

Papers and Originals

Indomethacin in Rheumatoid Arthritis: an Evaluation of its Anti-inflammatory and Side Effects

PHELIM DONNELLY,* M.D., M.R.C.P.I., D.PHYS.MED.; KENNETH LLOYD,* M.R.C.P.
HUBERT CAMPBELL,† M.A., M.B., B.S.

Brit. med. J., 1967, 1, 69-75

Since its introduction in 1963 indomethacin (1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindol-3-acetic acid) has been reported as an analgesic of value in the treatment of osteoarthritis (Hart and Boardman, 1963; Wanka *et al.*, 1964; Percy *et al.*, 1964) and ankylosing spondylitis (Katz *et al.*, 1963; Hart and Boardman, 1963; Smyth and Godfrey, 1964; Percy *et al.*, 1964; Rothermich, 1964; Michotte and Wauters, 1964; Boland, 1964), and as an agent that effectively reduces joint swelling and inflammation in acute gout (Hart and Boardman, 1963; Smyth *et al.*, 1963a, 1963b; Michotte and Wauters, 1964; Percy *et al.*, 1964; Norcross, 1963; Kåss, 1965). Similar though less striking results have been obtained with indomethacin in rheumatoid arthritis (Hart and Boardman, 1963; Norcross, 1963; Wanka *et al.*, 1964; Percy *et al.*, 1964; Catoggio *et al.*, 1964; Clark 1964; Rothermich, 1964; Datey, 1964; Smyth *et al.*, 1964; Thompson, 1964; Smyth, 1965; Thompson and Percy, 1966). Kelly (1964a, 1964b) found the benefit "often astonishing," while Boland (1964) was unable to demonstrate conclusively any effect of the drug on patients with rheumatoid arthritis. In the treatment of rheumatic fever Vignau *et al.* (1965) concluded that the advantages of indomethacin were outweighed by its side-effects.

A high incidence of side-effects in proportion to therapeutic effect with this drug in rheumatoid arthritis has been observed (Dixon *et al.*, 1963; Boland, 1964; Lövgren and Allander, 1964; Percy *et al.*, 1964; Boyle, 1965). Percy *et al.* (1964) had to withdraw 13 out of 21 patients taking 200 mg. each day, and Katz *et al.* (1965) withdrew 35 out of 97 patients on doses of 100 to 400 mg. a day, for this reason. Hart and Boardman (1963) reported side-effects in 31 out of 52 patients on a daily dose of 50 to 300 mg. Rubens-Duval and Villiaumey (1964) reported 72% side-effects in patients on a daily dose of over 200 mg., and Robinson (1965) could maintain therapy in less than 50% of patients receiving 125 to 150 mg. a day. On the other hand, Robecchi *et al.* (1964), using doses of 75 to 150 mg. each day, had only one withdrawal with 28 patients and found that though side-effects were frequent they were not unduly troublesome. These findings indicate that the therapeutic index of this drug is low.

Hart and Boardman (1963) demonstrated no greater efficiency with the higher range of dose and recommended 50-150 mg. as a satisfactory daily dose of indomethacin consistent with minimal side-effects.

Present Trial

This trial was designed (1) to test the analgesic and anti-inflammatory effects of indomethacin in rheumatoid arthritis over a short term in a relatively low dose, and (2) to note the true incidence of side-effects.

Patients were accepted for the trial on the basis of active inflammation of six or more proximal interphalangeal joints of the fingers. This criterion was specified because of the ease of measurement of swelling and tenderness of these joints. Patients with flexion deformity of the fingers or firm non-tender thickening of the proximal interphalangeal joints resulting from long-standing joint changes were excluded.

Thirty patients with "classical" or "definite" rheumatoid arthritis were chosen (A.R.A. criteria, Ropes *et al.*, 1957). There were 18 women and 12 men aged 28 to 72, average 52.6 years, with disease of six weeks to 24 years' duration, averaging 8 years 2 months. The duration of disease in nine was from six weeks to four years, in 12 from five to nine years, and in nine for 10 years or more.

A number of patients were already receiving long-term drug therapy, and the dose of these drugs was unaltered during the period of the trial. Six were receiving hydroxychloroquine 600 mg./day, one was receiving oxyphenbutazone, and one Thylin (nifenazone). Adrenocorticosteroids had been given for the previous two years to two patients. One patient on weekly injections of 50 mg. of gold had received a total of 550 mg. of Aurothiomalate at the time of entry into the trial.

Design

The trial lasted for ten weeks, including a "pre-trial" week at the beginning of which an assessment was carried out in order to accustom the patients to the trial procedure; these measurements were discarded. During this week two capsules of placebo were administered—a fact known to the examiner but not to the patient—with the intention of minimizing any placebo response by the time of entry into the trial proper at the end of this week when the first recorded assessment was carried out.

After this week the trial began, a double-blind crossover technique being used over two four-week periods, separated by a week during which all patients received two capsules a day of the placebo. This second placebo week was intended to minimize any possible "carry-over" effect of the drug into the placebo weeks in the group who received the active drug initially.

Indomethacin in standard commercial 25-mg. capsules was matched by a similarly coloured placebo powder (mainly lactose) in identical capsules sealed in similar containers. Two separate dose sequences were prepared. Patients in group 1 received

* Department of Physical Medicine and Rheumatology, United Cardiff Hospitals.

