INDOMETHACIN IN IN-PATIENT TREATMENT OF RHEUMATOID ARTHRITIS

BY

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Indomethacin has been used in the treatment of rheumatic disease for over 3 years. Preliminary reports of the effectiveness of the drug were encouraging (Rothermich, 1963; Norcross, 1963) Katz, Pearson, and Kennedy (1963) also found the drug to be beneficial but treatment had to be discontinued in over 20 per cent. of patients because of side-effects. Hart and Boardman (1963) showed that indomethacin produced a measurable reduction in swelling of the proximal interphalangeal joints in patients with rheumatoid arthritis and that, when a placebo and the drug were used alternately, significant rebound effects commonly occurred with the commencement of placebo treatment. Side-effects principally headache, dizziness, dyspepsia, and mental disturbances, were frequent being observed in over 50 per cent. of patients treated with a dose exceeding 200 mg. A trial of the drug by Wanka, Jones, Wood, and Dixon (1964) showed that indomethacin was effective when compared with a placebo, and a comparative trial against phenylbutazone by Percy, Stephenson, and Thompson (1964) showed that 200 mg. indomethacin was approximately equivalent to 300 mg. phenylbutazone daily, although a decidedly higher incidence of side-effects occurred with indomethacin.

During this period of development of the drug it was supplied in tablet form and the doses used ranged from 150 to 400 mg. daily. Wanka and others (1964), using this preparation and range of dose, reported one case of intestinal haemorrhage and one of perforated gastric ulcer. Lövgren and Allander (1964) used a similar dosage in eighteen patients with rheumatoid arthritis, six of whom had a previous history of peptic ulcer but had negative barium meals immediately before treatment; five patients developed peptic ulcers, two of these having no previous history, and three of the five had severe bleeding.

During the past 2 years indomethacin has been supplied in capsule form and the manufacturers have recommended an initial dose of 50 mg. daily, gradually increasing to a maximum of 150 mg. The incidence of side-effects was stated to have fallen from 50 to 10-30 per cent. of all treated patients (Today's Drugs, 1964) as a result of using capsules and more conservative dosage, and Clark (1964) reported satisfactory improvement in many patients of a large group with rheumatoid arthritis using this scale of dosage. Recently Hart and Boardman (1965) have compared 75 mg. indomethacin daily with 300 mg. phenylbutazone daily, in out-patients with rheumatoid arthritis. A double-blind cross-over trial was carried out, each drug being given for a period of 28 days. No significant differences were found in the relief of symptoms although there was a greater reduction of morning stiffness with phenylbutazone. There were no significant differences in strength of grip or in improvement in ring sizes of proximal interphalangeal joints, but indomethacin tended to have a greater effect on the latter. The preference of patients was in favour of phenylbutazone. The incidence of side-effects of indomethacin in this short-term trial are not stated, but in long-term studies on patients with rheumatoid arthritis, osteo-arthritis, and ankylosing spondylitis, the authors found that 37 per cent. of the patients developed side-effects of drug treatment.

The present study has been carried out to evaluate indomethacin in a dose of 50 to 100 mg. in the in-patient treatment of patients with rheumatoid arthritis. Salicylates are currently the mainstay of drug therapy while the patient is being treated with rest in bed and splintage followed by graded exercises. It was our aim to decide if indomethacin could effectively replace salicylates under these circumstances.

Hajnal, Sharp, and Popert (1959) have drawn

attention to the considerable effect of "spontaneous improvement" in hospitalized patients. In addition to rest in bed and splintage, other features such as increasing familiarity with hospital environment and in the case of strength of grip, practice in the use of the apparatus, contribute to the improvement shown. This must be dissociated from the effect of drug therapy before the value of a new drug can be assessed.

Patients Studied and Methods Employed

34 women and eight men with classical and definite rheumatoid arthritis (1958 A.R.A. Criteria—Ropes, Bennett, Cobb, Jacox, and Jessar, 1959) were studied. Before entering the trial each patient spent one week settling into the hospital routine. During this period analgesia was provided by soluble aspirin and was maintained at the pre-admission dose provided that this did not exceed 4 g. daily. If the patient was already on corticosteroids, the dose was maintained at the pre-admission level during the first week and throughout the trial.

