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Indomethacin and Phenylbutazone: a Comparison

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Early papers on indomethacin reported promising results from its use as a non-specific anti-inflammatory agent in the treatment of the chronic rheumatic disorders (Paul and Strottman, 1963; Ballabio *et al.*, 1963), with dramatic results in gout (Smyth *et al.*, 1963). A controlled clinical trial demonstrated significant preference for indomethacin against placebo in rheumatoid arthritis (Dixon *et al.*, 1963). Measurable reduction of joint swelling as a result of treatment with indomethacin was reported in active rheumatoid arthritis (Hart and Boardman, 1964). There was no significant difference between indomethacin and phenylbutazone (Percy *et al.*, 1963)—in this trial the treatment period on each drug was one week and the indomethacin used was in tablet form, which, for various reasons, has been replaced by a gelatin-coated capsule.

This paper reports the results of a double-blind trial in which the effect of phenylbutazone is compared with that of indomethacin capsules, each drug being given for one month to patients with active rheumatoid arthritis. A brief account is also given of the results obtained from the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis with indomethacin during a period of two and a half years.

I. Double-blind Trial

All 26 patients who took part in the double-blind trial of indomethacin and phenylbutazone had classical rheumatoid arthritis or definite rheumatoid arthritis as defined by a Committee of the American Rheumatism Association (1959). The diagnosis of the classical form of the disease is applied to those patients in whom 7 out of the 11 criteria listed by the A.R.A. are present. A diagnosis of "definite" requires the presence of five of the criteria. Phenylbutazone, 100 mg. three times a day, was given to 13 patients in the first month, and indomethacin, 25 mg. three times a day, to 13, therapy being changed to the other agent at the end of the month. To provide double-blind conditions they received active indomethacin and dummy phenylbutazone in one month, and in the other active phenylbutazone and dummy indomethacin. The group who started on indomethacin had a mean age of 47.6 years; five were males and eight females. The mean duration of disease was 6.7 years. The patients who received phenylbutazone in the first month had a mean age of 48.8 years, an average length of history of 6.2 years, and there were four males and nine females. There were six patients with classical and seven with definite rheumatoid arthritis in each group. These patients were assessed by their own daily record of pain, stiffness, and loosening-up time, and the measurement of joint tenderness, joint swelling,

and grip strength at each visit (Hart and Boardman, 1963). All were attending the out-patient clinic at monthly intervals. They were assessed at the start of treatment and at the end of each trial period of 28 days. Their personal opinion as to the more satisfactory treatment period was recorded at the end of the trial.

Results

When asked at the end of the trial, before the identification of the specific treatment periods, which month was the more satisfactory, 15 patients preferred phenylbutazone, 10 found them to be equally effective, and one preferred indomethacin. This difference is statistically significant ($P < 0.001$).

A comparison of the pain record of each patient in the month on phenylbutazone with that of those on indomethacin revealed that this parameter improved selectively in five in phenylbutazone and in two on indomethacin, 19 finding no difference. A clinically significant alteration of pain was taken to be 25% or more in the month. Likewise, assuming a 25% difference to be significant, five were less stiff during phenylbutazone therapy and one on indomethacin, 20 finding no detectable difference. There is obviously no significant difference in these symptoms between the two groups.

An alteration in the duration of early-morning stiffness was assumed to be of clinical significance if it exceeded 30 minutes. In the first month, on phenylbutazone, there was improvement in the loosening-up time in seven patients and deterioration in one, five being unchanged. On indomethacin there was improvement in three, deterioration in four, and no change in six. These changes are not statistically significant ($\chi^2 = 1.4$; $n = 1$; $0.3 > P > 0.2$). In the second month, on indomethacin, improvement occurred in three patients, and this parameter worsened in two, eight exhibiting no change. On phenylbutazone there was no change in six, four improved, and three deteriorated.

A difference in grip strength of 50 mm. of mercury was assumed to be clinically significant. In the first month, on phenylbutazone, none improved, five deteriorated, and eight remained unchanged. On indomethacin three improved, one deteriorated, and there was no change in nine. There was no statistically significant difference between the groups ($\chi^2 = 1.5$; $n = 1$; $0.3 > P > 0.2$). In the second month, on indomethacin, 11 patients remained unchanged, one improving, and one deteriorating. In comparison, on phenylbutazone, there was no change in 10 patients, improvement occurring in three. There was obviously no significant difference.