† Department of Social and Occupational Medicine, Welsh National School of Medicine, Cardiff.

indomethacin first for four weeks, followed by placebo for a further four weeks; those in group 2 received placebo followed by the drug. An incremental dosage scheme was adopted in order to reduce the incidence of side-effects (Hart and Boardman, 1963, 1964; Suzman, 1964; Dilsen and Dilsen, 1964; Thompson, 1964). Each four-week period began with two capsules a day. The dose was then increased by one capsule a day at the beginning of each of the ensuing three weeks. Thus when indomethacin was administered the patients received a daily dose of 50 mg., 75 mg., 100 mg., and 125 mg. respectively during each of the four consecutive weeks (Fig. 1).

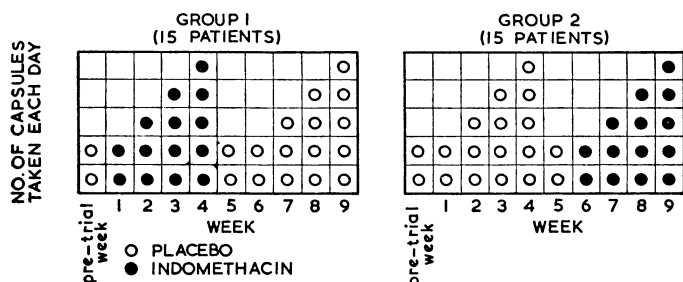


FIG. 1.—Dosage scheme of trial.

The patients were instructed to swallow the capsules with fluid, during or immediately after a meal, and were requested to return the container with any remaining capsules each week in order to receive their supply for the following week.

The first 30 patients examined in the outpatient clinic who fulfilled the criteria of the trial were accepted. They were numbered 1 to 30 consecutively as they entered the trial, each number having previously been allocated at random to either group 1 or 2.

Assessments

Weekly assessments were carried out, the following criteria being used: (1) hand articular index, (2) pool of finger swelling, (3) systemic index (Lansbury, 1958), and (4) patient's opinion.

Hand Articular Index

The amount of small joint involvement of the hands was assessed by the presence of tenderness on firm palpation of the proximal interphalangeal and metacarpophalangeal joints, no attempt being made to grade the degree of tenderness present. The result was expressed as a sum of the number of joints so affected, the maximum possible being 20.

Pool of Finger Swelling

The degree of swelling of each proximal interphalangeal joint was recorded with jeweller's ring-gauges. These consist of a collection of 52 rings of graded sizes from the smallest labelled "A" through "A $\frac{1}{2}$," "B," "B $\frac{1}{2}$," to the largest "Z $\frac{1}{2}$." The circumference of all eight proximal interphalangeal joints and of the two thumb terminal joints, whether affected by arthritis or not, was determined by the smallest ring that could be passed over each joint. The letter size of the rings was equalated numerically from 1 to 52; swelling too large to accommodate the largest ring was recorded as "53." Therefore the sum of the measurements of these 10 joints allowed a theoretical maximum score of 530.

Systemic Index

This index was devised by Lansbury (1958) as a composite numerical expression of five characteristics of rheumatoid

arthritis and is used as an indicator of activity of the disease. Its compilation utilizes five factors: (1) number of analgesic tablets taken each day, (2) duration of morning stiffness, (3) onset of fatigue, (4) strength of hand grip, and (5) E.S.R. (Westergren).

1. Patients were instructed to continue to take any analgesic tablets (usually aspirin) that they had already found effective and tolerable, but they were to regulate the dose and frequency of these tablets according to the demands of the pain. Put simply, "no pain, no tablets; much pain, many tablets; little pain, few tablets." This instruction was repeated each week and the patients were asked to record or remember the number of tablets taken daily, or the number per dose and the frequency of administration.

2 and 3. Patients were asked to note the duration of body stiffness after rising each morning and the length of time elapsing before the onset of fatigue every day.

4. Strength of grip was measured by using a folded rectangular rubber bag in a fabric cover measuring 12 by 6 cm. when deflated. This was connected to a sphygmomanometer recording to 300 mm. Hg and inflated to a pressure of 20 mm. Hg with the valve closed. The height sustained by a single maximum-effort squeeze with each hand was recorded as the mean for both hands. Adequate rehearsal of the method was given at the pre-trial examination.

Each of these estimations was accorded a number as indicated by reference to the standard table of Lansbury and the systemic index expressed as the sum of these numbers; the higher the number the more active is the arthritis.

Patients' Opinion of the Effectiveness of the Capsule

This was judged by their general well-being and their feeling as regards their "rheumatic" symptoms over the week preceding. They were requested to express this as either "much better," "better," "no change," "worse," or "much worse." This was recorded each week as "+2," "+1," "-1," or "-2" respectively. In addition, at the end of the trial the patients were asked their opinion of the capsules and whether they wished to continue taking them.

In addition, on entering and leaving the trial two further assessments were carried out:

Functional grade.—Grades 1–5 were used as recommended by the Joint Committee of the M.R.C. (1954).

Articular Index.—This is a means devised by Lansbury to express numerically the total area of joint inflammation as indicated by tenderness or pain on passive movement. Joints are graded according to size and allocated appropriate numbers: the larger the joint the higher the number; the higher the index the more extensive the arthritis. Thus comparison of total scores indicates expansion or contraction of the pool of joint inflammation.

These estimations entailed 2,740 separate observations which were made by one of us (P. D.) with the exception of 168 observations made over one two-week period.

Side-effects

The incidence and nature of side-effects were recorded weekly. Great care was taken not to inform the patients of any specific side-effect that might be expected, and they were not asked to report any untoward feelings or occurrences. No direct questions were put in this matter; the recorded side-effects were all elicited as a result of spontaneous remarks by the patients in the course of conversation about their general health and well-being.

