CURRENT TRENDS IN THERAPY OF RHEUMATOID CONDITIONS*

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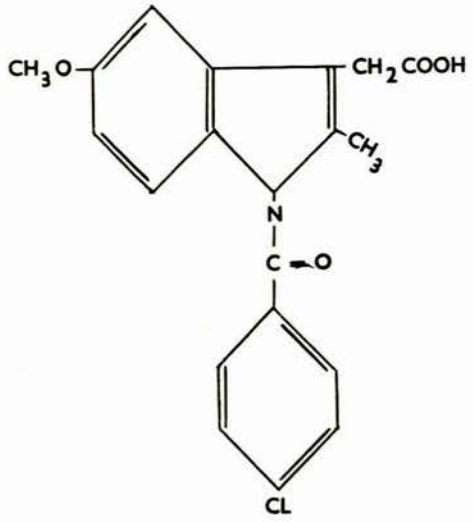
Apart from the use of salicylates, the first major advance in the therapy of rheumatoid conditions was the utilization of cortisone or adrenocorticotropin hormone which was reported by Hench and his collaborates in 1949.[1] The first clinical trials with phenylbutazone were done in the same year. At that time it was used in Europe in combination with aminopyrine, and the clinical use of phenylbutazone by itself was not begun until 1951. All the drugs, steroid and non-steroid, which have been used for arthritis, have side-effects which are too well known to need listing. The advent of indomethacin has therefore been received with considerable interest in the therapy of arthritis.

INDOMETHACIN

1. *Formula*



This is an anti-inflammatory, antipyretic and to some extent, analgesic drug.

2. *Properties*

It is non-steroidal and is independent of the adrenal hypophyseal axis. There is no change in the thymus and adrenal weight on administration of the drug. Experimentally there is no sodium retention. There are no antihistaminic nor antiserotonin properties.

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3. *Anti-inflammatory and Antipyretic Activity*

(*a*) Eighty-four times more potent than phenylbutazone in the inhibiting granuloma test.

(*b*) Twenty times more powerful than phenylbutazone in the carrageenin oedema assay.

(*c*) Twenty times more powerful than phenylbutazone in the rabbit antipyretic test.

(*d*) Ten times more powerful than phenylbutazone in the rat antipyretic test.

Indomethacin, Cortisol and cyproheptadine have different spectra of activity. Cyproheptadine is effective against oedema induced by serotonin or egg white, hydrocortisone is active only at a high dose. Indomethacin is ineffective. The mechanism of action of indomethacin in preventing oedema is selective and is different from cyproheptadine and hydrocortisone. Experimentally, the effectiveness of steroids was increased 3- to 4-fold when given to animals also receiving indomethacin. Indomethacin is not a potent analgesic drug in the sense that morphine is, but tests designed to detect mild analgesic activity indicated that it is more potent than aspirin.

4. *Absorption, Distribution, Metabolism*

The drug is well absorbed in man and the peak plasma level is 4 hours after ingestion. After the peak the plasma half-life is 12 hours in man and 4 hours in rats.

Plasma indomethacin is virtually all unchanged in man, 94% being bound to a non-diffusable plasma constituent.

In man, excretion is rapid. 33% is found in the urine within 4 hours and 50 - 90% within 24 hours. In man, it is excreted in the urine mainly as a glucuronide conjugate and to a small extent as the free compound especially in the stools. Evidence from dogs indicates that the drug is well absorbed from the gastro-intestinal tract as free indomethacin. It is conjugated in the liver, excreted by way of the bile back into the gastro-intestinal tract, where glucuronide is cleaved from indomethacin, which is reabsorbed, thus completing the cycle. The drug remains in the enterohepatic cycle until excreted.

5. *Kidney*

Renal studies on dogs have indicated that clearances of uric acid, creatinine, sodium and potassium are unaffected.

6. *Central Nervous System*

Specific tests failed to reveal significant anticonvulsant internuncial blocking, behavioural or other peripheral or

central effects. Indomethacin appears to be devoid of appreciable atropine-like effects, adrenergic or ganglion-blocking properties as well. In anaesthetized dogs, no activity referable to the autonomic nervous system was detected. Reflex pressor responses were unaffected, nor were there modifications of the direct vascular effects of injected methacoline, various sympathomimetics or angiotensin.

7. *Cardiovascular System*

Intravenous injection did not alter arterial pressure, heart rate or configuration of the electrocardiogram.

8. *Pregnancy*

No foetal malformations were observed after a two-generation reproduction study in mice and rats.