As 17 of the 26 patients had no tender joints at any time during the trial this was an unsatisfactory parameter.

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Assuming a change of three ring sizes in joint size to be significant, there was no difference in 17 patients, five were better on indomethacin, and four on phenylbutazone. The improvement in joint size, in the first month, in the patients on phenylbutazone, was by four rings. On indomethacin the improvement was by 35 rings. This difference is not statistically significant ($t = 1$; $n = 24$; $0.2 > P > 0.1$). In the second month indomethacin was associated with an improvement of 21 ring sizes, compared with 17 on phenylbutazone.

II. Long-term Studies

Over a period of two and a half years a mixed group of patients with rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis were treated with indomethacin. In some cases it was possible to compare results with those previously obtained with pyrazole derivatives.

Rheumatoid Arthritis

Ninety-seven out-patients and 21 in-patients with classical or definite rheumatoid arthritis (American Rheumatism Association Committee, 1959) were followed up for two and a half years. Ninety were females and 28 males. Their average age was 53.3 years, and the mean duration of rheumatoid arthritis was 8.1 years. The sheep-cell-agglutination titre was positive in 85 patients.

The in-patients were assessed by their own daily record of pain, stiffness, and the duration of early-morning stiffness, together with twice-weekly estimations of grip strength, joint tenderness, and joint size (Hart and Boardman, 1963). Identical placebo was administered to conceal the exact time of the start and the withdrawal of indomethacin by blind substitution. The E.S.R. was measured weekly. Four grades of response were recognized in the out-patients with rheumatoid arthritis, according to the criteria of therapeutic response defined by the American Rheumatism Association Committee (Steinbrocker *et al.*, 1949), recorded in this paper as good, fair, poor, or nil; the E.S.R. was excluded from this assessment. In all patients in whom treatment had included a pyrazole derivative indomethacin was compared with phenylbutazone or oxyphenbutazone, their relative effectiveness being recorded at arbitrary maintenance dosage. This was 300 mg. daily for the pyrazoles, 200 mg. daily for indomethacin tablets, and 75 mg. daily for the capsule preparation. The prolonged effect of indomethacin was checked by the observation of rebound deterioration on withdrawal of the drug.

Osteoarthritis

With one exception the 52 patients with osteoarthritis were treated in the out-patient clinic. They included 35 females and 17 males with an average age of 61.2 years and a mean duration of symptoms of 4.5 years. A good response was one with 85% control of symptoms as assessed by the sufferer, the residual pain constituting minor discomfort only and not interfering with daily activity. A fair response was one in which there was therapeutically useful improvement but not to the extent of removing all serious discomfort. A poor response was one in which there was some slight symptomatic improvement, insufficient to be of therapeutic value.

Ankylosing Spondylitis

There were 26 males and six females in the group of 32 patients with ankylosing spondylitis, the average age being 37.6 years and the mean duration of disease 13.4 years.

Results

Rheumatoid Arthritis In-patients

Pain and stiffness were reduced in 15 of the 21 in-patients, there being no change in five and side-effects in one. Early-morning stiffness improved in eight, remained static in six, and was too short initially for assessment in six; in one patient side-effects prevented assessment.

Grip strength improved by more than 50 mm. of mercury in seven patients. It improved slightly in one patient, remained unchanged in six, and was an unsatisfactory parameter in seven—in five as a result of side-effects, and in two because of lack of involvement of the hands. Joint tenderness improved in five patients, was unchanged in two, and side-effects interfered in five; in nine there were no tender joints.

Compared with the baseline, there was reduction of joint size on indomethacin of 79 ring sizes in seven patients, while three deteriorated by 11 ring sizes. There was no change in five. Assessment was unsatisfactory in six because of side-effects and lack of involvement of the hands.

There was no significant change in the E.S.R. in response to the administration of indomethacin.

Of the 21 in-patients 19 had previously received a pyrazole derivative. The preference was for indomethacin in six, and for phenylbutazone or oxyphenbutazone in four; nine patients were unable to detect significant difference.