Routine urine examination, haemoglobin estimation, and total white cell and differential counts were performed weekly. Serum albumin and globulin levels and electrophoretic differentiation, as well as thymol turbidity, flocculation, serum bilirubin, alkaline phosphatase, and glutamic and oxaloacetic transaminases, were performed at the conclusion on all patients completing the trial.

During the course of this trial Bruckner and Randle (1965) reported hepatotoxicity associated with the use of indomethacin. Because of this, further toxicity studies were extended beyond the trial period on those patients who continued taking indomethacin, and will be the subject of a separate communication.

Results

Twenty-eight patients completed the trial. Two patients were withdrawn; one as a result of side-effects which were found to be associated with the placebo and one because of irregular attendance.

Although there was a strict random allocation of patients to groups 1 and 2, these two groups were not comparable during the control period. Those who were given the placebo before the indomethacin were more severely affected by rheumatoid arthritis than were those who were treated with indomethacin first and given the placebo subsequently.

The score by the systemic index of group 1 was 55 during the control period and for group 2 was 71, a difference of 16 units. This difference persisted throughout the trial, so that at the end of it group 1 had a mean systemic index of 44 units and group 2 of 57 units. Fortunately, there was a full range of all grades of patients in both groups; in group 1 the range of scores for the systemic index during the control period was from 73 units to 19 and in group 2 from 117 to 18.

A similar difference between these two groups could be shown for each of the indices used as a measure of disease. For all indices except one, group 2 was more severely affected than group 1 during the control period and remained so throughout the trial period.

Articular Index

A change of 10 or more in the articular index at the completion of the trial compared with the admission figure was taken to indicate either spread or regression of the arthritis.

Of the 28 patients 11 had a smaller index on completion, in nine it increased, and in eight there was no change. The timing of active therapy did not appear to affect this result. Of the 14 patients who received indomethacin in the last month one showed no change, six were worse, and seven better, as judged by the articular index.

1. Hand Articular Index

This is a measure of the patients' response to pain as well as the extent of the pain experienced. Both groups of patients showed a reduction of sensitivity to squeezing of finger joints during the course of the trial, and the rate of regression in the response to this procedure was the same for both groups irrespective of whether they were on the drug or on the placebo.

During the month on placebo the average number of painful joints for all patients was 9.2, whereas during the month on indomethacin the average was 9.5 joints affected, a completely negligible difference (see Statistical Tables). The number of patients who were better during the month on placebo was 15; 12 were better during the month on indomethacin and one was unchanged.

There was no evidence of any "carry-over" effect during the first two weeks after the use of indomethacin, nor was there any evidence of deterioration during the period on the placebo.

2. Pool of Finger Swelling

The use of jewellers' ring-gauges helped to eliminate the subjective response; none the less, there was a marked improvement in both groups of patients over the period. This may

have been due partly to increasing patient-tolerance to the rings and partly to the physician's increase in pressure when applying the rings.

Both groups responded in the same way on indomethacin. Group 1 improved slightly during the month and then continued to improve when placed on the placebo, and group 2 responded slightly on the placebo but continued to respond when treated with the active principle. Fifteen patients did better during the month on the placebo, whereas 13 did better on the indomethacin. The net result was that the mean score for both groups was identical at 366 units per patient. None of these differences are of formal statistical significance (see Statistical Tables).

Patients were selected for the presence of inflammatory finger-joint swellings. As some of these swellings were too large for measurement by the standard range of jewellers' ring-gauges, they were recorded as "53." Consequently, it was not possible to record fluctuations in their size. Accordingly, this factor would tend to reduce the amount of shift recorded in the pool of finger swelling. This point was examined by taking the six patients with a pool of finger swelling of "500" or over and comparing them as a group with the remaining 22 patients.

It was confirmed that though the contraction of the pool of swelling was less marked and the rate of improvement less steep in the group with the larger swellings the overall trend of this and the other measurements did not differ. Accordingly, this factor did not significantly affect the results.

3. Systemic Index

(i) *Analgesic Tablets*.—Group 1 showed a decline during the period of treatment with a relapse when this was changed to a placebo, whereas there was no difference at all in the habits of group 2, who were rather more severely affected by the disease and were using more tablets. The mean difference between the two periods was negligible (see Statistical Tables). Fifteen patients took more tablets during the treatment period and 11 more during the placebo period; two remained unchanged.

(ii) *Duration of Morning Stiffness*.—This showed no consistent trends. Ten patients felt that they had improved during the treatment and 10 during the placebo period. Eight were the same during both months (see Statistical Tables).

(iii) *Fatigue*.—The delay in onset of fatigue suggests that indomethacin has some important "tonic" effect, but it is interesting to note that in this test alone group 1 was worse than group 2 during the control period. Group 1 rapidly improved on indomethacin and relapsed again on placebo, whereas group 2 grew worse on the placebo and improved on the drug. The overall effect was that the mean delay in fatigue was 5.9 hours on indomethacin and 5.1 hours on the placebo; this difference is not statistically significant (see Statistical Tables). Thirteen patients thought they were less fatigued during the treatment month and seven during the placebo month; eight detected no difference.

