

*Leading article*

## Toward optimal use of corticosteroids in ulcerative colitis and Crohn's disease

Gastroenterologists have cause for pride in two classics of the medical literature. The collaborative trial of cortisone in ulcerative colitis was well timed, bold in concept and design, and a model of clarity.<sup>1</sup> Over 20 years passed before a similar large scale trial was undertaken in active Crohn's disease but the result was the same: corticosteroid treatment was validated and its role was better defined.<sup>2</sup>

The rationale of corticosteroid treatment in these two disorders remains unknown. In experimentally induced inflammation corticosteroids decrease capillary permeability, reduce migration of macrophages and polymorphonuclear cells into the inflamed area, interfere with phagocytosis of antigens by macrophages, stabilise lysosomal membranes, and inhibit cell-mediated immunity.<sup>3</sup> Until we know the predominant action of these drugs in ulcerative colitis and Crohn's disease we cannot hope to design specific treatments aimed at altering particular aspects of the inflammatory response. The lack of animal models is a hindrance and at present studies have to be made on human tissue. Showing that corticosteroids inhibit prostaglandin synthesis in tissue culture of rectal biopsies from patients with ulcerative colitis is an example of a method which could be explored further.<sup>4</sup>

Until more data of this type are available, we must make the best use possible of other measurements available to us. Therapeutic trials measure clinical response and by this means we can answer questions about the relative efficacy of different types of corticosteroid, of different dose schedules or modes of administration, or of the same treatment in different types of disease. The other measurement which can give useful information is that of drug levels in body fluids or tissues.

Techniques for the measurement of cortisol have yielded useful information about endogenous steroid secretion and treatment with corticotrophin or hydrocortisone itself.<sup>5–7</sup> Synthetic glucocorticoids, however, such as prednisone or prednisolone, are more commonly used in treatment and these drugs have proved difficult to assay in therapeutic doses. Several techniques have become available in recent years including radioimmunoassay, competitive protein binding, chromatographic, and isotopic methods.<sup>8</sup> As a result much information is now available about the pharmacokinetics of these drugs.<sup>8 9</sup>

Even though drug levels can be measured the results are difficult to interpret in clinical terms because the biological effects of the drug on endogenous cortisol secretion, or on experimentally induced inflammation persist longer than would be predicted from the plasma level. Thus the plasma half-life of prednisolone after intravenous administration is around three to four hours, but the biological half-life is 18–36 hours.<sup>3 8 9</sup>

Furthermore, although anti-inflammatory activity appears to be quantitatively related to the concentration of active steroid in the tissue,<sup>3</sup> no clear relation has been observed between plasma level achieved and the therapeutic response in colitis.<sup>6,7</sup> The situation is further complicated by the fact that therapeutic activity (and the liability to side effects) are related, not to total drug levels, but to drug levels unbound to protein. The main proteins concerned are transcortin (corticosteroid binding globulin) with low capacity and high affinity, and albumin, with high capacity but low affinity. It can be predicted that at low drug doses a greater proportion of the drug will be bound to protein than at higher doses and measurements show that with decreasing levels of serum albumin the proportion of free prednisolone rises with an associated increase in drug side effects.<sup>10</sup>

The elegant paper by Shaffer and his colleagues in this issue shows the value of studying corticosteroid absorption when the intestine is diseased.<sup>11</sup> When compared with a normal control group, absorption of prednisolone given by mouth was reduced in seven patients with Crohn's disease as judged by isotopic measurements in plasma, urine, and faeces (three patients). All but one of the patients had ileal disease of mild to moderate severity, but there was no steatorrhoea or excess protein loss from the gut. These observations differ from those of Tanner *et al* who found, by measurement of prednisolone serum levels using a specific radioimmunoassay, that the mean peak levels and areas under the curve were not significantly different from normal in nine patients with Crohn's disease given 20 mg of prednisolone by mouth.<sup>12</sup> There was, however, greater variation in the patients than in the control subjects. Five of their nine patients had disease predominantly involving the colon and it is noteworthy that the two highest prednisolone levels recorded were in such patients, and the two lowest were in patients with small bowel involvement. Four of the five patients with colonic disease underwent colectomy and the authors comment that serum levels were particularly high in those with the most active disease.

The observations of Shaffer *et al* cannot therefore be extrapolated to every patient with Crohn's disease. Their work now needs to be extended to compare prednisolone absorption in patients with Crohn's disease having small or large bowel involvement, and having slight or severe evidence of inflammation. Their technique should also be used to study patients with ulcerative colitis of differing severity for there is evidence that absorption of prednisolone given by mouth is delayed, if not necessarily decreased, in a severe acute attack.<sup>13</sup>

Prednisolone is often used in the outpatient treatment of small bowel Crohn's disease and the observation that absorption may be decreased is particularly relevant to long-term treatment. So far there is no support from controlled therapeutic trials to justify the use of prednis(ol)one in a relatively small dose over a period of months or years in patients with quiescent disease with the aim of preventing relapse.<sup>2,14,15</sup> Clinicians are therefore taught to withdraw corticosteroids as soon as possible after treatment of an acute attack. As the dose of corticosteroid is progressively reduced, however, patients often tell us that their symptoms become worse below a certain level, often around 10 mg of prednisolone daily. Perhaps we are being overcautious because, if not all of the dose is absorbed, benefit is actually being achieved with a smaller systemic dose than we

think and the risk of side effects is correspondingly decreased. Is it possible that the hypothetical 'threshold' level corresponds to a dose at which a relatively high proportion of the prednisolone absorbed is bound to protein and is thus biologically inactive?

