but it seems unlikely that the effects that we have described here will be important when GH-RIH is considered as treatment in cases of GH excess, though long-term studies are needed in normal people and in those with pituitary disease.

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Indomethacin—Aspirin Interaction: A Clinical Appraisal

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Summary

Plasma profiles of indomethacin after a 50-mg oral dose were constructed in six healthy volunteers before and after a week of aspirin treatment. Aspirin did not interfere with indomethacin plasma levels.

To examine the clinical effect of concurrent indomethacin and aspirin treatment 20 patients with seropositive rheumatoid arthritis were given indomethacin 100 mg/day, aspirin soluble 4 g/day, and the two drugs taken together in random order. Analysis of the clinical indices of inflammation—articular index and mean pain score—and of the efficacy of each treatment showed no significant differences between the three treatment groups.

With the proliferation in the number of anti-rheumatic drugs available, the case for giving two or more non-steroidal anti-inflammatory drugs concurrently remains unproved.

Introduction

There is still controversy about the effect of concurrent aspirin treatment on plasma indomethacin levels, and as aspirin and indomethacin are commonly used together¹ it is important to establish the clinical significance of any interaction. We assessed the effect of aspirin administration on plasma indomethacin

profiles in normal people and also investigated the clinical effect of each drug alone and in combination by a double-blind crossover assessment in 20 patients with rheumatoid arthritis.

Patients and Methods

Profile Study.—After a light breakfast indomethacin 50 mg was given by mouth to six normal people and blood was collected then and at 30, 60, 90, 120, 180, and 240 minutes after ingestion. Soluble aspirin 4 g/day was then given for one week using soluble aspirin 500-mg tablets in four equal doses and the indomethacin 50-mg profile was repeated.

Double-blind Crossover Study.—Twenty patients with seropositive rheumatoid arthritis according to the American Rheumatism Association criteria were also studied. The mean age of the patients was 56.2 years and the mean duration of disease was 8.2 years. The patients were given in random order two-week treatment periods of aspirin and placebo, placebo and indomethacin, and aspirin, and indomethacin. The treatments were randomized using a Latin square matrix. The patients were assessed by a single observer at the same time of day on day 14 of each treatment period. Standard methodology was used for measuring an articular index of joint tenderness,² grip strength in the right and left hand,³ and pain score.²² The patients were given a chart on which they recorded the degree of joint pain each night before they retired to bed.²² At the end of the trial patients were asked to compare the three treatment regimens. For statistical purposes the efficacy ratings were given a total score of 9: 5 for the most preferable, 3 for the next most preferable, and 1 for the least preferable treatment. If two treatments were equal the points available after consideration of the other treatment were divided equally.

Plasma indomethacin levels were measured using the spectrofluorimetric method⁴ of Hucker with the modification described by Emori.⁵ There was no interference with the indomethacin assay when aspirin 10 mg/100 ml or 20 mg/100 ml was added to plasma standards containing 2 µg/ml or 5 µg/ml of indomethacin. The results were analysed statistically using Student's *t* test for paired values.

Results

Profile Study.—The results of the plasma profiles of a 50-mg oral indomethacin dose before and after a seven-day course of aspirin

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Plasma profiles of indomethacin after 50-mg oral dose in six normal volunteers before and after aspirin 4 g/day taken for one week. Results are means $\pm$ S.E. of mean.

Conversion: SI to Traditional Units—Indomethacin 1 μ mol/l $\approx$ 0.36 μ g/ml.

4 g/day in six normal people is shown in the fig. There was no significant difference between the two indomethacin plasma profiles.

DOUBLE-BLIND CROSSOVER TRIAL

Of the 20 patients who entered the trial 14 completed the three treatment periods and only these patients were included in the final analysis of the clinical indices. Three patients on aspirin, two on indomethacin, and one on the combined treatment dropped out.

Clinical Indices

The scores of clinical indices are shown in table I. The mean initial pain score of the patients was 3.8, which was significantly different from the mean treated pain score in each treatment group ($P < 0.01$). This indicates that the patients did have reversible clinical indices that were responsive to treatment.