(iv) *Hand Grip*.—The ability to squeeze the bag improved with practice, and once again there was evidence of a "learning" effect in the changes. Group 1 was consistently better than group 2, but group 1 improved rapidly on indomethacin but failed to continue this improvement on placebo, whereas group 2 improved on the placebo and continued to improve on the drug. The net result was that the mean grip during indomethacin was 189 mm. Hg and during the month on placebo was 185, a difference of 4 mm. Hg to the advantage of indomethacin (see Statistical Tables). Sixteen patients were better during the period on indomethacin and 12 during the placebo period.

(v) *Erythrocyte Sedimentation Rate*.—The E.S.R. is the only measurable variable that is not influenced by subjective feeling or observer error. The two groups were initially quite different

from each other; group 1 had an E.S.R. of 55 mm. and group 2 of 71 mm., a difference of 16 mm. When group 1 was started on the drug there was an increase in the E.S.R., and when the placebo replaced it there was a sharp fall. Similarly, group 2 improved while on the placebo, but as soon as the drug was used the E.S.R. increased once again to a level higher than that during the control period. During the treatment period the mean rate was 48.6 mm. and during the placebo period it was 42.4 mm., a difference of 6.2 mm., with a standard error of 3.8 ($t=1.8$ $P=0.1$). Though the difference does not reach a formal statistical significance, the consistency of the pattern suggests that in fact indomethacin has an action to increase the E.S.R. (see Statistical Tables). Seven patients improved during the month on indomethacin and 21 during the month on placebo.

The *Systemic Index* is arrived at from aggregation of the results of the above five methods of measurement. It is already clear that there were no important differences. However, the systemic index was much higher in group 2 than in group 1, but both groups of patients improved steadily during the period of the trial. The mean score of the 28 patients during their month of treatment was 54.4 and during the month on placebo was 55.7, a difference of 1.3 ± 4.0 —a difference which is not statistically significant (see Statistical Tables). Sixteen patients were better during the treatment month, 11 during the placebo month, and one was unchanged.

4. Subjective Opinion

Almost all patients felt that they had benefited by the treatment during the period of the trial, 13 thought they were better during the month on indomethacin, 13 preferred the month on placebo, and two were unable to distinguish the two periods (Fig. 2).

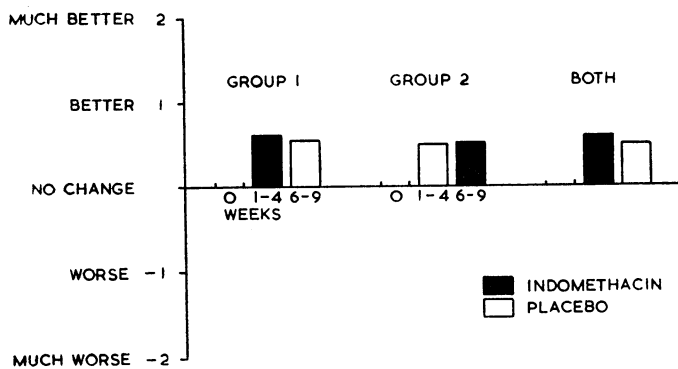


FIG. 2.—Subjective opinion

5. Functional Grade

There were no significant differences here, and the results are set out in Table I.

The inclusion of patients with long-standing disease did not affect the results; extraction of these results and comparison with the remaining patients and with those having disease of short duration showed no difference.

All the results have been reported as an average of four examinations during the month on indomethacin compared

TABLE I

Functional Grade	Entering Trial					Total
	I	II	III	IV	V	
I	17	1	0	0	0	18
II	0	2	3	0	0	5
III	1	0	3	0	0	4
IV	0	0	0	1	0	1
V	0	0	0	0	0	0
Total	18	3	6	1	0	28

with a similar average while on a placebo. No substantial difference to any of the conclusions was made when the results for the fourth examinations alone at the end of each four-week period were compared with each other. The trends of the various responses during these two periods appeared to be similar, and hence should be attributed to some cause other than specific drug action.

Side-effects

The commonest side-effects were headache and gastrointestinal upset. Though the incidence was equal for both indomethacin and placebo, the frequency was higher with indomethacin.

Side-effects occurred in 18 (60%) of the 30 patients while taking indomethacin and in 17 (56.7%) while taking placebo. In 9 (30%) patients side-effects were reported with both placebo and indomethacin, in 10 (33.3%) when taking placebo only and in 11 (36.6%) with indomethacin alone. These are itemized in Table II.

TABLE II.—Side-effects

Type of Side-effect	Patients Affected		Weeks Affected	
	Indo-methacin	Placebo	Indo-methacin	Placebo
C.N.S.	13	14	20	16
Headache	8	8	15	8
Sleepiness	3	1	3	2
Depression	1	2	1	2
Giddiness	1	2	1	2
Muzzy head	0	1	0	1
G.I.T.	16	12	25	14
Dyspepsia	5	3	6	4
Nausea	3	5	10	5
Anorexia	1	1	1	2
Vomiting	3	3	3	3
Diarrhoea	2	0	3	0
Activation of D.U.	1	0	1	0
Activation of hiatus hernia	1	0	1	0
Miscellaneous	10	8	12	11
Rash	2	1	3	2
Increase of arthralgia	2	1	3	2
Neck stiffness	1	1	1	2
Thrombophlebitis	1	1	1	1
Stroke	1	0	1	0
Fatigue	1	0	1	0
Scleral injection	1	0	1	0
Faint feelings	0	1	0	1
Excess sweating	0	1	0	2
Muscle weakness	1	1	1	1

One patient in group 2 withdrew from the trial because of severe side-effects which occurred during the first week of placebo administration. One man with duodenal ulcer and one woman with hiatus hernia, both diagnosed radiologically before the trial, experienced recurrence and worsening of dyspeptic symptoms while on indomethacin.

