Trial of an Anti-inflammatory Agent (Indomethacin) in Low Back Pain with and without Radicular Involvement

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Summary: A short-term double-blind sequential trial of indomethacin against placebo in the treatment of low back pain, with and without nerve root pain such as sciatica, showed that indomethacin was significantly more effective than placebo in the group with nerve root pain. On the other hand, no difference was found between the treatments in the patients with uncomplicated low back pain. This difference may result from an effect of indomethacin on the inflammatory process around the nerve root which has been shown to be present when this is compressed.

Introduction

Many studies (Hart and Boardman, 1963, 1965 ; Wanka, Jones, Wood, and Dixon, 1964 ; Thompson and Percy, 1966 ; Rothermich, 1966) have been carried out on the anti-inflammatory effects of indomethacin in the treatment of various types of joint disorder. Little, however, has been written on the use of this drug in soft-tissue lesions. The present paper describes the results of a trial of the drug in the treatment of low back pain with and without radicular involvement.

Patients

New patients attending the outpatient clinic of the Department of Physical Medicine and Rheumatology of the North Middlesex Hospital for the treatment of low back pain were assessed. For inclusion in the trial they had to be suffering from musculoskeletal conditions causing acute or acute-on-chronic lumbar pain. Lumbar *x*-ray examination was used to exclude those with neoplastic, metabolic, or other bone disease. Patients who were pregnant, those with diabetes, epilepsy, and peptic ulcer, and those over 60 years of age were excluded. In effect, patients in the trial were suffering from clinically diagnosed prolapsed intervertebral disc, with or without radicular pain such as sciatica, or from non-specific musculoskeletal low back pain.

Methods

When considered suitable for study, patients were divided into separate diagnostic groups for each part of the trial, depending on the presence or absence of root pain. All patients were instructed to adhere to a basic regimen of strict back discipline. An initial clinical assessment of the degree of disability was made and recorded on special record sheets. This was done on the basis of two objective and two subjective criteria, as follows:

Objective Criteria.—(1) Measurement in full spinal flexion of the distance between the spines of the twelfth thoracic and first sacral vertebrae with a flexible tape measure. The two reference points were marked with an indelible pencil. (2) Measurement of the maximal degree of straight-leg raising, with the patient lying on his back and the angle measured from the horizontal, by means of a special large wooden divider with marked angle graduations.

Subjective Criteria.—(1) Pain. (2) Restriction of movement. Both these were scored on a scale: 0=absent, 1=mild, 2=moderate, and 3=severe.

Patients were then allotted the next serial number in their diagnostic category, and given the appropriate numbered bottle containing either indomethacin capsules 25 mg. or identical placebo. At first they were told to take one capsule four times a day and return in one week. After 10 patients had been treated, however, it became apparent that headache and nausea were troublesome, and the dosage for subsequent patients was altered to one capsule three times a day for two days, then one capsule four times a day for the next five days. The allocation of bottles had been made, separately for each diagnostic group, in blocks of 10, so that for each 10 patients treated five would receive indomethacin and five placebo.

Patients were also given a personal record card to take home and record day by day the severity of pain and of restriction of movement according to the rating scale from 0 to 3. They were also requested to record any headaches or gastrointestinal upset on a similar rating scale. They were instructed not to take any other analgesic tablets.

After one week all patients were seen again. They were reassessed by the two objective criteria and the results were recorded. Their subjective record cards were collected and attached to their record sheets, and they were asked in general terms about any other possible side-effects. An overall comment by the physician was added.

Analysis

Sequential analysis was used, based on a small closed design such that $2\alpha=0.05$, $\theta=0.85$, $1-\beta=0.95$, $N=29$ (Armitage, 1960). Results during the trial were recorded on the graphs by an observer (M. F. G.) not involved in clinical care of the patients.

Separate analyses were made for each of the two diagnostic groups, which were in effect two separate trials. Within each diagnostic group two sequential graphs were made simultaneously, one for objective and one for subjective assessment. For this purpose two composite indices were prepared by combining respectively the results of the two objective criteria and the two subjective criteria of improvement. The scoring system for the measurement criteria was as follows:

Objective Criteria.—(1) A change after treatment of less than ½ in. (1.3 cm.) in the measurement of lumbar spinal flexion was disregarded. One point was awarded for each complete ½ in., and scores were either positive for an increase or negative for a decrease. (2) A change of less than 10° in straight-leg raising was disregarded. One point was awarded for each complete 10°, either positive or negative, or for a change from painful to painless full flexion if less than 10°. Where a change was recorded in both legs the one with a greater change was scored.

