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EDITORIAL

Steroids and peptic ulcer: an end to the controversy?

Introduction

Meta-analyses usually yield clear answers to focused questions. The possible association or corticosteroids with peptic ulcer is a remarkable exception to this rule.

Throughout almost 20 years of controversy, Conn and Chalmers with various coauthors, have produced a total of five analyses [1–5]. Conn did not find a relation between steroids and ulcers [1, 3] whereas Chalmers did [2, 4].

There are problems with all of the analyses, especially the earliest ones. The difficulties facing meta-analysts in this field are well illustrated by Conn & Poynard who noted ambiguities in the randomization, double-blindedness, selection criteria, or presentation of complications in more than half of the papers and in approximately 40% of all items evaluated [3]. They also identified important flaws in the meta-analyses, including Conn's own [3].

The good point about the paper published in this issue of the Journal [5] is that it appears to end the controversy. In the following Editorial, potential biases are discussed and suggestions of their probable impact are given when possible.

Selection of articles

Both Conn and Chalmers excluded articles in which complications were not clearly enumerated for each treatment group. This led to the exclusion of 30 of 147 trials in the latest meta-analysis [5]. This strategy would tend to cause bias in favour of Conn's hypothesis, because an article which described two ulcers in a steroid group but failed to state that there was none in the placebo group, would be excluded. It would therefore have been interesting to know whether the addition of the 30 excluded trials would have changed the conclusions of Conn's paper. In contrast, Chalmers' group seems to have included 14 trials in which complications were mentioned only for steroid-treated patients [3]. This difference could be an important reason for the different results of the opponents.

Chalmers' group included trials in which the steroid group received potentially ulcer-inducing chemotherapy [3]. Conn & Poynard pointed out a number of other problems, and claimed that 28 of their opponents 71 trials did not satisfy their own inclusion criteria [3].

Finally, both groups excluded many studies because of poor presentation of data; for example, 130 of 201 studies [2] and 54 of 147 studies [5]. Ironically, the study with most patients, a tuberculosis trial from 1965, stated simply that ulcer was as frequent in the placebo group, but gave no numbers. This study was excluded by Chalmers' group only.

Randomization

Both groups accepted pseudo-randomization such as date of birth or coin toss, although this may lead to exaggeration of the measured effect [6].

Whether the method leads to under- or over-ascertainment of side-effects is not known. However, for steroids it would probably lead to over-ascertainment of ulcers. When the randomization is not concealed, it may be difficult to maintain investigator blinding. Thus, the study with most ulcers, in which birth date was used as the allocation method, had been repeatedly unblinded [3].

The ulcer hypothesis has been known for a long time, and the threshold for sending patients for gastroscopy or X-ray could be lower when the physician knows that the patient is on steroids. This would reveal more silent ulcers in steroid-treated patients. As the prevalence of ulcer in the general population has been estimated to be as high as 5% [7], this could very well be a serious bias.

Blinding

Both groups included double-blind as well as non-double-blind studies. The association between steroids and ulcer was stronger in the non-blinded trials [2]. That this is probably a detection bias, as explained above, is supported by the fact that the

prevalence of peptic ulcer amongst the control patients in 34 unblinded studies was only 0.2%, whilst it was 1.5% in 37 double-blind studies [3].

Chalmers' group blinded the data extraction process. Although theoretically attractive, it remains to be proven that this laborious procedure leads to less bias than open data extraction.

Incidence or prevalence?

It was usually not possible to distinguish between prevalence and incidence of ulcers. If the prevalence is 5% and the incidence of new cases is 0.2% per year [7], it will be very difficult to detect an effect of steroids. Even a fivefold increase in ulcers would only increase the prevalence by 0.8% [7].

Unpublished data

Unpublished data tend to have smaller treatment effects than published ones [8]. Therefore, most meta-analysts now prefer to include unpublished data and to seek additional details from the authors, although the attempt may be frustrating at times.

To avoid potential response bias, Chalmers' group did not include such data. The direction of any bias is difficult to predict, as the original authors presumably were more interested in the effect than in the complications, and because few of the steroids were of commercial interest in the time-period studied.

Comparisons of the meta-analyses

In his first paper, Conn reported an ulcer rate of 1.0% in the controls and 1.4% in the steroid-treated patients in the double-blind studies [1]. Chalmers' group found rates of 0.8 vs. 1.8% ($P < 0.001$) for all trials and 1.5 vs. 2.6% when only double-blind trials were included (not statistically significant) [2].

After heavy criticism of the paper by Chalmers' group, Conn & Poynard redid their analysis [3], but even after exclusion of 10 studies, the *P*-value only changed from 0.04 to 0.06 and the relative risk from 1.4 to 1.3. Exclusion of the trial with the largest number of ulcers changed the values in a similar way. Inclusion of the large tuberculosis trial, assuming ulcer rates of either 1 or 4%, raised the *P*-value from 0.04 to 0.23, but again changed the relative risk only slightly, from 1.4 to 1.2.

Chalmers reproduced his earlier results later but only published a summary table [4].

In their present study, Conn & Poynard accuse Chalmers' group of a 'curious disparity' of more studies and fewer patients. In fact, it is the accusation which is curious, as Conn has given good reasons for the disparity earlier [3]. They also reserve the flaws to their opponents, although they previously admitted similar flaws in their own analysis.

The rate of new ulcers was only 0.3 vs. 0.4% in the present study, whereas the estimated annual incidences were 1.7 vs. 2.1% and symptoms compatible with ulcers occurred more often in steroid-treated patients ($P < 0.01$).

Conclusions

Conn & Poynard conclude that ulcer may be a rare complication of steroid therapy, but if so, it is clinically insignificant.

The inverse of the rate difference between two treatments is the number of patients one needs to treat to prevent one patient from getting a complication [9]. Assuming, for simplicity, that ulcer prophylaxis is 100% effective, between 100 and 1000 patients would need to be treated to avoid one ulcer, according to the rate estimates provided by the two research groups.

Thus, the conclusion of the present study seems valid: in clinical practice, one should not worry about any possible association between steroids and ulcers. Prophylaxis with anti-ulcer drugs appears to be unwarranted.

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