The occurrence of thrombophlebitis in one man on indomethacin was matched by a similar occurrence in one woman receiving placebo. Both had a previous history of thrombophlebitic episodes.

Transient loss of power in one arm was reported by a man with hypertension after receiving indomethacin 50 mg./day for two days. Rapid improvement occurred and no further episodes were observed, though indomethacin was continued. Cerebral vascular accidents have been recorded previously in patients on indomethacin (Coste *et al.*, 1964).

Statistical Tables

Mean Scores and Standard Error of Mean.—The mean scores during the control period were based on one reading from each patient, and the mean scores during the treatment and placebo periods were based on four readings from each patient.

The difference is taken in every case, so that a plus sign indicates that the patients were better on indomethacin, a negative sign that they were better on the placebo. Group 1: 14 patients treated with indomethacin followed by placebo. Group 2: 14 patients treated with placebo followed by indomethacin.

Hand Articular Index. Number of Joints Painful

Group	Control Period	Indomethacin	Placebo	Difference
Group 1 ..	11.9	9.6 ± 0.9	7.6 ± 0.9	-2.0 ± 1.3
" 2 ..	12.7	9.4 ± 0.8	10.7 ± 0.8	+1.3 ± 1.1
All patients ..	12.3	9.5 ± 0.6	9.2 ± 0.6	-0.3 ± 0.9

Pool of Finger Swelling. Sum of Jewellers' Ring-gauges Passed Over the Finger

Group	Control Period	Indomethacin	Placebo	Difference
Group 1 ..	374	366 ± 10	349 ± 10	-17 ± 14
" 2 ..	388	366 ± 10	383 ± 10	+17 ± 14
All patients ..	381	366 ± 7	366 ± 7	0 ± 10

Use of Analgesic Tablets. Number of Tablets Used Daily to Relieve Pain

Group	Control Period	Indomethacin	Placebo	Difference
Group 1 ..	5.9	4.3 ± 0.5	4.8 ± 0.5	+0.5 ± 0.7
" 2 ..	7.5	7.5 ± 0.7	7.6 ± 0.8	+0.1 ± 1.0
All patients ..	6.7	5.9 ± 0.4	6.2 ± 0.5	+0.3 ± 0.6

Morning Stiffness. Duration in Hours Until Stiffness Relieved

Group	Control Period	Indomethacin	Placebo	Difference
Group 1 ..	1.9	1.9 ± 0.35	2.0 ± 0.43	+0.1 ± 0.56
" 2 ..	2.0	2.0 ± 0.34	2.0 ± 0.23	0.0 ± 0.41
All patients ..	1.9	2.0 ± 0.24	2.0 ± 0.24	0.0 ± 0.35

Duration of Fatigue. Hours Until Onset of Fatigue

Group	Control Period	Indomethacin	Placebo	Difference
Group 1 ..	4.5	6.0 ± 0.6	5.2 ± 0.6	+0.8 ± 0.8
" 2 ..	5.9	5.8 ± 0.6	4.9 ± 0.5	+0.9 ± 0.8
All patients ..	5.2	5.9 ± 0.4	5.1 ± 0.4	+0.8 ± 0.6

N.B.: An increase in this score means the patient has improved.

Hand Grip. Pressure (mm. Hg) in Sphygmomanometer Bulb

Group	Control Period	Indomethacin	Placebo	Difference
Group 1 ..	164	196 ± 9.5	195 ± 9.1	+1 ± 13
" 2 ..	153	183 ± 10.4	176 ± 9.3	+7 ± 14
All patients ..	158	189 ± 7.1	185 ± 6.5	+4 ± 10

N.B.: An increase in this score means the patient has improved.

Erythrocyte Sedimentation Rate. mm. (Westergren)

Group	Control Period	Indomethacin	Placebo	Difference
Group 1 ..	44.7	46.1 ± 4.0	39.5 ± 3.7	-6.6 ± 5.5
" 2 ..	49.1	51.0 ± 3.3	45.3 ± 3.6	-5.7 ± 5.1
All patients ..	46.9	48.6 ± 2.7	42.4 ± 2.6	-6.2 ± 3.7

Systemic Index. Units

Group	Control Period	Indomethacin	Placebo	Difference
Group 1 ..	55	48.9 ± 3.0	48.2 ± 3.8	-0.7 ± 4.8
" 2 ..	71	59.8 ± 4.2	63.2 ± 4.7	+3.4 ± 6.3
All patients ..	63	54.4 ± 2.6	55.7 ± 3.0	+1.3 ± 4.0

Discussion

This trial differs in three important respects from all trials previously reported. Two of these concern modifications to the standard double-blind crossover techniques.

1. The placebo effect that often occurs early during the administration of any drug was diminished by the addition of a pretrial week of placebo only. As a result the baseline figures obtained at entry and used for subsequent comparison, though smaller, were more accurate.

2. Another week of placebo administration was inserted at the crossover in order to minimize dilution of measurements, early in the placebo month, by carry-over of drug response in those patients receiving the drug first.

3. The incremental dose schedule was fixed, and remained unaltered despite the occurrence of side-effects and apparent therapeutic response.

In many of the previously reported trials the dose of indomethacin was permissive, depending on the above factors, with consequent variation in the maximum daily dose achieved in the individual patient, varying from 75 to 300 mg.