Subjective Criteria.—The change was recorded as the difference between the first entry on the patient's personal record card of graded severity of pain or restriction of movement—that is, before treatment—and the average of the last three daily entries. Where

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two of the last three entries were the same this result was compared with the pretreatment figure. Points were scored as positive for a decrease and negative for an increase.

The objective index was produced by adding the scores for improvement in lumbar spine flexion and straight-leg raising. Similarly the scores for improvement in pain and in restriction of movement were added to provide a subjective composite score.

The sequential graphs were made by pairing successive patients in each treatment group according to their entry number in the trial. In each diagnostic group, and for both the objective and the subjective composite indices, a treatment preference was recorded when the scores differed by at least one point. A mark was then made on the appropriate graph—at 45° in a north-easterly direction for a preference for indomethacin or south-east for a preference for placebo. If a patient had to stop treatment before the end of a week, because of side-effects, for example, the other member of that sequential pair was also excluded from the analysis.

The trial in each diagnostic group was stopped when both sequential graphs had reached a boundary point.

Results

Fifty patients in the group with nerve root involvement had been treated before the trial reached a conclusion. Five of these did not complete treatment because of side-effects, so that 20 pairs were available for sequential analysis. Figs. 1 and 2 show that the upper boundary points were reached in both analyses, indicating that indomethacin was a better treatment than placebo, with a probability <0.05, judged both objectively and subjectively.

Sixty patients were treated in the group with prolapsed intervertebral disc or low back pain without nerve root involvement. Five of these had side-effects which prevented them finishing the course of treatment, so that 25 pairs were available for sequential analysis. Figs. 3 and 4 show that a middle boundary line was reached by both graphs. Thus no statistically significant difference was apparent between indomethacin or placebo in these patients.

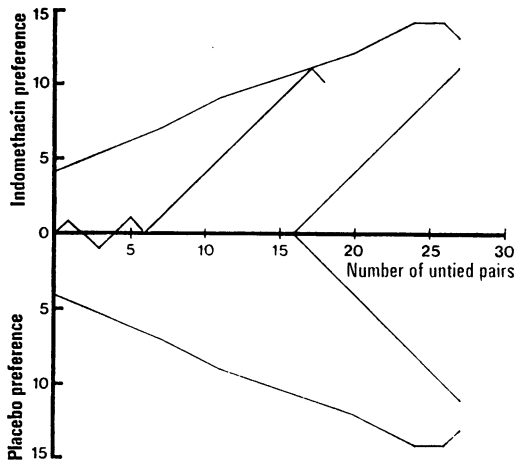

FIG. 1.—Objective preferences. Patients with nerve root involvement.

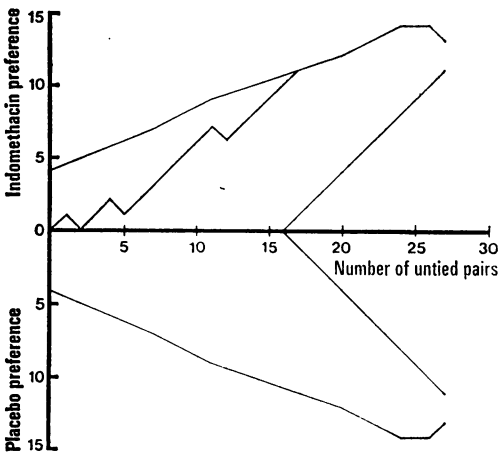

FIG. 2.—Subjective preferences. Patients with nerve root involvement.

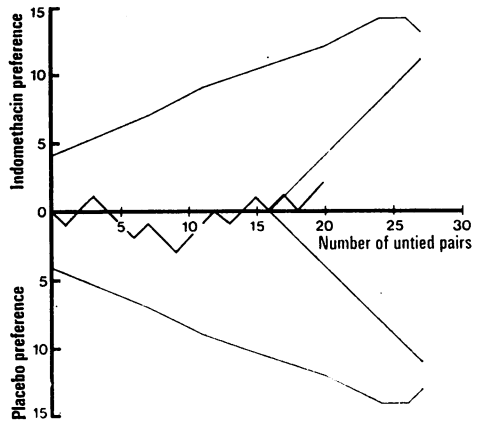

FIG. 3.—Objective preferences. Patients with uncomplicated low back pain.

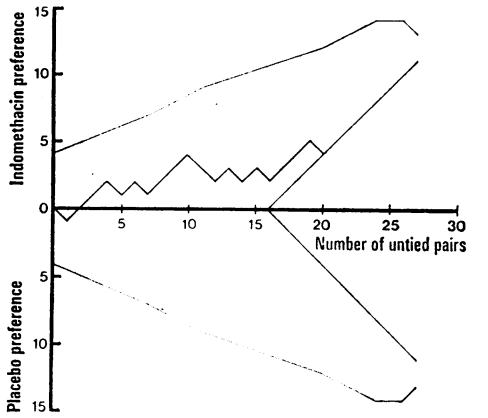

FIG. 4.—Subjective preferences. Patients with uncomplicated low back pain.