The possible benefit of long-term corticosteroid therapy in controlling chronic inflammation can only be investigated by a controlled trial in which clinical and pharmacological measurements are combined. If relapses of disease occur in some patients after treatment of an acute relapse as prednisolone is withdrawn, but less frequently in other patients in whom a constant therapeutic dose is maintained, then the lowest effective dose which maintains remission can be correlated with drug levels in the body.

Similar considerations apply to the treatment of ulcerative colitis. In this disease we need to establish whether or not there is a legitimate distinction between the prevention of relapse, implying that there is complete 'remission' with absence of inflammation, and suppression of continued lowgrade inflammation. Prednisone, 15 mg daily over six months did not appear to prevent relapse.<sup>16</sup> It is possible, however, that prolonged corticosteroid treatment can suppress persistent inflammation. A controlled trial of similar design to that already described is indicated in patients with chronic continuous disease. It would also be interesting in such trials to study the synergistic effect of azathioprine which appears, as in other inflammatory disorders, to exert a steroid sparing effect in both Crohn's disease and ulcerative colitis.<sup>17 18</sup>

Little is known about the relative therapeutic merits in acute ulcerative colitis and Crohn's disease of corticosteroids given either intermittently to produce short lived high peak drug levels, or near continuously to yield a relatively constant lower level of drug in the blood.<sup>19</sup> This is another appropriate question for study by controlled trial. Intermittent doses may have some advantage in avoidance of side effects and convenience. Thus prednisolone given in one dose of 40 mg daily appears to be as effective as the same total dose spread through the day in the treatment of acute colitis.<sup>20</sup> The same dose of prednisolone on alternate mornings, at a time when the blood cortisol is highest, has given encouraging results in active chronic colitis.<sup>21</sup> Results in other disorders suggest that long term suppression of endogenous corticosteroid secretion is reduced, or absent with such an alternate day regime.<sup>22 23</sup>

Few attempts have yet been made to establish by prospective trial a relationship between dose and response in acute disease. There is some evidence in ulcerative colitis that prednisone 40 or 60 mg daily is more effective than 20 mg daily.<sup>24</sup> It seems likely that there is a threshold dose below which no therapeutic activity is detectable, but there is a maximal dose beyond which no further benefit accrues, and graded response between these two extremes. Can we distinguish differences between those patients who respond and those who do not? Are we so constrained by justifiable fear of corticosteroid therapy that we withhold adequate treatment until late in the disease when structural change has supervened? Ought we to investigate the possible benefit of giving a single large dose, or a very few smaller doses of a corticosteroid at the first symptoms of recurrent inflammation, before damage to the mucosa has occurred?

Levels of corticosteroid in body fluids are relatively easier to measure than the critical therapeutic levels in the inflamed tissue. Topical

corticosteroids applied from the lumen of the gut, are frequently used in the treatment of inflammatory bowel disease with the aim of attaining high tissue levels in the involved mucosa and there is at present interest in the properties of corticosteroids which are poorly absorbed into the blood.<sup>25 26</sup> Studies in the rat have shown that a well absorbed drug such as prednisolone enhances the absorptive and digestive capacities of enterocytes but has little effect on mucosal structure or cell kinetics. An equivalent dose of betamethasone-17-valerate, a locally acting corticosteroid, has a similar effect on the enterocytes, but also inhibits crypt cell turnover with marked hypoplasia of the jejunal mucosa.<sup>27</sup> Careful studies of the effect of poorly absorbed corticosteroids on the mucosa of the normal small and large intestine are thus needed, in addition to therapeutic trials.

An outside observer could justly express some disappointment about the progress made over the last 27 years in exploiting the knowledge that cortisone can benefit a patient with colitis. New techniques and sharpening of interest may enable us to build more rapidly on the foundation of knowledge now available, so that we can learn in the next few years how to achieve maximal benefit with minimal adverse effects from these useful drugs.