In a somewhat similar trial Ward (1964), using indomethacin 200 mg./day in tablet form, demonstrated improvement in morning stiffness and joint tenderness but no change in finger swelling (measured by ring size), grip strength, or in the patients' assessment of pain. In a subsequent double-blind (but *not* crossover) trial, using 150 mg./day in capsule form, he confirmed the above findings except that pain was lessened, and an additional measurement of swelling of larger joints (estimated by eye) was said to show improvement by indomethacin. Thus his claim for beneficial effects was based on subjective measurements only.

Within the dose and time limitations of our trial there was no indication of any anti-inflammatory, detumescent, or analgesic effect of indomethacin on patients with rheumatoid arthritis that could be detected statistically by the eight criteria used.

Two measurements remained unchanged throughout the 10 weeks of the trial—duration of morning stiffness and patients' opinion. Four others showed changes that could not be regarded as significant.

Only two of the criteria used were affected by indomethacin—E.S.R. and time to onset of fatigue—though the changes demonstrated did not reach the level of formal statistical validity.

The delay in onset of fatigue, without other evidence of improvement, was quite noticeable. Many of the patients reported considerable increase in the amount of physical activity they were able to undertake. This effect of indomethacin has not been previously reported. The rise in E.S.R. has been reported—Miehke (1965) found an increase in 21 out of 53 rheumatoid patients who were on indomethacin, and Rubens-Duval and Villiaume (1964) reported raised E.S.R. in some patients. Persistence of an already elevated E.S.R. despite clinical improvement has been noted by Viara and Marrazzi (1964), Katz *et al.* (1965), and Robecchi *et al.* (1964). The mechanism of this E.S.R. rise is obscure and is being investigated.

An important practical point emerges; in patients with rheumatoid arthritis receiving indomethacin it would seem that the E.S.R. can no longer be regarded as a reliable indicator of disease activity.

The two most important clinical indicators of inflammation used in this trial were the hand index and pool of finger-joint swelling. Both of these showed systematic improvement throughout the course of the trial, suggesting that the factors influencing these changes were the results of learning and placebo rather than the expression of any pharmacological effect that could be attributed to indomethacin. These improvements were not the result of changes to be expected in some patients attending for the first time after a recent onset or exacerbation

of arthritic disease. All patients, with one exception, were selected from the regular panel of the follow-up clinic, from patients with fixed review appointments. This general placebo response was borne out by the patients' opinion of the effect of the capsule; 24 of the 28 patients completing the trial elected to continue taking indomethacin capsules even though only 14 were actually receiving the drug at the time of their decision.

There was no evidence of any decrease in joint pain within two to three days, but we did confirm the measurable reduction in finger-joint swelling reported by Hart and Boardman (1963) with doses varying from 50 to 150 mg.; we have demonstrated that this is a learning effect. Katz *et al.* (1963) noted a therapeutic response within 24 to 48 hours, and Ballabio *et al.* (1963), administering doses of indomethacin as low as 100 mg./day, claimed to show anti-inflammatory effects in rheumatoid arthritis within a few hours of administration. We failed to confirm this. Neither did we find evidence of the rebound exacerbation associated with sudden cessation of indomethacin treatment experienced by other workers (Katz *et al.*, 1965).

The use of an "all-or-none" response to digital pressure applied by the assessor as an indication of joint tenderness was thought to be a more accurate measurement for assessing inflammation at weekly intervals than grading the response. It was thought that, even with the same physician taking the measurements, it was impossible to apply the same pressure at weekly intervals with sufficient accuracy to make grading of any value.

We failed to show any analgesic effect of indomethacin, as judged by a fall in the number of analgesic tablets taken each day. The apparent beneficial effect demonstrated in group 1 was offset by the lack of response in group 2, who had the more severe disease. No conclusion can be made from these results. Despite repeated instruction that analgesic tablet dose was to be related to the degree of arthralgia some patients were reluctant "to take tablets." Others, particularly those in group 2, were disinclined to alter a long-established rigid dose-scheme of analgesic tablets. On the other hand, incidental discomfort, not related to the arthritis, as with coryza, influenza, headaches, and even side-effects of the drug, affected the number of aspirin tablets taken by those who carried out their instructions precisely. Of all the measurements used it was thought that this was the least reliable.

With adequate time spent on explanation and rehearsal, our method of measurement of grip strength was accurate enough to justify its substitution for the more time-consuming method suggested by Lansbury (1958). A pretrial comparison of these two methods showed very little difference.

The patients' opinion of the effectiveness of the capsules was found to be a subjective and unreliable indicator on which to base a judgement. In addition to the "normal" clinical variation in feeling of well-being and mood, the incidence and type of side-effects associated with the use of the capsules obviously influenced the patients' opinion. It was also found that the expressions "worse" or "much worse" could apply to the day of assessment or to the previous day, rather than to the week as a whole; the patients' memory of their feelings over the previous week tended to be influenced by their immediate feelings on the day of examination.

The systemic index of patients receiving indomethacin would have shown improvement on this trial were it not for the rise in E.S.R. On the other hand, any fall in the index would then have been due entirely to the effect of the indomethacin in delaying the onset of fatigue; for the other three measurements—grip strength, dose of analgesic tablets, and duration of morning stiffness—remained unaffected.

We took great care to avoid suggesting side-effects to our patients, but in spite of this symptoms occurred with approximately equal incidence during drug and placebo administration and followed a similar pattern in both groups. However, the frequency was greater with indomethacin, notably as regards

headache and gastrointestinal upset. It is worthy of note that the only patient withdrawing from the trial developed headache, nausea, anorexia, and skin rash after receiving only placebo for four weeks. This picture indicates that suggestion did in fact play a large part in producing side-effects. We could not eliminate cross-chat in the waiting-room between patients in the trial and also between other patients taking indomethacin outside the trial.