Patients were excluded from the study if they had known peptic ulceration or severe dyspepsia or were intolerant of aspirin, or if the grip test could not be adequately performed by reason of severe anatomical deformity of the hands or if the strength of grip exceeded 300 mm. Hg.

The patients were allotted alternately to indomethacin or soluble aspirin on entry. The first drug was given for a 2-week period and then the other drug was administered for a further 2 weeks, so that half the patients received indomethacin followed by soluble aspirin, and the other half received soluble aspirin followed by indomethacin. The soluble aspirin was specially coloured and flavoured and the patients were unaware of the identity of the tablets. It was given in a dose of 4 g. daily throughout the 2-week period. Indomethacin was given in a dose of 25 mg. twice daily for 2 days, followed by 25 mg. three times daily for 6 days and then 25 mg. four times daily for the remaining 6 days.

Of the 42 patients, 38 completed the study. Two patients were withdrawn while taking soluble aspirin, one because of severe deafness and the other on account of repeated vomiting. One patient developed profound dizziness on indomethacin and the drug had to be withdrawn. The fourth patient was given an incorrect dose of indomethacin during the second week of treatment and was therefore excluded from the analysis. Of the remainder, twenty patients had commenced the trial taking soluble aspirin and eighteen patients had started with indomethacin. Five of those starting on soluble aspirin were taking prednisolone with a mean daily dose of 9 mg.; seven of those starting on indomethacin were taking prednisolone with a mean daily dose of 10 mg.

Clinical Assessment.—Assessments were carried out on the first day of the trial and thereafter at weekly intervals until the completion of the study. As far as possible the patients were assessed at the same time of day throughout and the daily physiotherapy was not given until the assessments had been made. Strength of grip of both hands were recorded weekly. Swelling of the proximal interphalangeal joints was measured using jeweller's rings. These rings were labelled from A to Z with intermediate half-sizes; the diameter of size A was 0.476 in. and the increase in diameter from size A to B was 0.015 in. The patients were questioned concerning headache, dizziness, and dyspepsia, and any other side-effects were noted. At the end of the study the patients' preference for one drug or the other was recorded.

Analysis of Results

The mean strength of grip at the commencement of the study and at weekly intervals throughout the trial was calculated for each series of patients (Table I).

TABLE I
MEAN VALUES FOR WEEKLY ESTIMATIONS OF
STRENGTH OF GRIP (mm. Hg) FOR PATIENTS STARTING
ON SOLUBLE ASPIRIN AND INDOMETHACIN

Starting Drug		Soluble Aspirin	Indomethacin
No. of Cases		20	18
Grip (mm. Hg.)	Initial	145.65	159.28
	Week 1	163.90 } Aspirin	194.11 }
	Week 2		194.50 } Indomethacin
	Week 3	183.80 } Indomethacin	199.17 }
	Week 4		202.06 } Aspirin

Improvement was most marked during the first week of treatment with both drugs and in this week the average improvement was almost twice as great in those starting on indomethacin as in those starting on soluble aspirin. In the second week the indomethacin group—although then on a slightly higher dosage, having changed from 25 mg. three times daily to 25 mg. four times daily—showed on average no improvement in mean strength of grip but the value in the soluble aspirin group continued to improve, so that after 2 weeks the difference had narrowed considerably. During the second half of the study both groups showed some further average improvement, which was again more steady in those starting on aspirin, who were now on indomethacin; over the whole of the second fortnight those now on soluble aspirin showed only half the improvement of the other group. The total improvement after 4 weeks was virtually identical in the two groups.