9. *Toxicity Studies in Animals*

Adverse side-effects commonly encountered during treatment with anti-inflammatory drugs include fluid retention and gastro-intestinal irritation. Acute administration of indomethacin to rats produces fluid retention and signs of gastric irritation, but the doses required were higher than those proved to be effective in the granuloma inhibition test. Also the potency of the compound relative to phenylbutazone was only 1/8 to 1/4 as great in these tests as in the granuloma assay. Gastric irritation in the experiments required prior fasting of the rats. Feeding the animals beforehand protected them, though fluid retention and gastro-intestinal irritation may be potential side-effects with indomethacin; the compound may have a favourable therapeutic ratio in these respects. Extensive toxicological studies of indomethacin have demonstrated that its toxicity is primarily related to the development of superficial to perforating ulcerative lesions of the gastro-intestinal tracts in experimental animals.

Acute oral LD_{50} values for the mouse and rat are respectively approximately 50 and 12 mg./kg., but are greater than 100 mg./kg. for a dog, rabbit and guinea-pig. In all of the species of animal studies, the toxicity of indomethacin has been related to alterations of the gastro-intestinal tract. The signs of toxicity have included anorexia, diarrhoea and weight loss as well as ulceration of the gastro-intestinal tract and peritonitis. There has *not* been any depression of the bone marrow or any lesion or toxicity noticed in the liver. The results of these toxicity studies show that none of the species of experimental animals employed will tolerate indomethacin in daily doses as large as will be tolerated by man. The differences, i.e. the reason for the lower toxicity in man than in experimental animals, appear to be related to differences in metabolism and in elimination of the drug.

METHODS AND MATERIALS OF STUDY

Initially, double-blind studies were started, but it became apparent that patients' improvements were usually dramatic enough to differentiate the true capsule from the placebo. All patients who experienced improvement had rebound of symptoms when placebo was substituted. It was therefore considered possible to continue the trial without placebo aid.

1. The original group of patients[2] followed up for 9 months to 1 year were followed up for a period of 2 years. The series consisted of:

(*i*) Group of classical rheumatoid arthritis (classical rheumatoid arthritis as defined by the American Rheumatoid Association, 1959).[3] They originally numbered 28. All were treated previously with large doses of steroids for from 6 months to 5 years. All patients either had complications from their steroids or were inadequately relieved by therapy. These patients had had rheumatoid arthritis for periods varying from 6 months to 5 years. The capsules of indomethacin were used, but in the dyspeptic group suppositories replaced oral administration after 1 year of initial capsule therapy.

(*ii*) The second group of classical rheumatoid arthritis, followed up for a period of 2 years, numbered 20. These patients had no previous therapy. Ten of these had significant swelling and 10 little or no swelling.

(*iii*) Three cases of juvenile rheumatoid arthritis, varying from 11 to 15 years of age, were also followed up for a period of 2 years.

2. *Mixed arthritis.* Forty cases treated.

3. *Gout.* Fifteen cases. These patients received inadequate response to colchicine or alternatively could not tolerate colchicine therapy.

4. Polyarteritis, 3 cases; polymyositis, 5 cases; and disseminated lupus erythematosus, 5 cases. The patients with polymyositis were treated previously with high-dosage steroids for a number of years and had iatrogenic Cushing's syndrome.

5. *Ankylosing spondylitis.* Three cases were treated with indomethacin and were followed up for a period of one year. One patient had no previous therapy while the other 2 had been subjected to irradiation, phenylbutazone and steroids with inadequate response.

The range of ages in the arthritides varied from 11 to 75 years. Since the original study 300 patients have been added to our trial, but statistical analysis is not yet available. Patients were regularly seen in the outpatient department at 2- to 4-weekly intervals. There was no change in their physical routine, and most of these patients were followed up for a period up to 2 years. Routine investigations done on all patients treated with indomethacin consisted of urinalysis, full blood count and sedimentation rate (Westergren), urea and electrolytes, SGOT and SGPT, alkaline phosphatase, and stools were examined for occult blood. In addition, any side-effects were noted and recorded.

PARAMETERS OF IMPROVEMENT

1. Lansbury's Systemic Index,[4] which is essentially an estimation of early-morning stiffness, development of fatigue, sedimentation rate and number of aspirins needed for relief of pain. Each of these features was given percentages of functional incapacity and the total added up to give the Lansbury Systemic Index.

2. Rough estimation of the decrease in swelling.

3. Steinbroker's classification of functional activity.[5]

The difficulties in the assessment of the parameters were noted and appreciated especially since the very nature of the disease involved exacerbations and remissions and also depended to some extent on the subjectivity of the patient.