Rheumatoid Arthritis Out-patients

In the 97 out-patients the response to indomethacin was good in 28, fair in 21, poor in 10, and nil in 38 patients. A comparison with a pyrazole derivative was possible in 80 patients. Indomethacin was preferred by 30, a pyrazole derivative by 19, and they were found to be equally effective in 31 patients.

Ankylosing Spondylitis

The response to indomethacin in the 32 patients with ankylosing spondylitis was good in 16, fair in six, poor in one, and nil in nine. In 19 patients the treatment of choice was indomethacin, and in nine it was phenylbutazone or oxyphenbutazone; four patients considered them to be of equal value.

Osteoarthritis

The response to indomethacin in the 52 patients with osteoarthritis was good in 30, fair in four, poor in seven, and nil in 11. It was possible to compare indomethacin with the pyrazoles in 39 patients. Indomethacin was the drug of choice in 15 and phenylbutazone or oxyphenbutazone in 13; 11 found them equally satisfactory.

Side-effects

Side-effects occurred in 104 of the 202 patients treated with indomethacin (51.48%); this consisted of 67 out of 101 (66.3%) on indomethacin tablets, and 37 out of 101 on capsules (36.6%).

The following complaints were noted, the incidence being recorded in brackets: headache (46), giddiness (25), dyspepsia (16), muzziness (16), nausea (12), vomiting (5), rash (4), diarrhoea (4), felt odd (2), sleepy (2), heavy legs (2), drunk (1), faint (1), mouth ulceration (1), unpleasant taste (1), depression (1), lassitude and nightmares (1), swollen tongue (1), costive (1), and shakiness (1).

In 88 patients side-effects occurred within seven days of starting indomethacin, in nine patients within seven to 14 days, and in two patients between 14 and 21 days. Side-effects occurred after three weeks in five patients only.

Dyspepsia occurred in 16 of the 202 patients (7.92%). In contrast, of the 170 patients who received a pyrazole agent

40 had dyspepsia (23.5%). In no patient was there overt evidence of gastro-intestinal haemorrhage, and none developed perforation. One patient with rheumatoid arthritis and one with osteoarthritis of the hip had slow gastro-intestinal blood loss, the administration of indomethacin being associated with a fall in the haemoglobin by 20–40% within a month.

Barium studies were available for 16 patients, all of whom had dyspepsia on phenylbutazone or oxyphenbutazone and eight on indomethacin. A duodenal ulcer was detected in seven patients, all intolerant of pyrazoles; indomethacin was tolerated by four of these patients and caused dyspepsia in three; these seven have received 995 patient days of treatment with indomethacin to date. In five patients with demonstrable gastric ulcers—one with a hiatus hernia also—all intolerant of phenylbutazone, indomethacin was associated with dyspepsia in one, being well tolerated in four patients; this group has received 571 patient days of treatment to date without serious gastro-intestinal complications. In three patients no abnormality was detected on barium-meal examination. All three were intolerant of phenylbutazone; indomethacin was associated with dyspepsia in two patients, and in one may have been the cause of anaemia by slow continuous blood loss. One patient, with both a hiatus hernia and gall-stones, suffered from dyspepsia on indomethacin, phenylbutazone, salicylates, and placebo.

Discussion

It is increasingly apparent that the therapeutic effect of indomethacin has many similarities to that of phenylbutazone, irrespective of the mode of action. Though painful symptoms are relieved by phenylbutazone, the action being remarkably even throughout the 24 hours, reduction of joint swelling occurs in only occasional cases of rheumatoid arthritis. The regular, predictable reduction of joint size with the corticosteroids, offset by the untoward effects of prolonged therapy, suggested that the advent of a new non-steroid preparation with this property would be a considerable advance. Of the many preparations tried in the last 17 years at the Westminster Hospital (F. D. H.) indomethacin has been the first non-steroid drug to produce a measurable reduction in joint size in selected cases of active rheumatoid arthritis. The spectrum of side-effects on indomethacin overlaps phenylbutazone slightly with respect to the gastro-intestinal tract but is otherwise quite different. It is possible that the response to indomethacin is not as consistent as that obtained from phenylbutazone over the 24 hours; in this series the overall response was slightly less than 60%.

