THE EFFECT OF FRUSEMIDE ON INDOMETHACIN PLASMA LEVELS

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- 1 The pharmacokinetic and clinical effects of concurrent oral indomethacin and frusemide administration were determined in eight patients with rheumatoid arthritis.
- 2 Oral frusemide significantly reduces the plasma level of indomethacin following concurrent administration of the two drugs orally.
- 3 A profile of pain index, articular index and grip strength following oral indomethacin (50 mg) was determined and although the decrease in articular index was less when frusemide and indomethacin were given together it did not reach statistical significance.

Introduction

Indomethacin is one of the most commonly used therapeutic agents in rheumatology (Lee, Ahola, Grennan, Brooks & Buchanan, 1974). It vies with aspirin as the drug of first choice in rheumatoid arthritis and seems to have particular value in certain clinical situations such as the relief of night pain in rheumatoid and osteoarthritis. It is also considered by some to be the drug of first choice in acute gout and ankylosing spondylitis.

Multiple drug therapy is common in patients with rheumatoid arthritis (Lee *et al.*, 1974) and potential interactions commonly occur (Mason, Brooks, Lee, Kennedy & Buchanan, in preparation). The therapeutic implications of the interaction of probenecid and indomethacin have already been described (Brooks, Bell, Sturrock, Famaey & Dick, 1974).

Patients with rheumatoid arthritis sometimes develop ankle oedema as a consequence of joint inflammation or associated congestive cardiac failure. As diuretics are used in both these situations we thought it of interest to investigate the acute effect of a potent diuretic frusemide on indomethacin levels in the plasma, at the same time monitoring the clinical response of the patient.

Methods

Eight patients with sero-positive rheumatoid arthritis according to the American Rheumatism Association criteria (Ropes, Bennett, Cobb, Jacox & Jessar, 1959) were studied on consecutive days. Five patients were female and three were male. The mean age of the patients was 53 years with a

range of 35-75 years. The mean duration of arthritis was 8 years with a range of 2-15 years.

All patients had been controlled with oral indomethacin and therapy was stopped 12 h before the test was commenced. All tests were commenced 2 h after a light lunch.

A 19 gauge butterfly needle was inserted into a forearm vein to facilitate blood sampling. Blood was collected at time 0 and at 30, 60, 90, 120 and 180 min following an oral dose of indomethacin (50 mg). The blood was collected in lithium-heparin tubes, centrifuged for 15 min at 2000 rev/min and the supernatant stored at -10°C . A 6 h sample of urine was also collected from the time of indomethacin ingestion and stored at -10°C .

The following day the indomethacin plasma profile was repeated but this time frusemide (40 mg) was administered together with indomethacin (50 mg). A 6 h urine specimen was again collected following the dose of indomethacin and frusemide.

At the same time that blood was withdrawn for indomethacin estimation the degree of pain was assessed by performing an articular index of joint tenderness (Ritchie, Boyle, McInnes, Jasani, Dalakos, Grieson & Buchanan, 1967) and the patients were also asked to assess their pain using a pain-assessment chart (Lee, Webb, Anderson & Buchanan, 1973). A measure of grip strength of the right and left hand using a rubber bag attached to an ordinary mercury sphygmomanometer and inflated to 30 mmHg before testing was also made (Lee, Baxter, Dick & Webb, 1974).

The indomethacin concentration in the plasma and urine was measured by a double extraction

spectrofluorimetric method extracting into heptane and then sodium carbonate as described by Hucker, Daccher, Cox, Brodie & Carswell (1966), and modified by Emori, Champion, Bluestone & Paulus (1973).

A water blank and plasma standards containing indomethacin (1 µg/ml-5 µg/ml) were analysed with each set of determinations.

No interference was seen in the fluorimetric determination of indomethacin when frusemide in concentrations of 5 µg/ml, 10 µg/ml, 15 µg/ml and 20 µg/ml was added to indomethacin plasma standards containing indomethacin (2 µg/ml and 5 µg/ml).

Statistical analysis of the results was carried out using the Student's *t* test for paired variants.