A high placebo response is a well-recognized feature in patients attending a rheumatological clinic, and this high level of placebo response implies susceptibility to other forms of suggestion; our results support this. This seems to indicate that the true incidence of side-effects attributable to the drug is very much less than the 50 to 70% recorded here and in other papers. We regard the 37% of patients who developed side-effects on indomethacin alone as a more realistic estimate, but even this figure may be an exaggeration, for 30% experienced similar side-effects while receiving placebo.

Summary

In a double-blind crossover clinical trial occupying 10 weeks indomethacin was given in capsule form for four consecutive weeks, starting with a daily dose of 50 mg. and increasing by one 25-mg. capsule a week to a maximum of 125 mg./day. The results on 30 patients with classical or definite rheumatoid arthritis are tabulated and discussed.

With the criteria of assessment based on the systemic index and articular index of Lansbury and measuring finger-joint swelling by means of jewellers' ring-gauges it was not possible to show that indomethacin produced any antiphlogistic effect that held statistical validity. The detumescent and analgesic effects demonstrated were shown to be the result of placebo and learning factors.

A tendency for indomethacin to accelerate the rate of erythrocyte sedimentation was revealed, and evidence for a specific anti-fatigue effect of the drug in rheumatoid arthritic patients is presented.

Side-effects are listed. Though they occurred more often with indomethacin, the incidence, type, and pattern were the same with both drug and placebo. The inference is made that suggestion played a part in determining both the incidence and the variety of side-effects encountered in the trial.

Compilation of our findings was considerably assisted by computer analysis of the figures; our thanks are due to Messrs. Merck Sharp and Dohme Ltd. for a grant to defray the expenses of this, also to Dr. Robert Hodgkinson, of the same firm, for his advice, for supplying the placebo and indomethacin capsules, and for arranging the randomization.

Our thanks are also due to the staff of the pathology and pharmacy departments of the Cardiff Royal Infirmary; to our secretaries and the medical illustrators who were so helpful; and to Nurse Jenkins, of our outpatient department, who assisted in the weekly clinics.

REFERENCES

- Ballabio, C. B., Giraldo, E., Girardi, G., Caruso, I., and Colombo, B. (1963). *Reumatismo*, **15**, 487.
 Boland, E. W. (1964). *Calif. Med.*, **100**, 145.
 Boyle, A. C. (1965). *Brit. med. J.*, **1**, 1191.
 Bruckner, F. E., and Randle, A. P. H. (1965). *Ann. phys. Med.*, **8**, 100.
 Catoggio, P. M., Centurion, A., Alberti, H., Roldan, H., and Canepa, I. (1964). *Arthr. and Rheum.*, **7**, 300.
 Clark, G. M. (1964). *Ibid.*, **7**, 300.
 Coste, F., Delbarre, F., Braun, S., and Nastorg, G. (1964). *Rhumatologie*, **16**, 415.
 Datey, K. K. (1964). *Proceedings of 8th Congress of Japan Rheumatism Association (Okayama)*, p. 198.
 Dilsen, N., and Dilsen, G. (1964). *Rhumatologie*, **16**, 443.
 Dixon, A. St. J., Jones, L., Wanka, J., and Wood, P. (1963). 5th European Congress on Rheumatic Disease (Stockholm).
 Hart, F. D., and Boardman, P. L. (1963). *Brit. med. J.*, **2**, 965.
 — (1964). *Practitioner*, **192**, 828.
 Käss, E. (1965). *Acta rheum. scand.*, **11**, 205.

- Katz, A. M., Pearson, C. M., and Kennedy, J. J. (1963). *Arthr. and Rheum.*, **6**, 281.
- (1965). *Clin. Pharmacol. Ther.*, **6**, 25.
- Kelly, M. (1964a). *Med. J. Aust.*, **2**, 541.
- (1964b). *Lancet*, **2**, 474.
- Lansbury, J. (1958). *Arthr. and Rheum.*, **1**, 505.
- Lövgren, O., and Allander, E. (1964). *Brit. med. J.*, **1**, 118.
- Medical Research Council and Nuffield Foundation (1954). *Ibid.*, **1**, 1223.
- Michotte, L. J., and Wauters, M. (1964). *Acta rheum. scand.*, **10**, 273.
- Mielke, K. (1965). *Münch. med. Wschr.*, **107**, 38.
- Norcross, B. M. (1963). *Arthr. and Rheum.*, **6**, 290.
- Percy, J. S., Stephenson, P., and Thompson, M. (1964). *Ann. rheum. Dis.*, **23**, 226.
- and Thompson, P. (1963). 5th European Congress on Rheumatic Disease.
- Robecchi, A., Marrazzi, G., and Viara, M. (1964). *Reumatismo*, **16**, 388.
- Robinson, R. G. (1965). *Med. J. Aust.*, **1**, 266.
- Ropes, M. W., Bennett, G. A., Cobb, S., Jacox, R., and Jessar, R. A. (1957). *Ann. rheum. Dis.*, **16**, 118.
- Rothermich, N. O. (1963). *Arthr. and Rheum.*, **6**, 295.
- (1964). *Proceedings of 8th Congress of Japan Rheumatism Association (Okayama)*, p. 159.
- Rubens-Duval, A., and Villiaume, J. (1964). *Rev. Rhum.*, **31**, 204.
- Smyth, C. J. (1965). *Arthr. and Rheum.*, **8**, 921.
- Amoroso, C., and Velayos, E. (1964). *Ibid.*, **7**, 345.
- and Godfrey, R. (1964). *Ibid.*, **7**, 345.
- Velayos, E. E., and Amoroso, C. (1963a). *Ibid.*, **6**, 299.
- (1963b). *Acta rheum. scand.*, **9**, 306.
- Suzman, M. M. (1964). *Rhumatologie*, **16**, 423.
- Thompson, M. (1964). *Ibid.*, **16**, 439.
- and Percy, J. S. (1966). *Brit. med. J.*, **1**, 80.
- Viara, M., and Marrazzi, G. (1964). *Rhumatologie*, **16**, 429.
- Vignau, A. I., Correa, E. T., Guasch, J. L., Schuster, A. C., Patri, A. M., Vaisman, S. B., and Mortimer, E. A. (1965). *Arthr. and Rheum.*, **8**, 501.
- Wanka, J., Jones, L. I., Wood, P. H. N., and Dixon, A. St. J. (1964). *Ann. rheum. Dis.*, **23**, 218.
- Ward, J. R. (1964). *Excerpta Medica International Congress*, No. 82, edited by S. Garattini and M. N. G. Dukes, p. 353. Amsterdam.