The double-blind trial confirmed that, under defined conditions, there was no significant difference between indomethacin, 75 mg. daily, and phenylbutazone, 300 mg. daily, in the relief of pain and stiffness in rheumatoid arthritis. Though the alteration of joint size on the two drugs was not statistically significant, the trend in each group suggested that this parameter improved specifically on indomethacin. The magnitude of the response obtained depends not only on the anti-inflammatory effect of the administered drug but also on the amount of soft-tissue inflammatory swelling present that is potentially capable of exhibiting reduction of size. It is unlikely that optimal conditions existed in these patients for reduction of joint size; they were selected from the regular attenders at the out-patient clinic and had disease of moderately long duration. That indomethacin was associated with reduction of joint size, as compared with the baseline, was demonstrated in the patients admitted to hospital.

Indomethacin was initially available in the form of tablets. These proved to be unsatisfactory and gelatin-coated capsules were substituted. The patients in the long-term studies received both preparations. These results are not given separately, except for side-effects, because the capsule is the only preparation available; a comparison of the two preparations revealed that the only difference of statistical significance was the incidence of side-effects.

The most consistently satisfactory results from indomethacin were obtained in patients suffering from ankylosing spondylitis (68.7%) and osteoarthritis (65.3%). Results for gout are reported separately (Boardman and Hart, 1965). Excellent results did occur in rheumatoid arthritis, in particular in patients with active disease, but there were also some dramatic failures, and overall benefit was obtained in only 50.5%.

Side-effects were a more frequent cause of therapeutic failure than inadequate drug potency. The change from the tablet to the capsule preparation was associated with a reduction in frequency from 66.3% to 36.6%, together with a decrease in the severity of untoward reactions. The most common pattern of side-effects consisted in headache, giddiness, muzziness, and nausea. These were transient, dependent on dosage, and occurred within the first few days of starting treatment.

Dyspepsia was relatively rare during indomethacin administration. Smyth *et al.* (1964), in a study of 63 patients with rheumatoid arthritis during an 18-month period, found one who developed peptic ulceration on indomethacin and one on placebo. Catoggio *et al.* (1964) had two cases of duodenal ulceration in a group of 33 patients. Clark (1964), in a study of 100 patients with rheumatoid arthritis, encountered peptic ulceration in 10, nine of whom also received corticosteroids; there were three instances of perforation and one of haemorrhage. Bilka *et al.* (1964) reported one patient, out of a total of 61, who developed a small gastric ulcer after 12 weeks of indomethacin therapy. Haemorrhage and perforation do not appear to be serious risks as judged on the figures of this series, in contrast to the findings of Lövgren and Allander (1964). Unlike their six patients with a history of gastric or duodenal ulceration treated in hospital, in our series four of seven patients with duodenal ulceration and four of five with gastric ulcers tolerated indomethacin well, the total period of therapy being 1,566 days. Nevertheless, with certain exceptions, dyspepsia occurring on indomethacin was considered an absolute indication for cessation of therapy. In our series antacids were not used for symptomatic control. Lövgren and Allander (1964) treated their patients in hospital with anticholinergics and antacid agents; it is possible that some of their problems arose as a result of the masking effect of these symptomatic remedies on what should be considered a warning symptom.

The dose probably suitable for most patients is 25 mg. three times a day, administered after food. It is suggested that to overcome the frequent early side-effects the dose should be increased slowly during the first week, from an initial 25 mg. daily. Dyspepsia due to indomethacin is an indication for the withdrawal of therapy.

During the two and a half years that indomethacin has been available to us it is of relevance to note that only three patients with rheumatoid arthritis have been started on long-term corticosteroid therapy or A.C.T.H. The fact that a non-steroid anti-inflammatory agent is now available may well make a profound difference to the present use of corticosteroids in this condition.

Summary

A double-blind cross-over trial was carried out to compare indomethacin, 75 mg. daily, with phenylbutazone, 300 mg. daily, each being given for a period of 28 days to patients with active rheumatoid arthritis. No significant differences were found between the two groups in the relief of symptoms, but the results obtained were indicative of greater reduction of early-morning stiffness on phenylbutazone and of joint swelling on indomethacin. The personal preference, expressed at the end of the trial, was in favour of phenylbutazone.