Results

Plasma concentrations

The plasma concentration profile of oral indomethacin (50 mg) is seen in Table 1. These results parallel closely those already reported (Brooks *et al.*, 1974). The plasma levels of indomethacin are lower after concurrent

administration of frusemide (40 mg) and the difference in levels reaches statistical significance for the 30 and 60 min samples ($P < 0.05$). There is also a statistically significant increase in the 6 h urinary excretion of indomethacin when frusemide is taken with indomethacin.

Articular index

The articular index decreases as the level of plasma indomethacin rises but the changes are slightly delayed (Table 2). The lowest articular indices in our study occurred at 120 min and the articular index then began to increase. Although the articular indices after ingestion of indomethacin and frusemide together were higher than following indomethacin alone, the difference did not reach statistical significance.

Pain score

The pain score also decreased with increasing indomethacin plasma levels but did not show any rise within the time span studied (3 h) (Table 3). Although pain score values were higher when frusemide was given with indomethacin, the difference was not statistically significant.

Table 1 Indomethacin plasma levels (mean $\pm$ s.e. mean, $n = 8$) following oral indomethacin (50 mg) alone and together with frusemide (40 mg)

	Time (min)					Mean 6 h urinary excretion of indomethacin (µg)
	0	30	60	120	180	
Indomethacin plasma level (µg/ml)	0	2.4 $\pm$ 0.47	2.48 $\pm$ 0.4	1.56 $\pm$ 0.08	1.3 $\pm$ 0.12	1044 $\pm$ 154
Indomethacin plasma level with frusemide (µg/ml)	0	1.4 $\pm$ 0.26	1.8 $\pm$ 0.25	1.4 $\pm$ 0.18	1.2 $\pm$ 0.15	1879 $\pm$ 327
<i>P</i>		<0.05	<0.01	NS	NS	<0.025

Table 2 Articular index profile (mean $\pm$ s.e. mean, $n = 8$) following oral indomethacin (50 mg) alone and together with frusemide (40 mg)

	Time (min)				
	0	30	60	120	180
Articular index on indomethacin	20.87 $\pm$ 3.97	18.25 $\pm$ 4.01	14.13 $\pm$ 3.38	13.62 $\pm$ 3.4	14.37 $\pm$ 3.76
Articular index on indomethacin and frusemide	20.37 $\pm$ 3.69	18.12 $\pm$ 3.8	16.6 $\pm$ 4.2	13.87 $\pm$ 3.26	15.12 $\pm$ 3.8
<i>P</i>	NS	NS	NS	NS	NS

Table 3 Pain score (mean $\pm$ s.e. mean, $n = 8$) following oral indomethacin (50 mg) alone and together with frusemide (40 mg)

	<i>Time (min)</i>				
	0	30	60	120	180
Pain score on indomethacin	2.5 $\pm$ 0.378	2.0 $\pm$ 0.378	1.37 $\pm$ 0.375	1.13 $\pm$ 0.226	1.13 $\pm$ 0.226
Pain score on indomethacin and frusemide	2.5 $\pm$ 0.378	2.12 $\pm$ 0.295	1.625 $\pm$ 0.375	1.37 $\pm$ 0.375	1.25 $\pm$ 0.313
<i>P</i>	NS	NS	NS	NS	NS

Table 4 Grip strengths (mean $\pm$ s.e. mean, $n = 8$) following oral indomethacin (50 mg) alone and together with frusemide (40 mg)

	<i>Time (min)</i>				
	30	60	90	120	180
Grip strength (mmHg) following indomethacin:					
Right hand	99 $\pm$ 12	102 $\pm$ 11.6	102 $\pm$ 9.92	104 $\pm$ 9.5	104 $\pm$ 10.75
Left hand	104 $\pm$ 10.5	106 $\pm$ 9.16	104 $\pm$ 9.29	103 $\pm$ 7.7	106 $\pm$ 10.04
Grip strength (mmHg) following indomethacin and frusemide:					
Right hand	107 $\pm$ 11	110 $\pm$ 11.13	111 $\pm$ 10.29	109 $\pm$ 9.9	113 $\pm$ 11.72
Left hand	103 $\pm$ 9.97	109 $\pm$ 11.35	108 $\pm$ 11.19	110 $\pm$ 10.8	111 $\pm$ 11.72

Grip strengths

Grip strength was measured at the same time that plasma indomethacin levels were determined but these did not show any significant variation either during the period observed or after the addition of frusemide (Table 4).

