INOSINE PRANOBEX IN MUCOCUTANEOUS HERPES

SIR,—We read with interest Dr Mindel's letter (March 16, p 631) on the use of inosine pranobex for mucocutaneous herpes, particularly his comment about the need for properly conducted clinical studies showing a significant and consistent effect. We have just completed a large multicentre double-blind placebo-controlled study in domiciliary practice involving patients with herpes labialis. Full details will be published elsewhere but your readers may be interested in a summary of the results.

812 patients were randomised to receive a 7-day course of 1 g inosine pranobex four times daily (n=404) or matching placebo (n=408). The two treatment groups were well matched in terms of sex, age, primary (143 active, 168 placebo) or recurrent (261 active, 240 placebo) attacks, and other prognostic variables, including lesion stage (prodromal, vesiculation, exudation, or scab formation) on entry.

The clinical response (assessed as good, fair, poor, or no response on day 7) was highly significantly in favour of inosine pranobex in patients with both primary lesions ($p<0\cdot0001$ chi-squared test with Yates' correction) or recurrent episodes ($p<0\cdot001$). Patients given active therapy had a significantly better overall response than those taking placebo, irrespective of the stage of the lesion on presentation: prodromal ($p<0\cdot01$), vesiculation ($p<0\cdot0001$), and exudation ($p<0\cdot05$). Only in patients whose lesion(s) had already progressed to scab formation before therapy began was there no significant difference in the response to active or placebo medication. This finding was not unexpected.

Similarly, the mean reduction in total "symptom score" (based on the pre-treatment and post-treatment evaluation of pain, itching, and inflammation on a four point scale) was significantly greater in primary cases in the active group ($p<0\cdot01$, unpaired t-test with checking for unequal variance). The greatest symptomatic relief attributable to inosine pranobex was in relieving itching and reducing inflammation. This was particularly apparent for all patients with herpes labialis treated in the prodromal stage. Significantly fewer new lesions also developed in this group of patients given inosine pranobex ($p<0\cdot01$ chi-squared test with Yates' correction).

Inosine pranobex was well tolerated, with an equal number of minor adverse effects reported by patients in the placebo group. Only two patients stopped taking inosine pranobex because of side-effects. Seven similar cases were observed amongst patients given placebo.

This large placebo-controlled study shows that the use of inosine pranobex in patients with primary or recurrent herpes labialis produces a significantly beneficial effect in terms of overall response and in reducing the severity of associated symptoms.

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SIR,—Dr Mindel (March 16, p 631) argues against the statement in your Jan 26 editorial that inosine pranobex "looks clinically useful" in mucocutaneous herpes. Although a study I took part in years ago is misquoted, I agree in part with Mindel's general conclusion and would like to offer an explanation for the cloudiness surrounding this drug which has already been licensed for sale in sixty countries. Mindel cites an abstract and then complains about lack of detail. Had he attended the meeting in which the poster was presented (or indeed read the abstract carefully) he would know that the scoring system we used was simple and easy to understand; that the evaluations were not made at some "unspecified point in time"; that a statistical analysis was done showing the drug (22 patients) to be superior to placebo (20 patients) ($p<0\cdot01$); and that we did not claim that the drug "was very good" but that tolerance to it was very good. I have since left the hospital where this study was done but the trial was extended to 70 patients and the difference between placebo-treated and inosine pranobex treated patients remained significant.

Like Mindel, however, I do wonder why this and other studies which are on file with the manufacturers—and which most probably were used to justify the licensing of the drug—have not yet been published in full. Neither his letter nor your editorial mentions a double-blind, cross-over study in 18 patients, reported in full in 1983,[1] which showed no difference between placebo and inosine pranobex at a dosage of 1 g four times a day for 7 days.

An important point not, to my knowledge, adequately addressed by the manufacturers is the dosage. 3–4 g daily for 4–7 days was used in most studies. With this regimen we observed a biphasic effect in several patients and in medical staff (including myself)—ie, after 1 or 2 days of improvement in the burning sensation and objective signs, new lesions appeared at distant sites around the mouth resulting in worsening and extension of the relapse. Secondary generalisation of herpes zoster in a non-immunocompromised patient given 3 g inosine pranobex for 5 days has been reported.[2] I have previously commented on this point and suggested that in some patients the best regimen might be just 1 day of treatment with a total amount of 3 g.[3]

Inosine pranobex has immunopotentiating and immunosuppressive effects in vitro, immunosuppression being observed with high dosages.[4] Fundenberg's group[5] have treated nine patients with alopecia areata at a dosage of 50 mg/kg daily for 14 days and then 50 mg/kg for three days a week for 6 months; they reported induction of mitogen-dependent lymphokine production and an increase in T-cell rosette formation with transformed B cells. A dose-dependent response to inosine pranobex was found in only five patients. To my knowledge an immunosuppressive effect in vivo has not been demonstrated in man, but preliminary observations by Dr A. Pompidou (personal communication) suggest that while T helper cells appear to be stimulated early during treatment, T suppressor cells are stimulated a little later on.

I suggest that this biphasic effect may be both dose and treatment duration dependent but may vary from one patient to another.

Apart from the practical importance of such a possible dose-dependent effect, this problem may represent a major drawback to clinical trials since one patient may be unresponsive to or even have his illness aggravated by a dosage that benefits another.

I agree with your editorial's suggestion that inosine pranobex be compared to oral acyclovir. However, what daily dose and duration of therapy with inosine pranobex should be evaluated to induce which particular biological effect?

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UPPER INTESTINAL ENDOSCOPY

SIR,—Endoscopy has changed the face of gastroenterology in the past two decades, as many wise people have noted. Dr Clark's polemic (March 16, p 629) will be greeted with sadness by the many gastroenterologists in the UK who are attempting to provide effective clinical services under difficult circumstances. A similar lack of vision by some establishment figures in the early 1970s led to the formation of a Society for Digestive Endoscopy, separate from the British Society of Gastroenterology. This illogical split was healed 5 years ago, so that gastroenterology in Britain is again integrated. Most British doctors who perform endoscopy are well trained in gastroenterology, and realise that the endoscope is only a tool. Some concentrate much of their energy on endoscopy, others very little.

Much can be said about the interface between endoscopy and barium radiology, but to conclude, with highly selected references, that "there is then no real advantage for endoscopy over radiology in making a diagnosis" flies in the face of experience. Furthermore, to suggest that too many endoscopies are being done in Britain is to show profound ignorance of the real world, where many patients are