In a mixed group of patients treated over two and a half years indomethacin was effective in improving the symptoms of osteoarthritis (65.3%) and of ankylosing spondylitis (68.7%). In rheumatoid arthritis failures were more frequent, a satisfactory response being recorded in 50.5% of cases.

Side-effects on indomethacin capsules, at an average maintenance dose of 75 mg. daily, occurred in 36.6% of patients in the mixed group. The common side-effects were headache, giddiness, muzziness, nausea, and vomiting. Dyspepsia was not a major problem, occurring in 7.92% of patients; it was only rarely dose-dependent and occurred at any time during long-term administration in contrast to the other side-effects, which were dependent on dose and developed almost always within the first 14 days of treatment.

Addendum

Since the completion of this study, one patient on indomethacin, 200 mg. daily, and prednisolone, 8 mg. daily, with a history of duodenal ulceration, present 20 years earlier, developed dyspepsia after six months on indomethacin. This was followed by a haematemesis which required blood transfusion. In many of the cases of haematemesis reported this combination of drugs was used.

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Heroin Addiction in the United Kingdom (1954–1964)

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The pattern of narcotic addiction in the United Kingdom has changed in the past 10 years. Most addicts recorded before 1954 had become addicted accidentally in the course of therapy or belonged to professions with easy access to drugs—for example, doctors, nurses, and pharmacists. Since then the number of younger addicts has grown, mostly from contact with other addicts. The slow fall in the number of known addicts on the Home Office index has changed to a rising number, suggesting that two separate processes were at work, the increase being due to an increasing number of “non-therapeutic” addicts (*Lancet*, 1964). This paper reports a fresh survey of all the heroin addicts known to the Home Office between 1954 and 1964 inclusive. Heroin addicts were chosen for this survey because most of the newly recorded addicts took this drug. Their number has increased strikingly compared with those addicted to other narcotics (Official Reports).

Home Office Figures

The index or register kept by the Home Office is commonly misunderstood. It is compiled from information reaching the Home Office from various sources. The most important are the routine inspections of retail pharmacists' records. These inspections are carried out by the police, and when they show regular or unusual supplies of drugs to particular individuals this is reported to the Home Office. Further inquiry is made, usually by a regional medical officer of the Ministry of Health, or Scottish Home and Health Department, to discover whether the case is one of addiction or of genuine medical necessity. The police also report cases of addiction encountered in the course of other inquiries. Further cases may be reported to the Home Office by doctors, hospitals, social workers, or similar sources. Addiction is not at present notifiable, and doctors have no statutory duty to report such cases. However, if a doctor prescribes narcotic drugs for an addict, the addict's name will eventually reach the index after inspection of the records of the pharmacist dispensing the drugs.

The annual statistics published by the Home Office show only

those addicts known to have been taking drugs during the previous year. They exclude those who are not known to be currently taking drugs—for example, addicts in prison, abroad, those obtaining all their drugs from illicit sources, as well as those permanently or temporarily cured. These figures do not give an accurate estimate of the total number of addicts, for three groups will not be noted:

- (1) Those in the early stages who obtain all their drugs from addict friends or other black-market source.
- (2) Those who do this permanently, who will never be known to the Home Office unless notified by the police.
- (3) Those who have temporarily had their names removed from the register for one of the reasons already given.

Most of the addicts on the index have usually been addicted for a year when first noted, so that the numbers recorded will always be a year behind the true figure.

Results of Survey

This survey reviews every person known to be addicted to heroin in 1954 and all further cases of this addiction notified from then until the end of 1964. Fifty-seven heroin addicts were known in 1954 and 450 new cases were added in the following 10 years. A separate form was prepared giving date of birth, sex, nationality, source of addiction, and the state of addiction in each of the succeeding years to 1964. All deaths were recorded, with the cause where known. The present figures differ slightly from those previously published as further information has become available. For example, some people in earlier reports had been using assumed names; others believed to have disappeared had died; and some believed off drugs in a particular year are now known to have been addicted then.

Most new cases since 1955 have been British. The number has increased and the rate is accelerating (Table I). If this continues, between 200 and 300 new British heroin addicts will be recorded in 1965 and a further increase later. Most had become addicted from some non-therapeutic source (Table II). They fell into three age groups (Table III). Those who became addicted in the course of treatment were aged over 60. British

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