In order to exclude at least part of the random variations known to play a considerable role in

patients suffering from rheumatoid arthritis, the further statistical analysis shown in Table II was based on the means of the two assessments of each patient after weeks 1 and 2 and after weeks 3 and 4, when the patients had been under treatment with each drug for a sufficient period of time for it to have influence on the test results. The analysis was done as recommended for cross-over trials in the appendix to a paper by Hajnal, Sharp, and Popert (1959). This method allows the measurement not only of the difference in the effect of the two drugs but also of the effect of "spontaneous improvement" which comprises the effect of all other treatment and environmental factors, including practice in the use of the apparatus for the grip test.

As the range of mean strength of grip varied considerably in our patients—from as low as 72 mm. Hg to 300 mm. Hg (the highest registered by our apparatus)—it was felt that the proportionate difference between the mean grip values on the two drugs was more meaningful than the numerical difference; the proportions were taken in percentages of the higher of the two values compared. The relevant statistical calculations were made from both numerical and proportionate differences.

It will be seen (Table II) that spontaneous improvement was about twice as great as the drug effect and statistically far more significant whether the calculation was done numerically or proportionately; but the drug effect, in favour of indomethacin, just reached 5 per cent. significance in the proportionate calculation. [If we had based our calculation on the difference between initial assessment and the end of week 2 and between the ends of weeks 2 and 4, *i.e.* without attempt to exclude random variations, the drug effect would have worked out numerically slightly larger (7.2 mm. Hg) but statistically not significant, and proportionately it would have been smaller and still less significant, and the effect of "spontaneous improvement" would have about doubled, with ample statistical significance.]

Ring sizes were assessed in similar fashion. We did not work out actual ring sizes but only the improvements from week to week as shown in Table III. It will be seen that the largest mean improvement with both drugs occurred in the first week but this was not as large in comparison with other weeks as the improvement in grip strength. There was no persistent trend over the 4 weeks; in the first and in the last week of the trial those on indomethacin, and in the second and third week those on aspirin were doing a little better, while the total improvement over the 4 weeks was virtually the same in the two groups.

TABLE III
WEEKLY MEAN IMPROVEMENTS IN RING SIZES FOR
PATIENTS STARTING WITH SOLUBLE ASPIRIN AND
INDOMETHACIN

Starting Drug		Soluble Aspirin	Indomethacin
No. of Cases		20	18
Ring Sizes	Week 1 Week 2	4.03 3.30 } Aspirin	4.72 2.25 } Indomethacin
	Week 3 Week 4	1.35 3.75 } Indomethacin	1.89 3.42 } Aspirin
	Total	12.43	12.28

On studying the figures it will be apparent that there was no difference between the two drugs. An analysis on lines comparable to that for strength of grip was carried out and confirmed this finding. It also showed that most of the improvement which occurred was attributable to "spontaneous improvement".

Drug Toxicity.—The side-effects encountered during the two treatment periods are shown in Table IV (opposite); included are those which occurred in the four patients who were not considered in the analysis. Headaches were commonly encountered during indomethacin treatment but they were not severe and often subsided after a few days

TABLE II
MEAN STRENGTH OF GRIP DURING SOLUBLE ASPIRIN AND INDOMETHACIN TREATMENT PERIODS AND
DIFFERENCES BETWEEN THESE VALUES
[INDOMETHACIN RATINGS (A) MINUS SOLUBLE ASPIRIN RATINGS (B)]

Starting Drug	No. of Cases	Mean Strength of Grip (mm. Hg)		(A) minus (B)	
		Mean of Weeks 1 and 2	Mean of Weeks 3 and 4	mm. Hg	In Percentage of Higher Value
Soluble Aspirin	20	(B) 168.75	(A) 186.05	17.30	9.42
Indomethacin	18	(A) 194.31	(B) 200.62	-6.31	-2.77
Drug Effect	(mm. Hg)	$\frac{1}{2}[17.3 + (-6.3)] = 5.5 \pm 3.37$ (standard error)		P < 0.12	
Spontaneous Improvement	(mm. Hg)	$\frac{1}{2}[17.3 - (-6.3)] = 11.8 \pm 3.37$ (standard error)		P < 0.003	
Drug Effect	In percentage of higher value	$\frac{1}{2}[9.42 + (-2.77)] = 3.32 \pm 1.64$ (standard error)		P < 0.05	
Spontaneous Improvement	In percentage of higher value	$\frac{1}{2}[9.42 - (-2.77)] = 6.09 \pm 1.64$ (standard error)		P < 0.001	