Side-effects.—The patients' personal record cards included questions about headache and gastrointestinal upset. Other side-effects were not specifically asked for, and there is therefore a bias in the Table towards these two side-effects. The Table

Side-effects

	Treatment Group	
	Indomethacin	Placebo
Headache	23 (8 severe)	14 (3 severe)
Gastrointestinal upset ..	13 (3 severe)	6 (1 severe)
Faint and peculiar ..	1	0
Giddiness or dizziness ..	0	2
Stiff legs	0	1
Pain on coughing ..	1	0
Patients who stopped treatment because of side-effects	2 (1 Headache. 1 Headache and bilious)	3 (1 Headache. 1 Dizzy and sick. 1 Legs stiff)
Patients with no side-effects	27 out of 55	35 out of 55

shows the side-effects that were recorded in all patients who entered both diagnostic groups of the trial (110 patients, half treated with indomethacin and half with placebo). One patient in each treatment group failed to attend for follow-up and two indomethacin-treated patients were excluded for reasons other than stopping because of side-effects (1 misdiagnosis, 1 stopped because of shellfish poisoning). One patient with gastrointestinal upset in each treatment group had this symptom before treatment, and one patient with headache on indomethacin had previous headaches from cervical spondylosis.

Discussion

These trials were conducted to investigate the therapeutic effectiveness of indomethacin in a selected group of patients suffering from low back pain and in another group of patients suffering from low back pain associated with radicular involvement, and to find out if there was a different response to the drug in the two groups. The results show that indomethacin in the dose used was ineffective in the treatment of uncomplicated low back pain but that there was a significant preference for indomethacin over placebo in the group of patients with low back pain associated with radicular involvement.

The exact location of the lesion producing symptoms in the group without root pain is difficult to define precisely, since it is not possible to differentiate between lesions of the annular ligament, posterior ligament, or other deep ligamentous or connective-tissue structures. All these tissues, however, are well supplied with nerve endings but are relatively avascular (Barnett, Davies, and MacConaill, 1961). In the group of patients with root pain the pathological process responsible for the nerve root involvement is considered to be due to a protruded lumbar intervertebral disc. It is generally accepted that the actual mechanical stretching or pressure on a nerve root by the protrusion may cause pain, but it is less well recognized that as a result of this pressure an inflammatory lesion may occur in and around the nerve root.

Bucy (1961) stated that "frequently at operations the affected nerve root is swollen and that the root pain of a herniated intervertebral disc lesion is produced by the compression of a spinal nerve root which is acutely inflamed." Key (1954) reported that at operation the nerve root may be reddened, inflamed, swollen, and exquisitely sensitive or may show little deviation from normal, but he considered that in many of these nerve roots, even where no obvious gross disease was seen at operation, a traumatic neuritis was present and that these interstitial changes in the nerve roots may account for the persistence of pain after operation. Irsigler (1951) reported the histological findings from a patient suffering from lumbar root compression due to a herniated disc lesion of six months' duration. At operation the compressed nerve root was inadvertently resected and microscopical examination of the resected portion showed that the intraneural vessels were enlarged and there was infiltration with lymphocytes, leucocytes, and histiocytes. From these findings a diagnosis of acute interstitial neuritis was reported.

Indomethacin has been shown both experimentally (Winter, Risley, and Nuss, 1963) and clinically to have anti-inflammatory properties. Its analgesic properties, however, are less potent, and Sunshine, Laska, Meisner, and Morgan (1964) have established that 25 mg. of indomethacin are equivalent to 300 mg. (5 gr.) of aspirin. An inflammatory state has been shown to exist in and around the nerve root in a proportion of patients suffering from radicular pain and these patients could theoretically be helped by an anti-inflammatory drug. In the patients with low back pain due to a ligamentous lesion no inflammatory state has been shown to exist and active inflammation would be unlikely to occur in such relatively avascular structures. Under these circumstances an anti-inflammatory drug would not be beneficial and the analgesic effect of indomethacin equivalent to 300 mg. of aspirin four times a day may not be sufficient to control the patients' symptoms.

These trials were not designed to demonstrate the total length of time that indomethacin needed to be given to obtain a complete remission but merely to investigate if it was a useful drug in the treatment of these disorders. In fact most of the patients in the treatment group relapsed in varying degrees after one week's medication and required further courses of the drug to maintain their clinical improvement.

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