RESULTS

Our results are summarized in Figs. 1 - 3:

RESULTS AFTER 2 YEARS INDOMETHACIN THERAPY IN RHEUMATOIDS WITH PREVIOUS STEROID ADMINISTRATION

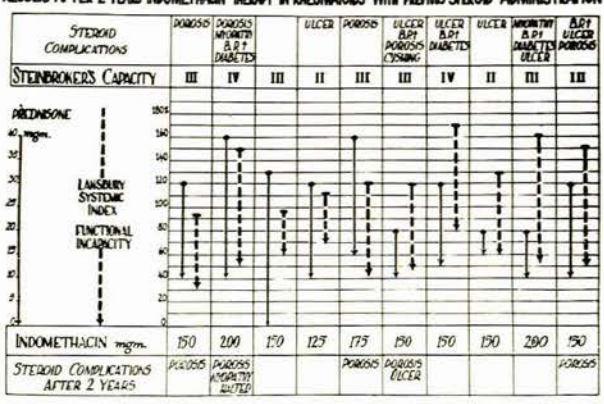

Fig. 1. See text.

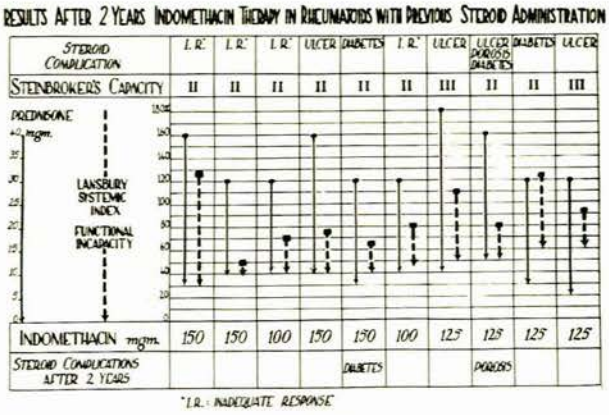

Fig. 2. See text.

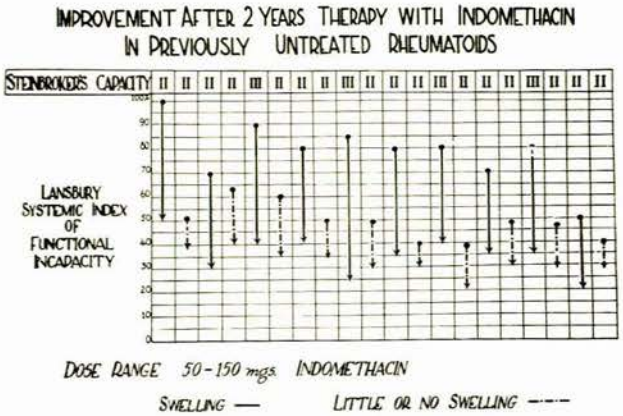

Fig. 3. See text.

DISCUSSION

The results presented at the International Symposium of Non-Steroidal and Anti-Inflammatory Drugs held in Milan during September 1964,[2] were very similar to our results obtained after 2 years.

1. *Rheumatoid arthritis with previous therapy.* After 2 years on indomethacin, with doses ranging from 50 to 150 mg., all patients were gradually able to reduce their steroid requirements from as high as 40 mg. prednisone (or equivalent in other preparations) to 0 - 10 mg. prednisone (Figs. 1 and 2). Reduction in prednisone was done gradually over a period of 6 weeks. It was considered best not to remove the prednisone completely in some patients lest the patients should inadequately respond to stress owing to their prolonged previous therapy and probable adrenal atrophy. The complications induced by the steroids, namely hypertension, diabetes, and ulcers, regressed in most patients. Patients were put on a routine ulcer regime, especially those who complained of dyspeptic symptoms. In addition, those patients who had indigestion or heartburn, were put on indomethacin suppositories, 50 or 100 mg. *nocte et mane*. The osteoporosis was unaffected. One case of myopathy was halted. The functional incapacity, as measured by the John Lansbury Systemic Index, improved in all patients. The sedimentation rate (Westergren) tended to lag behind the other parameters of the Lansbury Systemic Index. There was a definite improvement as regards decrease in swelling of involved joints. Patients' functional capacity as measured by the Steinbroker's classification, improved by at least one grade. The rheumatoid nodules in one patient—on the extremities as well as the scalp—regressed. Eight patients preferred their previous therapy.

2(a). *Rheumatoid arthritis without previous therapy.* In the series of patients not previously treated with steroids, there was also an improvement as regards the Lansbury Systemic Index (Fig. 3). Patients with swelling of the joints responded to a greater extent than those without swelling, and this is well demonstrated on the graph (Fig. 3).