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TABLE IV
SIDE-EFFECTS ATTRIBUTABLE TO SOLUBLE ASPIRIN
AND INDOMETHACIN IN 42 PATIENTS

Side-effect	Drug	
	Soluble Aspirin	Indomethacin
Headache	10	17
Dizziness	3	4
Deafness	6	0
Dyspepsia	10	10
Vomiting	3	1
Diarrhoea	3	0
Rash	0	1
Sweating	1	1

although the indomethacin was continued. The high incidence of headaches reported during soluble aspirin treatment is surprising and in only one instance was it possible for the headache to have carried over from indomethacin to soluble aspirin treatment periods. Direct questioning of the patients regarding headache may have been responsible for this finding. Severe dizziness occurred in only one patient during indomethacin treatment and necessitated withdrawal from the trial. Gastro-intestinal disturbances were more troublesome during soluble aspirin treatment and caused the withdrawal of one patient from the study. A slight rash developed on the feet and ankles of one patient while on indomethacin but this did not interfere with the continuation of the study.

Patient Preference.—This is shown in Table V. All three patients who were withdrawn from the trial because of severe side-effects on one drug completed 2 weeks of treatment on the other drug and are shown as preferring that drug.

TABLE V
PATIENT PREFERENCE

Preference	No. of Cases
For Soluble Aspirin	21
For Indomethacin	13
None	7
Total	41

Discussion

The anti-inflammatory action of indomethacin has been demonstrated convincingly under experimental conditions. Winter, Risley, and Nuss (1963) showed that the drug had a powerful effect in inhibiting granuloma formation in rats. In addition, inflammatory oedema induced by carrageenin was suppressed. Boris and Stevenson (1965) found that

indomethacin was the most powerful of a group of five anti-inflammatory agents in inhibiting the inflammatory reaction induced by carrageenin in rats, the others being flufenamic acid, mefenamic acid, oxyphenylbutazone, and phenylbutazone in order of decreasing potency. Under clinical conditions, Hart and Boardman (1963) confirmed this anti-inflammatory action using 150-300 mg. of the drug daily. In view of the high incidence of side-effects with this range of dose we wished to study the effect of indomethacin in a dose not exceeding 100 mg. daily in the in-patient treatment of rheumatoid arthritis and to compare it with soluble aspirin in a dose commonly used in these patients. Studies had already been carried out by Hart and Boardman (1965) and Thompson and Percy (1966) and the drug was found to have considerable therapeutic value in patients with a variety of rheumatic diseases.

In recent years salicylates have been shown convincingly to have anti-inflammatory properties in experimental animals. Spector and Willoughby (1963) showed that systemic sodium salicylate has an inhibitory effect on the volume of exudate in turpentine-induced pleurisy in the rat and causes a non-specific suppression of the action of many substances that increase vascular permeability. Kelemen (1963) studied acute inflammatory oedema in rats using ^{131}I serum albumin. He considered that there were two components to the inflammatory response. One was inflammatory swelling which was diminished by salicylate. The other, a possible tissue component, preceded visible swelling, persisted after the oedema had disappeared, and was unaffected by salicylate. In view of this work on salicylates in experimentally-induced inflammation, it must be borne in mind that doses of 4 g. daily in patients with rheumatoid arthritis may have anti-inflammatory activity of the same order of magnitude as that shown by indomethacin in low dosage.

In this study we have used strength of grip and improvement in swelling of the proximal interphalangeal joints measured by jeweller's rings to assess the weekly improvement throughout the trial period. Analysis of mean strength of grip during periods of treatment with soluble aspirin and indomethacin has shown that drug effect was approximately one half of the effect attributable to spontaneous improvement. It has also been shown that indomethacin had a greater effect than aspirin in improving strength of grip and that this difference was just significant at the 5 per cent. level. On the other hand, there was no difference between the two drugs in their effect in reducing swelling of the proximal interphalangeal joints and most of the

improvement which occurred was the result of spontaneous improvement.