TABLE I—Mean Scores ($\pm$ S.E. of Mean) of Various Indices for 14 Patients with Rheumatoid Arthritis according to Treatment

	Aspirin and Placebo	Indomethacin and Placebo	Indomethacin and Aspirin
Pain score	2.52 $\pm$ 0.22	2.38 $\pm$ 0.2	2.65 $\pm$ 0.2
Articular index ..	17.7 $\pm$ 2.8	19.1 $\pm$ 2.5	17.2 $\pm$ 2.5
Patient assessment ..	3.28 $\pm$ 0.28	3.14 $\pm$ 0.22	3.07 $\pm$ 0.24
Patient preference ..	2.8 $\pm$ 0.22	3.3 $\pm$ 0.36	2.8 $\pm$ 0.34
Grip strength (mm Hg):			
Right hand	116 $\pm$ 8	110 $\pm$ 12	112 $\pm$ 7
Left hand	115 $\pm$ 9	106 $\pm$ 9	106 $\pm$ 8

Pain Scores—Mean pain score⁵ over the 14-day treatment period was calculated for each patient and for each treatment group. There was no significant difference between the treatment groups in mean pain score value.

Articular Index—The mean articular score taken on day 14 of each treatment period was compared, and there was no significant difference in the values.

Patient Assessment of the efficacy of the drug in relieving pain showed no significant differences between the three treatment groups.

Patient Preference—The patient preference scores took into account side effects of the treatment as well as pain relief. Indomethacin fared best of all but the difference between indomethacin and the other two treatments was not significant.

Grip Strength—There was no difference in the grip strength measurement in the right and left hand between the three treatment regimens.

Side Effects

Table II shows the adverse effects experienced by the 20 patients in the 60 treatment periods. Side effects were experienced in 21 treatments (32%) and necessitated cessation of treatment in two patients. Ten of the adverse effects occurred on the combination treatment though none of these required cessation of treatment.

TABLE II—Number of Patients with Side Effects during Double-blind Crossover Trial. Numbers in Parentheses are Numbers of Patients who Dropped out during Treatment Period

	Headache or Lightheadedness	Indigestion	Buzzing in Ears	Uncontrolled Joint Pain
Aspirin	1		4 (2)	(1)
Indomethacin	4	1	1	(2)
Indomethacin and Aspirin	5	2	3	(1)

Discussion

Despite criticism of the early clinical therapeutic trials on indomethacin⁶ more recent controlled studies have clearly shown that the drug has analgesic and anti-inflammatory effects in patients with rheumatoid arthritis.⁷ The trial conducted by the American Rheumatism Association⁸ in 100 patients with rheumatoid arthritis showed that indomethacin was not superior to placebo, but the patients were allowed aspirin ad libitum, and the effect of indomethacin may have been reduced by the aspirin. Reduction in serum concentrations of indomethacin with concurrent aspirin treatment has been reported in patients with rheumatoid arthritis,⁹ rats,¹⁰ and normal people,¹¹ though recent studies with oral indomethacin¹² and indomethacin suppositories¹³ failed to show any significant fall in plasma indomethacin levels when aspirin was taken concurrently. In experimental inflammation in animals the concurrent administration of aspirin and indomethacin was no more effective in reducing inflammation^{14 15 23} than each drug alone.

Though only 14 patients completed the trial the results show that no single treatment has real therapeutic advantages over the others. The order in which the treatments were given was not significantly different.

Though a two-week treatment period probably does not adequately reflect the long-term usefulness of a treatment for rheumatoid arthritis and, though no treatment yet available significantly changes the disease, valid comparisons between drugs can be made over two weeks, particularly with the double-blind methods we used. Our results confirm those of other double-blind clinical trials of aspirin against indomethacin^{16 17} and also show that taking the two drugs together does not relieve pain better than taking each drug separately.

Lee¹⁸ could not differentiate between the non-steroidal anti-inflammatory drugs at a statistical level using subjective indices as a measure of efficacy. Our patients preferred indomethacin to either aspirin or aspirin and indomethacin combined, though this difference was not significant.