No side-effects were noted during the study.

Discussion

Indomethacin is rapidly absorbed by mouth in the fasting state although the achievement of peak plasma levels is delayed when the drug is taken with food (Champion, Paulus, Mongan, Okun, Pearson & Sarkisson, 1972). There is considerable between-patient variation in plasma indomethacin profiles but using the same conditions a high degree of reproducibility can be achieved in individual patients (Brooks, unpublished observations).

Indomethacin is secreted by the proximal tubule in man (Skeith, Simkin & Healey, 1968) this process being blocked to a large extent by probenecid. However, without the use of

sophisticated micropuncture techniques it is not possible to tell exactly which part of the tubule is involved in the secretory process or if there is further resorption at a more distal level.

Frusemide is a potent diuretic which is absorbed rapidly from the gastro-intestinal tract. Detectable frusemide levels appear in the serum within 10 min and reach a peak at between 60 and 70 min, disappearing about 4 h after ingestion (Kelly, Cutler, Forrey & Kimbel, 1974). Frusemide acts at a number of sites in the renal tubule interfering with the sodium and chloride pump in the proximal tubule (Deetjen, 1966). This study demonstrates an interaction between frusemide and indomethacin, two drugs which are prescribed together in routine clinical practice. The significantly lowered indomethacin plasma level at 30 min is hard to explain on increased renal excretion as although frusemide does increase urine flow within 30 min of ingestion it is unlikely to be able to produce such a marked change in indomethacin level within that time. Frusemide and indomethacin may interact in the gut competing for absorption sites or in the plasma by competing for protein binding sites as both are carried on plasma proteins (Forrey, Kimpel, Blair

& Cutler, 1974; Hvidberg, Lausen & Jansen, 1972).

Significantly more free indomethacin was excreted in the urine after frusemide was given concurrently but in both cases the total free indomethacin excreted was small (1 and 2 mg respectively) in comparison to the administered dose (50 mg). Further work is at present being carried out to determine the concentrations of indomethacin urinary metabolites and examine the effect of frusemide on these.

The effectiveness of indomethacin in relieving joint pain can be seen from the decrease in articular index and pain score. It was of interest to note the delay in achievement of the minimum articular index following oral indomethacin. This occurred 2 h after the oral dose and did not occur when plasma indomethacin levels were at a maximum. Emori *et al.* (1973) reported simultaneous kinetics of indomethacin in plasma and synovial fluid showing that indomethacin reached a maximum concentration in the synovial fluid compartment 2 h after an oral dose. This delay in passage across the synovial membrane may play some part in the delayed clinical response to indomethacin in the acute situation.

As the plasma indomethacin levels fell the articular index showed a delayed rise.

The pain score showed a steady decrease throughout the period of observation but did not bear a relationship to the plasma profile or to the articular index profile. As all these studies were performed in the afternoon the effect of morning

stiffness and pain which will tend to decrease during the day despite drug therapy was thought to be minimal.

There was no significant change in the grip strength measurements during the period of observation and this is probably a reflection of the relative non-reversibility of disease in the patients studied (mean duration of disease 8 years).

Although the difference in articular index of joint tenderness and pain score before and with frusemide was not statistically significant in the number of patients studied, the values for both articular index and pain score were higher when frusemide was given concurrently with indomethacin.

The data we have presented demonstrates an interaction between frusemide and indomethacin. The mechanism of this interaction is at present unclear but the early changes in indomethacin plasma profile and the increased urinary excretion of indomethacin suggest that the interaction is at an absorptive and an excretory level. Further work is at present in progress to investigate these hypotheses.

Although not statistically significant clinically we feel that frusemide should not be used as a maintenance diuretic in patients with rheumatoid arthritis or if it is to be used should not be given at the same time as indomethacin.

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