2(b). *Juvenile rheumatoid arthritis.* The 3 patients with juvenile rheumatoid arthritis responded well to therapy and this was particularly gratifying since these young patients did not have steroids with their probable complications. The doses of indomethacin varied from 50 mg. to 150 mg. per day, and as the condition of the patients improved, so the dose was reduced.

3. *Mixed arthritis.* In the group of mixed arthritis, cases with swelling responded very well, the swelling being decreased and the functional movements improved. Fifteen cases showed mild improvement; 10 cases showed little or no improvement.

4. *Gout.* The 15 patients with gout, all in the acute phase, received excellent improvement as judged by relief of pain and decrease in the inflammatory reaction. The improvement was noticed within 4 hours and became maximal after 6 - 8 hours. The dose of indomethacin relieving the pain was 50 mg. *stat.* followed by 50 mg. 6-hourly until complete improvement resulted. In a few of these patients, suppositories were used instead of the oral therapy owing to gastro-intestinal irritation. Usually within 24 - 48 hours the patients were completely relieved.

5. *Disseminated lupus erythematosus, 5 cases.* One patient, a female of 36 years, was well maintained with indomethacin alone for a period of 6 months, after which she became refractory to the drug. Steroids were required in high doses to reduce her arthritis (50 mg. prednisone), but after readministering indomethacin, 100 mg. daily, her steroid requirements were reduced to 10 mg. prednisone daily with adequate relief. She has been followed up for a period of 2 years and improvement has been maintained.

The other 4 patients had had steroids in high dosage for a few years, but the administration of indomethacin allowed a reduction of steroid to a fraction of the original.

6(a). *Polyarteritis nodosa.* Of the 3 cases of polyarteritis nodosa, all proved by muscle biopsy, one patient was well maintained with 50 - 150 mg. indomethacin per day with relief of the arthritis and decrease in sedimentation rate and C-reactive and mucoproteins. The other 2 patients had steroids combined with their indomethacin, and it was felt that the indomethacin had a very definite steroid-sparing effect.

6(b). *Polymyositis.* The 5 patients with polymyositis proven by biopsy, electromyography and raised serum aldolase, had all previously been treated with steroids in such high doses as to produce Cushing's syndrome. These patients were impelled to have doses of prednisone varying

from 20 to 50 mg. per day in order to relieve their stiffness and weakness. In these patients indomethacin, 50 - 150 mg. per day, permitted a reduction in steroid requirements with an improvement of stiffness and weakness. One patient after 9 months of indomethacin therapy became refractory to the beneficial effects of indomethacin and her steroid requirements rose steeply.

6(c). *Ankylosing spondylitis.* One patient who had ankylosing spondylitis was a young girl aged 19 years who had no previous therapy. On the administration of indomethacin, 150 mg. per day, backache and pain decreased and sedimentation rate improved. This patient has been followed up for a period of one year and improvement has been maintained. Two other patients, one aged 14, the other a male aged 30, had previous therapy, irradiation, phenylbutazone and steroids, with not only poor response, but osteoporosis resulting from the steroid therapy. On indomethacin there was an improvement in that the subjective sensation of pain improved, and in the young patient the respiratory excursion increased from $\frac{1}{2}$ to 1 inch over a period of one year.

GENERAL FEATURES OF DRUG ACTIVITY

1. *Primary and secondary resistance.* In the therapy of 300 patients over a period of 2 years, it was noted that there were patients who were refractory to the beneficial effects of indomethacin *ab initio*. There was no apparent reason for this primary resistance. Occasionally patients may respond very well initially, but after some days or weeks of therapy, the response may decrease. Not infrequently the patient may overcome this secondary resistance to the drug after a period of removal of the drug.

2. In patients in whom sepsis was obviously present, indomethacin was administered with particular care because being such a potent anti-inflammatory drug, the possibility existed of a spreading of the infection. It has been stated by Winter *et al.*[6] that indomethacin experimentally has been found not to enhance infective or inflammatory processes. In fact, Winter has shown that there is an increased phagocytic activity. From this we can conclude that in the presence of sepsis, indomethacin could be administered. However, Solomon[7] has suggested that in the presence of infection clinically it might be wise to administer it with caution—one case of tuberculous arthritis became disseminated on therapy.

3. Since the liver and the kidney play an important part in the metabolism and excretion of the drug, patients in whom there is disease in these organs were given smaller doses to avoid toxic effects.