J E LENNARD-JONES

*Academic Unit of Gastroenterology  
The London Hospital  
Whitechapel, London E1 1BB*

#### References

- 1 Truelove SC, Witts LJ. Cortisone in ulcerative colitis: final report on a therapeutic trial. *Br Med J* 1955; **2**: 1041–8.
- 2 Summers RW, Switz DM, Sessions Jr JT, Bektel JM, Best WR, Kern Jr F, Singleton JW. National Cooperative Crohn's Disease Study: results of drug treatment. *Gastroenterology* 1979; **77**: 847–69.
- 3 Swartz SL, Dluhy RG. Corticosteroids: clinical pharmacology and therapeutic use. *Drugs* 1978; **16**: 238–55.
- 4 Hawkey CJ, Truelove SC. Effect of prednisolone on prostaglandin synthesis by rectal mucosa in ulcerative colitis: investigation by laminar flow bioassay and radioimmunoassay. *Gut* 1981; **22**: 190–3.
- 5 Friedman M, Hinton JM, Lennard-Jones JE. Adrenal and clinical responses to corticotrophin and prednisone in inflammatory disease of the colon. *Gut* 1969; **10**: 194–7.
- 6 Kaplan HP, Portnoy B, Binder HJ, Amatruda T, Spiro H. A controlled evaluation of intravenous adrenocorticotrophic hormone and hydrocortisone in the treatment of acute colitis. *Gastroenterology* 1975; **69**: 91–5.
- 7 Powell-Tuck J, Buckell NA, Lennard-Jones JE. A controlled comparison of corticotrophin and hydrocortisone in the treatment of severe proctocolitis. *Scand J Gastroenterol* 1977; **12**: 971–5.
- 8 Pickup ME. Clinical pharmacokinetics of prednisone and prednisolone. *Clin Pharmacokinet* 1979; **4**: 111–28.
- 9 Al-Habet S, Rogers HJ. Pharmacokinetics of intravenous and oral prednisolone. *Br J Clin Pharmacol* 1980; **10**: 503–8.
- 10 Lewis GP, Jusko WJ, Burke CW, Graves L. Prednisone side-effects and serum protein levels. *Lancet* 1971; **2**: 778–81.
- 11 Shaffer JL, Williams SE, Turnberg LA, Houston JB, Rowland M. Absorption of prednisolone in patients with Crohn's disease. *Gut* 1983; **24**: 182–6.
- 12 Tanner AR, Halliday JW, Powell LW. Serum prednisolone levels in Crohn's disease and coeliac disease following oral prednisolone administration. *Digestion* 1981; **21**: 310–5.

- 13 Elliott PR, Powell-Tuck J, Gillespie PE *et al*. Prednisolone absorption in acute colitis. *Gut* 1980; **21**: 49–51.
- 14 Smith RC, Rhodes J, Heatley RV *et al*. Low dose steroids and clinical relapse in Crohn's disease: a controlled trial. *Gut* 1978; **19**: 606–10.
- 15 Bergman L, Krause U. Postoperative treatment with corticosteroids and salicylazosulphapyridine (Salazopyrin) after radical resection for Crohn's disease. *Scand J Gastroenterol* 1976; **11**: 651–6.
- 16 Lennard-Jones JE, Misiewicz JJ, Connell AM, Baron JH, Jones FA. Prednisone as a maintenance treatment for ulcerative colitis in remission. *Lancet* 1965; **1**: 188–9.
- 17 Lennard-Jones JE. Azathioprine and 6-mercaptopurine have a role in the treatment of Crohn's disease. *Dig Dis Sci* 1981; **26**: 364–8.
- 18 Kirk AP, Lennard-Jones JE. Controlled trial of azathioprine in chronic ulcerative colitis. *Br Med J* 1982; **284**: 1291–2.
- 19 Berghouse LM, Elliott PR, Lennard-Jones JE, English J, Marks V. Plasma prednisolone levels during intravenous therapy in acute colitis. *Gut* 1982; **23**: 980–3.
- 20 Powell-Tuck J, Bown RL, Lennard-Jones JE. Comparison of oral prednisolone given as single or multiple daily doses for active proctocolitis. *Scand J Gastroenterol* 1978; **13**: 833–7.
- 21 Powell-Tuck J, Bown RL, Chambers TJ, Lennard-Jones JE. A controlled trial of alternate day prednisolone as a maintenance treatment for ulcerative colitis in remission. *Digestion* 1981; **22**: 263–70.
- 22 Anonymous. When to try alternate-day corticosteroid therapy. *Drug Ther Bull* 1976; **14**: 49–51.
- 23 Bakran I, Korsic M, Durakovic Z, Vrhovac B, Tajic M. The effect of alternate-day prednisone therapy on cortisol secretion rate in corticosteroid-dependent asthmatics. *Int J Clin Pharmac* 1977; **15**: 57–60.
- 24 Baron JH, Connell AM, Kanaghinis TG, Lennard-Jones JE, Jones FA. Out-patient treatment of ulcerative colitis: comparison between three doses of oral prednisone. *Br Med J* 1962; **2**: 441–3.
- 25 Lee DAH, Taylor M, James VHT, Walker G. Rectally administered prednisolone – evidence for a predominantly local action. *Gut* 1980; **21**: 215–8.
- 26 Kumana CR, Seaton T, Meghji M, Castelli M, Benson R, Thillainathan S. Beclomethasone dipropionate enemas for treating inflammatory bowel disease without producing Cushing's syndrome or hypothalamic pituitary adrenal suppression. *Lancet* 1982; **1**: 579–83.
- 27 Batt RM, Scott J. Response of the small intestinal mucosa to oral glucocorticoids. *Scand J Gastroenterol* 1982; **17**: suppl 74: 75–88.