Plasma prednisolone levels during intravenous therapy in acute colitis

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SUMMARY Maximum plasma levels in six acute colitics were about three times greater after an intravenous bolus of 20 mg prednisolone than the mean level achieved during infusion of the same dose (p<0.001) over eight hours; the level during infusion was about twice as great as the maximum recorded previously after a single 40 mg oral dose of prednisolone. These findings favour the use of intravenous administration in severe acute colitis. No difference was found between plasma levels of patients and six normal subjects after the intravenous bolus.

Severe acute colitis is generally managed by the use of intravenous rather than oral steroids. Prednisolone is widely chosen because of its low mineralocorticoid potency as compared with hydrocortisone. This study compares plasma prednisolone levels, measured by radioimmunoassay, after commonly used intravenous dosage schedules. After a bolus of intravenous prednisolone in patients with severe acute colitis the levels obtained were compared with those obtained after the same bolus dose administered to normal subjects. Plasma prednisolone levels were also measured in the patients during continuous infusion.

Method

CLINICAL
Six patients with severe acute colitis (Table) and six healthy volunteers were studied after obtaining their informed consent. After a bolus dose of 20 mg prednisolone intravenously blood samples were withdrawn from the opposite arm via an indwelling venous needle before and 30, 60, 90, 120, 150, 180, 240, 360, and 480 minutes after the dose (the 480 minute sample was omitted in controls). An intravenous infusion of 60 mg prednisolone in 5% dextrose over 24 hours was maintained for at least 24 hours before and continued during withdrawal of five samples at intervals of 120 minutes. Each sample was centrifuged and the plasma was stored at −20°C until analysis.

LABORATORY TECHNIQUES
Prednisolone and free prednisolone were measured according to the techniques previously described. It became apparent in the course of the study that the antiserum, which had been raised in sheep against prednisolone-21-hemisuccinate, though measuring prednisolone alcohol, detected only 0.7% of the 21-phosphate ester. The assay was therefore repeated after hydrolysis. One millilitre of plasma was extracted with ethyl acetate, redissolved in phosphate buffer, and hydrolysed with 0.1M hydrochloric acid. The mixture was re-extracted with ethyl acetate, dried down, and the residue redissolved in phosphate buffer. Radioimmunoassay was performed on this residue and the overall recovery for the procedure was between 85 and 90%. Plasma levels quoted in this paper are those obtained after hydrolysis of the ester unless otherwise specifically indicated.

STATISTICAL METHODS
The statistical significance of the results was estimated using Student's t test.

Results

BOLUS
No significant difference was found between plasma prednisolone values for patients and control subjects (Fig. 1). The mean peak levels were 986±35 ng/ml and 956±22 ng/ml respectively.
Plasma prednisolone levels during intravenous therapy in acute colitis

Table Details of patients studied

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age (yr)</th>
<th>Diagnosis</th>
<th>Extent of disease</th>
<th>Temperature* (°C)</th>
<th>Bowel actions/24 h</th>
<th>Haemoglobin+ (g/dl)</th>
<th>ESR (mm/h)</th>
<th>Baseline albumin (g/l)</th>
<th>Operation same admission</th>
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<tbody>
<tr>
<td>M</td>
<td>78</td>
<td>UC</td>
<td>Extensive</td>
<td>38</td>
<td>15</td>
<td>7.3</td>
<td>21</td>
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<tr>
<td>M</td>
<td>73†</td>
<td>UC</td>
<td>Extensive</td>
<td>36</td>
<td>Fluid colostomy output</td>
<td>13.6</td>
<td>49</td>
<td>31</td>
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<tr>
<td>F</td>
<td>24</td>
<td>Crohn's</td>
<td>Extensive</td>
<td>37*</td>
<td>11</td>
<td>10.8</td>
<td>50</td>
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<tr>
<td>F</td>
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<td>Indeterminate</td>
<td>Substantial</td>
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<tr>
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<tr>
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<td>Extensive</td>
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<td>5</td>
<td>10.4</td>
<td>55</td>
<td>27</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Highest in first 48 hours. † Lowest in first 48 hours. ‡ Previous sigmoid colectomy.

Wide variation was found between individuals in both groups in the amount of prednisolone alcohol detected before chemical hydrolysis of the ester. Prehydrolysis values varied from 16 to 99% of the total value after hydrolysis. There was no correlation with serum albumin.

CONTINUOUS INFUSION

The mean value of plasma prednisolone was 353±64 ng/ml of which 95±2% (SEM) was present as prednisolone alcohol rather than as the phosphate ester. There was variation in the values obtained in individual patients during continuous infusion as reflected in the SEM.

The maximum prednisolone value obtained in patients after a bolus of 20 mg was significantly higher (p<0.001) than the mean infusion level (Fig. 2).

Discussion

It is of interest to compare this study with a previous study of prednisolone levels after a 40 mg oral dose in acute colitics and normal controls,2 as shown in

![Graph](http://gut.bmj.com/)

Fig. 1 Plasma prednisolone after 20 mg prednisolone (as prednisolone-21-phosphate) intravenous bolus (mean ± SEM).
Fig. 2. In that study, a lower peak level and slower rate of drug disappearance in patients indicated delayed gastrointestinal absorption; in this study the gastrointestinal tract was bypassed and the prednisolone levels of patients and normal subjects were not significantly different.

Comparison of the two drug curves shows that the maximum level of $986\pm35$ ng/ml after a bolus of 20 mg intravenously is nearly five times greater than after an oral dose of 40 mg ($p<0.0005$), and the levels remain significantly greater until four hours after administration. When 20 mg prednisolone is delivered as an infusion over the eight-hour observation period the mean level of $353\pm64$, though approximately one-third the maximum bolus level, was also significantly greater than the maximum oral level of $206\pm35$ ng/ml ($p<0.05$).

It is widely held that intravenous therapy is more effective than oral corticosteroid therapy in acute colitis, although there has been no controlled trial. Oral treatment with prednisolone is frequently given as a single daily dose of 40 mg daily but the present results show that the maximum plasma level is almost doubled by giving a constant intravenous infusion of half that dose over eight hours and increased five-fold after an intravenous bolus dose of 20 mg. The results shown are limited to eight hours, but, in clinical practice, 60 mg given every 24 hours would either maintain a constant level over that period by infusion or give three peaks, one every eight hours. It is not known whether repeated high peak levels are of greater therapeutic benefit than a constant but lower concentration; this question can be answered only by a controlled clinical trial.

Two previous studies in patients with severe acute colitis have reported on plasma cortisol levels during hydrocortisone infusion, but in neither was there a correlation between the levels observed and the clinical outcome. In less severe colitis prednisone, 20 mg daily by mouth in divided doses, was less effective than 40 mg daily, though no further benefit was shown using a 60 mg dose. No information is available on the minimum plasma level associated with a therapeutic response, nor on the optimal therapeutic level in different types of colitis.

The observation that the rate of hydrolysis of prednisolone-21-phosphate, presumably to prednisolone alcohol, varies from patient to patient after intravenous injection was unexpected. It is not known whether or not the ester is biologically active. If the ester is not active the rate of hydrolysis...
Plasma prednisolone levels during intravenous therapy in acute colitis would affect the response to an intravenous bolus dose. The rate of hydrolysis does not affect the response to oral therapy or constant slow infusion, as in these circumstances practically all the prednisolone is present in the hydrolysed form.

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References

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