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ALTERATION OF PLASMA PREDNISOLONE LEVELS BY INDOMETHACIN AND NAPROXEN

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Eleven patients with stable rheumatoid disease (RD) who were receiving regular corticosteroid therapy (CS) were investigated to discover the effect on plasma prednisolone levels of additional therapy with the non-steroidal anti-inflammatory (NSAI) drugs, indomethacin and naproxen. There was a highly significant ($P < 0.001$) increase in free prednisolone levels after concurrent therapy with either indomethacin or naproxen for 2 weeks. Total prednisolone levels were unchanged. These results could provide an explanation for clinical reports that these two NSAI drugs possess a steroid-sparing effect.

Introduction

Prednisolone is an effective drug for controlling the symptoms of active rheumatoid disease (RD) although its value is limited by the high incidence of side effects.

In order to attain the lowest effective daily dose of prednisolone a NSAI drug is usually prescribed simultaneously. Previous work suggests that NSAI drugs act as steroid-sparing agents. This study was therefore designed to investigate whether these drugs alter plasma prednisolone levels. Indomethacin and naproxen were selected for investigation as they are commonly prescribed.

Methods

Eleven patients (five male, six female; aged 53–82, mean 68 years) with stable chronic RD, diagnosed according to American Rheumatism Association criteria (Ropes *et al.*, 1959), gave their informed consent to take part in the study.

All were receiving regular prednisolone therapy (2.5–10 mg daily, mean 5.1 mg) for between 1 and 23 years, mean 7.1 years. All were generally healthy with no history of hepatitis, renal or gastro-intestinal disease: pre-study liver function tests and serum electrolytes were normal. The haemoglobin ranged from 12.5–15.5 g/100 ml (mean 14.05 g/100 ml); the ESR from 14–62 (mean 33) mm.

Patients continued taking their normal daily dose of prednisolone and drugs required for other medical conditions throughout the trial but stopped taking additional anti-inflammatory or analgesic drugs 48 h before the start of the study. On Day 1 of the trial no drugs were taken until a blood sample (for serum albumin and basal plasma prednisolone levels) had been obtained at 09.00 h. Each patient then received 7.5 mg soluble prednisolone BP orally. Further blood samples were taken at 1, 2, 4 and 6 h.

The patients were then assigned to one of two groups, receiving either Indocid® 75 mg twice daily or Naproxen 250 mg twice daily for 14 days. On Day 15 of the trial, the routine followed on Day 1 was repeated with patients taking the morning dose of indomethacin or naproxen in addition to 7.5 mg prednisolone. Four patients who had received indomethacin were given naproxen for a further 14 days, after which the same investigative procedure was repeated. Patients were advised to eat their usual breakfast at the same time before each hospital attendance. Paracetamol was prescribed as an escape analgesic (1 g as required until 48 h before each attendance).

Blood samples were separated immediately and the plasma stored at −20°C until analysed. Total plasma prednisolone levels were measured by radioimmunoassay (Henderson *et al.*, 1979), and free prednisolone by an equilibrium-dialysis technique (Elliot *et al.*,

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1980). Serum albumin was determined on a Technicon SMA II by standard methods.

Results

The results for total plasma prednisolone levels are shown in Table 1. Peak levels of 124 ng/ml (± 6) were reached after 1 h, falling by 50% to 62 ng/ml (± 9) by 6 h. No significant differences were obtained after the addition of indomethacin or naproxen.

Free plasma prednisolone levels, expressed as a percentage of the total, are shown in Table 2. When compared with the control levels, a significant increase in free prednisolone levels was detected following addition of indomethacin or naproxen to the therapeutic regime.

Serum albumin levels varied from 32–45 g/l, mean 37.2 g/l (normal range 36–52 g/l). No patient showed any significant change between attendances.

Discussion

We have demonstrated that 14 days therapy with indomethacin or naproxen produces a significant increase in the free fraction of prednisolone.

Indomethacin and naproxen are both acidic and highly protein-bound drugs. As such they might be expected to compete for protein-binding sites with prednisolone and endogenous corticosteroids (CS). Previous studies on endogenous CS have produced conflicting results: Stenlake *et al.* (1969) reported that NSAI drugs, including indomethacin, did not affect the protein binding of 11-hydroxycorticosterone while Brodie (1965) found that indomethacin produced an increase of 10–40% in the unbound fraction.

Several factors could have influenced these results. Concomitant administration of other drugs is known to displace steroids from protein-binding sites (Brodie, 1965). However, in this study the only additional drugs were those required for unrelated clinical conditions and all these were unchanged throughout the trial. Variable post-prandial absorption of prednisolone has been reported (Henderson *et al.*, 1979) but this effect was minimised by advising patients to eat their usual breakfast at the same time before attendance. Free plasma prednisolone levels may also be affected by hypoalbuminaemia (Lewis *et al.*, 1971) but although the levels recorded in this study were at the lower limits of normal they remained constant for each patient.

The clinical effects of a protein-bound drug are generally considered to be exerted by the free fraction

Table 1 The effect of codosing with indomethacin or naproxen on total plasma prednisolone levels after an oral dose of 7.5 mg soluble prednisolone.

Therapy	*Time after ingestion (h)*				
	0	*1*	*2*	*4*	*6*
Prednisolone alone $n = 11$	Not detected	124 ± 6	116 ± 7	94 ± 8	62 ± 9
Prednisolone + indomethacin $n = 8$	Not detected	95 ± 11	117 ± 6	100 ± 7	64 ± 7
Prednisolone + naproxen $n = 7$	Not detected	124 ± 10	121 ± 6	90 ± 8	50 ± 6

Results expressed as mean total plasma prednisolone in ng/ml (± s.e. mean).

Table 2 The effect of codosing with indomethacin or naproxen on free plasma prednisolone after an oral dose of 7.5 mg soluble prednisolone.

Therapy	*Time after ingestion (h)*				
	0	*1*	*2*	*4*	*6*
Prednisolone alone $n = 11$	Not detected	14.2 ± 0.7	9.5 ± 0.5	8.7 ± 0.3	6.5 ± 0.3
Prednisolone + indomethacin $n = 8$	Not detected	14.2 ± 1	12.4 ± 0.5*	12.2 ± 0.5*	10.5 ± 0.7*
Prednisolone + naproxen $n = 7$	Not detected	16.2 ± 1	12.7 ± 0.6*	11.6 ± 0.5*	9.4 ± 0.2*

Results of free plasma prednisolone expressed as mean % total plasma prednisolone (± s.e. mean).
* Significantly different from control free prednisolone levels (Student's *t*-test, $P < 0.001$).

(Brodie, 1965; Koch Weser, 1972). Our results show that indomethacin and naproxen increase the free prednisolone fraction and therefore should act as steroid-sparing agents allowing a reduction in the daily dose of prednisolone whilst maintaining the same therapeutic effect. Several clinical studies support this hypothesis (Cury & Pernambuco, 1977; Flores & Rojas, 1975; Mathies & Wolff, 1975; Morkel, 1966; Rothermich, 1966).

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