4. No addiction has been noted to the drug over the period of 2 years.

5. In those patients who responded, the beneficial effect was noticed within 12 - 24 hours.

DISCUSSION OF SIDE-EFFECTS

1. *Central Nervous System*

(*i*) *Headache.* In patients receiving more than 200 mg. of indomethacin a day, headache became a frequent symptom. It tended to be frontal, throbbing in nature, with occasional fortification spectra. On the administration of methysergide, 1 or 2 mg. *b.d.*, i.e. 1-methyl-d-lysergic acid butanolamide (Deseril), the headache and often the accompanying vertigo disappeared completely. It is to be noticed that this antiserotonin drug, methysergide, has much the same alleviating effect on this vascular-type headache as it has on migraine. Patients who experienced mild headache tended to develop tolerance to the headache after a period of therapy. The headache was dose-related and decrease in the dose produced an alleviation in the symptom.

(*ii*) *Vertigo.* Two patients experienced marked vertigo on doses of 150 mg. and both responded extremely well to methysergide.

(*iii*) One patient complained of drowsiness.

(*iv*) One patient had a transient confusional state. This was a 65-year-old female who initially received 200 mg. per 24 hours. After the dose was decreased this confusional state disappeared.

(*v*) A feeling of unreality was described by one patient, but after the administration of methysergide the patient's symptoms disappeared. The patient was receiving 200 mg. indomethacin a day.

2. *Gastro-intestinal Tract*

Experimentally, gastro-intestinal irritation has been noted whether the administration has been intravenous or oral. It has been found in patients who have a dyspeptic background or peptic ulcers and could not tolerate indomethacin orally. Administration in the suppository form did not produce the indigestion and heartburn that indomethacin or salicylates produce when taken orally. It has been suggested therefore that part of the gastro-intestinal irritation is due to a local gastrostaxic effect similar to that produced by salicylates. In many of these patients who have had a previous background of ulcers precipitated and aggravated by their therapy, administration of indomethacin rectally resulted in no exacerbation of their symptoms. In those patients who did not have dyspeptic backgrounds indomethacin orally was well tolerated as a rule, providing they had their capsules with meals.

3. *Skin and Mucous Membranes*

One patient developed stomatitis and pharyngitis which was mild, and 1 patient developed a macular rash; in both patients, after stopping the drug, the complication disappeared. However, these patients insisted on restarting the drug and on a smaller dose the side-effect did not reappear.

Toxic Effects

As regards liver, bone marrow, kidney and heart, no toxic effects were noticed and it appeared that indomethacin had no serious side-effects on these organs.

CONCLUSIONS

Indomethacin was found to be a very powerful anti-inflammatory, antipyretic and also analgesic drug. It was used in rheumatoid arthritis, having significant beneficial effects in steroid sparing and also in the reduction of the steroid complications. Improvement of the arthritis was noticed in all parameters—swelling, Lansbury Systemic Index and Steinbroker's functional capacity. In addition, in one patient, the rheumatoid nodules disappeared. In juvenile rheumatoid arthritis the results were very good and thus avoided the hazardous effects of steroids on growing children. It has been noticed that indomethacin has its most profound effects on patients with

joint swelling. The steroid-sparing effect in polymyositis and also polyarteritis and disseminated lupus erythematosus is self-evident. Acute gout responded well. The side-effects have been localized in the nervous system, headache being the important feature in our series and this symptom as well as vertigo accompanying it, was aborted by the administration of small doses of methysergide (1 - 2 mg. *b.d.*). Gastro-intestinal complications were avoided by either the suppository administration or the routine addition of Kolantyl gel in the oral administration of the drug. The patients were also encouraged to take their tablet during mealtime. For patients with known ulcers or dyspeptic histories, suppositories were used with good response and no gastro-intestinal tract irritation. Side-effects on vital organs, namely liver, kidney, bone marrow and heart, were not observed.

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REFERENCES

1. American Rheumatoid Association (1959): Definition of Classical Rheumatoid Arthritis.
2. Berman, L. (1964): Paper presented at the International Symposium on Non-Steroidal and Anti-Inflammatory Drugs, Milan.
3. Primer on the Rheumatic Diseases, Part I (1944): J. Amer. Med. Assoc., **171**, 1205.
4. Lansbury, J. (1958): Arthr. and Rheum., **1**, 505.
5. Steinbroker, O., Traeger, C. H. and Batterman, R. C. (1949): J. Amer. Med. Assoc., **140**, 659.
6. Winter, C. A., Risley, E. A. and Nuss, G. W. (1963): J. Pharmacol. Exp. Ther., **141**, 369.
7. Solomon, L.: Personal communication.