Practice*, which they seem to find more powerful, scientifically correct, and less biased than our double-

blind dose titration study. The results of that study suggest a 4:1 clinical potency ratio between fluticasone and budesonide. We agree that such marked differences in results between two studies might very well be caused by bias in design of one of the studies. We encourage readers to read both papers and make their own assessments about which study design they find most scientifically correct and unbiased.

To further assess the likelihood of a 2:1 clinical potency ratio between the two drug-inhaler combinations in our study, we have made an analysis with hypothetical data, with MED for the patients receiving fluticasone being assessed as reported in the study but MED for the patients receiving budesonide being systematically shifted down by one dose step. If there was a 2:1

potency, the distribution of these hypothetical data would be the same for both treatments. However, a stratified Wilcoxon test yields p values less than 0.0001 in favor of budesonide, indicating that the potency ratio in our study was not even close to 2:1.

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