There was a greater preference of patients for soluble aspirin than for indomethacin in this trial. The incidence of headache during soluble aspirin treatment was surprisingly high, so that the patient preference can hardly be due to indomethacin headaches unless these were qualitatively different from the headaches reported during aspirin treatment. Greater pain relief from aspirin in the dosage used may have been important. Hart and Boardman (1963) stated that indomethacin had no analgesic action in the mouse or rat using methods then in use. The manufacturers claim, as a result of controlled clinical studies, that 50 mg. indomethacin is equal in analgesic effect to 600 mg. acetylsalicylic acid. If this is so, then the analgesia produced by aspirin in this study was much greater than that produced by indomethacin.

The high incidence of side-effects of indomethacin reported in the literature has made physicians cautious. Headache and dyspepsia were still fairly frequent in this study despite the low dosage employed and the slow build-up of the drug. On the other hand, the incidence of side-effects except headache differed little from that occurring with 4 g. soluble aspirin daily. There is little doubt that side-effects would have been reported less frequently with both drugs if patients had not been asked about specific symptoms. No serious complications such as gastro intestinal haemorrhage occurred, but the trial was of short duration and patients with severe dyspepsia or known peptic ulcer were not admitted to it. It is to be noted that, in the studies of Hart and Boardman (1965) and Thompson and Percy (1966), cases of neurological disturbance and gastro-intestinal bleeding were reported and that these side-effects could present after many months of treatment.

Summary

A cross-over trial of indomethacin and soluble aspirin has been conducted in in-patients with rheumatoid arthritis. The indomethacin was increased from 50 to 100 mg. during the treatment period, but the dose of soluble aspirin was maintained at 4 g. daily.

A method of analysis has been used which dissociates drug effect from other factors which may lead to the improvement with time usually observed in hospitalized patients regardless of medication. This has re-emphasized the important contribution of these factors.

Comparison of the two drugs has shown that strength of grip improved to a greater extent during indomethacin treatment and that this result was just significant at the 5 per cent. level. Decrease in swelling of proximal interphalangeal joints was very similar during treatment with the two drugs but 21 patients preferred soluble aspirin, whereas thirteen preferred indomethacin, and the remaining seven had no preference.

It is concluded that indomethacin should not replace aspirin in the routine treatment of in-patients with rheumatoid arthritis. However some patients appear to do better with indomethacin and it may therefore be useful in selected cases.

We wish to thank Professor J. H. Kellgren for advice and criticism in the preparation of this paper. Miss F. Bier performed the statistical analysis and we are greatly indebted to her.

REFERENCES

- Boris, A., and Stevenson, R. H. (1965). *Arch. int. Pharmacodyn.*, **153**, 205.
- Clark, G. M. (1964). *Arthr. and Rheum.*, **7**, 300.
- Hajnal, J., Sharp, J., and Popert, A. J. (1959). *Ann. rheum. Dis.*, **18**, 189.
- Hart, F. D., and Boardman, P. L. (1963). *Brit. med. J.*, **2**, 965.
- , — (1965). *Ibid.*, **2**, 1281.
- Katz, A. M., Pearson, C. M., and Kennedy, J. J. (1963). *Arthr. and Rheum.*, **6**, 281.
- Kelemen, E. (1963). In "Salicylates: An International Symposium sponsored by the Empire Rheumatism Council with the support of the Nicholas Research Institute, Ltd. Post-graduate Medical School of London, 1962", ed. A. St.J. Dixon, B. K. Martin, M. J. H. Smith, and P. H. N. Wood, p. 148. Churchill, London.
- Lövgren, O., and Allander, E. (1964). *Brit. med. J.*, **1**, 118.
- Norcross, B. M. (1963). *Arthr. and Rheum.*, **6**, 290.
- Percy, J. S., Stephenson, P., and Thompson, M. (1964). *Ann. rheum. Dis.*, **23**, 226.
- Ropes, M. W., Bennett, G. A., Cobb, S., Jacox, R., and Jessar, R. A. (1959). *Ibid.*, **18**, 49.
- Rothermich, N. O. (1963). *Arthr. and Rheum.*, **6**, 295.
- Spector, W. G., and Willoughby, D. A. (1963). In "Salicylates: An International Symposium sponsored by The Empire Rheumatism Council with the support of the Nicholas Research Institute, Ltd., Post-graduate Medical School of London, 1962", ed. A. St.J. Dixon, B. K. Martin, M. J. H. Smith, and P. H. N. Wood, p. 141. Churchill, London.
- Thompson, M., and Percy, J. S. (1966). *Brit. med. J.*, **1**, 80.
- Today's Drugs: Indomethacin (1964). *Ibid.*, **2**, 429.