Effect of Atrial Systole on Right Ventricular Stroke Output in Complete Heart Block

W. J. GILLESPIE,*† M.D.; D. G. GREENE,*‡ M.D.; N. B. KARATZAS,* M.D.
G. DE J. LEE,* M.D., F.R.C.P.

Brit. med. J., 1967, **1**, 75-79

The effect of atrial contraction in augmenting ventricular filling and the proper timing of this event late in ventricular diastole are thought to be important factors for producing optimal stroke output by the heart. Animal studies have repeatedly shown this (Gesell, 1915; Wiggers and Katz, 1922; Jochim, 1938; Linden and Mitchell, 1960; Skinner *et al.*, 1963), and in man there has been much renewed interest in the role of atrial function largely because of the development of electrical means for converting cardiac arrhythmias to sinus rhythm (Lown *et al.*, 1962; Oram *et al.*, 1963) and for pacing the heart in patients with complete heart block (Sowton, 1964). However, precise evidence in man about the part played by atrial contraction is still scanty, chiefly because no direct method is yet available in man for the measurement of beat-by-beat changes in stroke output.

Ideally it would be an advantage to contrive an experimental situation in which the behaviour of the normal human heart was studied under circumstances in which the ventricles contracted at a constant rate while the time interval between atrial and ventricular systole was varied systematically over the full range of the cardiac cycle. A unique group of healthy individuals enables such a study to be performed in man; and these are subjects with congenital complete heart block. We have therefore made beat-by-beat measurements of right ventricular stroke output in a group of these healthy subjects, and have compared our results with similar measurements made in a second group of patients with complete heart block associated with myocardial disease in order to examine the contribution made by atrial systole to ventricular stroke output in each group.

Methods

Beat-by-beat measurements of right ventricular stroke output were made indirectly from continuous measurement of pulmonary capillary blood flow, the body plethysmograph and nitrous oxide method (Lee and DuBois, 1955) being used. The pulsatile nature of lung capillary blood flow is due to the pulsatile ejection of blood from the right ventricle during each systole, so that beat-by-beat measurements of right ventricular

stroke volume may be obtained simply by integrating the volume of each lung capillary blood flow pulsation.

We used a whole-body plethysmograph whose ambient pressure was kept constant by means of a pneumatic servo flowmeter (Stott, 1963). This device automatically detected any change in plethysmograph pressure due to physiological events within the subject's lungs, and instantaneously corrected this change by injecting or extracting air from the chamber at exactly the same rate of gas flow as that occurring in the lungs. The rate of gas transfer by the flowmeter was recorded continuously. The device was linear over its working range of 0-200 ml./sec. gas flow, with a flat frequency response to 12 c./s. Pulmonary capillary blood flow was measured throughout the cardiac cycle by continuously recording the rate of N₂O uptake from the lungs after a single breath of 80% N₂O in oxygen. Details of the procedures undertaken to obtain these measurements have already been published in a paper from this laboratory (Bosman *et al.*, 1964).

In brief the subject lay comfortably inside the body plethysmograph and breathed through a mouthpiece connected to a solenoid-operated valve box opening to the plethysmograph atmosphere on one side and to a 5-litre bag containing 80% N₂O in oxygen on the other. After a preliminary period breathing air he was asked to breathe out fully; the solenoid valve was then switched to the N₂O bag and the subject took a maximal inspiration from the bag. He then breathed out in a slow and relaxed manner for 15 seconds while the plethysmograph-flowmeter curve of N₂O absorption was made. During this time expired N₂O concentration at the mouth was measured by an infrared N₂O meter in closed circuit with the body plethysmograph. The subject's electrocardiogram (lead II) was also recorded for timing purposes. After the N₂O procedure the subject was switched to breathe from the plethysmograph atmosphere once more. The breathing procedure for the air-

* Department of Cardiology, Radcliffe Infirmary; and the Department of the Regius Professor of Medicine, University of Oxford.

† Present address: Department of Medicine, University of Mississippi, Jackson, Miss.

‡ Present address: Department of Medicine, State University of New York at Buffalo, Buffalo General Hospital, Buffalo, N.Y.