Though the numbers were small most side effects occurred in the patients taking both medications concurrently. There is no evidence in the literature to suggest that side effects of these agents are additive but they probably are. Certainly the incidence of adverse drug reactions increases with the number of drugs prescribed.¹⁹ Lee *et al.*²⁰ found that adverse reactions to an anti-inflammatory or analgesic agent were responsible for outpatient attendance or hospital admission in 5% of patients with rheumatoid arthritis, and recently drugs have been implicated in the death of 16 out of 82 patients dying with rheumatoid arthritis.²¹

We feel instinctively that prescribing combinations of anti-inflammatory agents is wrong and hope that our study will act as a stimulus for further trials to clarify the position. Meanwhile patients with rheumatoid arthritis should be main-

tained on as few drugs as possible if only to reduce the traffic across the oesophageal mucosa.

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Carbon Monoxide Yields of Cigarettes and Their Relation to Nicotine Yield and Type of Filter

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Summary

Carbon monoxide (CO) yields of 11 popular brands of British cigarette, two types of cigarette containing tobacco-substitute, and one brand of cigar were measured under standardized conditions. Yields of the conventional cigarettes ranged from 5.0 to 20.2 mg per cigarette (1.3 to 4.7% by volume). The cigar yielded 81.7 mg (10.0%) CO and the two semi-synthetic cigarettes 17.2 (4.2%) and 28.2 mg (6.2%) CO. Puff-by-puff analysis showed an increase in CO concentration as a cigarette is smoked. In brands with nicotine yields over 1.0 mg no relationship was apparent between nicotine yield and CO yield, and the filters of cigarettes in this category did not appear to reduce the CO yield. In the low nicotine cigarettes with ventilated filters there appeared to be some correlation between nicotine yield and CO yield, and these filters were highly effective in reducing CO yield, owing mainly to the ventilation. We suggest that official publication of CO yields might motivate manufacturers to produce cigarettes with lower yields.

Introduction

In April 1973 the Government published for the first time the tar and nicotine yields of cigarettes sold in the United Kingdom.^{1,2} The purpose of such a "league table" is presumably to serve as a guide to those who seek a less harmful cigarette. But is it enough to be guided only by tar and nicotine yields? What about carbon monoxide?

In the 1920s the carbon monoxide (CO) content of tobacco smoke was shown to vary with the brand of cigar or cigarette.^{3,4} This was confirmed in America^{5,6} but there are no published figures for CO yields of British cigarettes. We have shown that the increase in blood carboxyhaemoglobin (COHb) due to smoking varies considerably with the brand of cigarette,^{7,8} which provides indirect evidence that cigarettes may vary in their CO yield. We have now made direct measurements of the CO concentration in mainstream smoke of a range of cigarettes on sale in Britain.

Materials and Methods

Selected brands of cigarette were purchased in batches of 100. Each batch in turn was placed in a single horizontal layer inside a Perspex tank kept at 21°C and 60% relative humidity and left there for at least 48 hours. Each cigarette was then weighed and the pressure drop across it at a fixed flow rate (19.2 ml/s) estimated. Damaged ones were then discarded. From each batch the ones having a weight within 20 mg and a draw resistance within 4% of the respective means were selected. Usually 15 to 25 cigarettes were returned to the conditioning chamber until needed for analysis.

The cigarettes were smoked in standard fashion using a smoking machine of our own design. This consisted of an electrically operated linear actuator operating a gas-tight glass syringe. The syringe port was connected via a three-way plastic tap to a piece of soft latex tubing, which acted as a cigarette holder. The cigarette was fixed in position and carefully lit with an electric cigar lighter. Each puff was exactly 35 ml and took $1.82 \pm \text{S.D. } 0.02$ s. The smoke was then expelled through two 8-nm Millipore filters in series (to remove particulate matter) and collected in a 1-litre plastic sampling bag.⁹ Smoking was continued in this way, with exactly one minute between puffs, until the burning end reached a mark a fixed distance from the unlit end. This distance was 20 mm or the tip overwrap plus 3 mm, whichever was the greater. The number of puffs needed to reach the mark was noted. The technique employed was so far as possible in line with standard procedure.¹⁰

The contents of the sampling bag were analysed for CO with a non-dispersive infrared analyser (Hartmann and Braun, URAS 2). The total yield of each cigarette was then calculated and expressed in mg. Though the measurement of CO necessitated the removal of water vapour produced in smoking the amount produced was too small to affect significantly the measured concentrations. At the low sensitivity required for measurement of CO the analyser was found to be insensitive to the levels of carbon dioxide produced by burning cigarettes.

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