Wanka, J., Jones, L. I., Wood, P. H. N., and Dixon, A. St.J. (1964). *Ann. rheum. Dis.*, **23**, 218.
 Winter, C. A., Risley, E. A., and Nuss, G. W. (1963). *Fed. Proc.*, **22**, 543.

certaines malades semblent bénéficier de l'indométhacine et on peut la trouver utile dans des cas particuliers.

L'indométhacine dans le traitement hospitalier de l'arthrite rhumatismale

RÉSUMÉ

On procéda à un essai *cross-over* de l'indométhacine et de l'aspirine soluble chez des malades hospitalisés, atteints d'arthrite rhumatismale. La dose d'indométhacine fut augmentée de 50 mg. à 100 mg. pendant la période de traitement, mais la dose d'aspirine soluble fut maintenue à 4 g. par jour.

On appliqua une méthode d'analyse qui permet de dissocier l'effet du médicament de celui des autres facteurs qui à l'hôpital ramènent l'amélioration indépendamment de la médication employée. A cette occasion on souligne l'importance de ces facteurs.

La comparaison de ces deux médicaments montra que la force de la main s'améliorait plus au cours du traitement par l'indométhacine et que ce résultat était exactement dans les limites de signification de 5 pour cent. La diminution du gonflement des articulations interphalangiennes proximales fut très similaire pendant le traitement par le deux médicaments, mais 21 malades préférèrent l'aspirine soluble, 13 malades préférèrent l'indométhacine et les autres n'indiquèrent aucune préférence.

On conclut que l'indométhacine ne doit pas remplacer l'aspirine dans le traitement régulier à l'hôpital des malades atteints d'arthrite rhumatismale. Toutefois,

La indometacina en el tratamiento hospitalario de la artritis reumatoide

SUMARIO

Se compararon, por el método de *cross-over*, la indometacina y la aspirina soluble en enfermos hospitalizados con artritis reumatoide. Durante el período de tratamiento la dosis de indometacina fué aumentada de 50 mg. a 100 mg., pero la dosis diaria de aspirina soluble se mantuvo a 4 g.

El método de análisis aplicado aquí permitió disociar los efectos del medicamento de otros factores que conducen a una mejoría en enfermos hospitalizados independientemente de la medicación. Se subraya la importancia de estos factores.

La comparación de estos medicamentos reveló que la fuerza de la mano aumentó más durante el tratamiento con indometacina y que este resultado se encontró exactamente dentro de los límites de confianza del 5 por ciento. La reducción de la hinchazón de las articulaciones interfalangiánas proximales fué muy similar durante el tratamiento con ambos medicamentos, pero 21 enfermos prefirieron la aspirina soluble, 13 enfermos la indometacina y los demás no indicaron preferencia alguna.

Se concluye que la indometacina no debe sustituir la aspirina en el tratamiento hospitalario habitual de enfermos con artritis reumatoide. Sin embargo, ciertos enfermos parecen responder mejor con indometacina y su empleo puede ser útil en casos particulares.