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A CLINICAL TRIAL WITH INDOMETHACIN (INDOMEE®) IN LOW BACK PAIN AND SCIATICA

By

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INTRODUCTION

General Remarks on Inflammation and Antiinflammatory Drugs

The antiphlogistic properties of certain drugs are often claimed to be combined with an analgesic effect (*Gabitza* 1964, *Sicuteri* 1964 and *Heimann* 1965). The background for this statement is the observed specific influence of the antiphlogistic agent on a particular sequence, the assumed painproducing oedema, in the process of inflammation. Some however have a centralanalgesic effect like *e.g.* phenylbutazone (Butazolidin®).

The inflammatory reaction is the response of mesenchymal tissues to irritation irrespective of its origin—mechanical, thermal, chemical or infectious. The sequence of events generally follows a well conformed pattern in which, however, the time factor and other tissue reactions may cause alterations so that an irregular interchange of events may ensue rather than a linear development.

This unspecific tissue response contains a destructive and a reparative phase both of which are closely interconnected. The first includes haemorrhage, formation of oedema, local acidosis, swelling and partial destruction of individual tissue components. Parallel to these reparative forces are instituted such as hyperemia, exsudation of fibrin, leucocytosis and phagocytosis. With these events in mind it may therefore be justified to use antiphlogistic agents with specific action on the destructive phase of inflammation which do not interfere with the reparative phase. Despite the assumed importance of oedema in repair

of injured tissues (*Asboe-Hansen* 1963) it may be of some advantage to combat its formation as it is supposed that inflammatory swelling causes pain. Moreover *Rhoads et al.* (1942) found that in retarded wound healing in hypoproteinemia oedema had a deleterious effect on the repair of tissues.

The action of antiphlogistic drugs thus becomes twofold the first being interaction in the destructive phase of inflammation and the second being analgesic in the diminishing effect on oedema.

Drugs used for antiinflammatory purposes have not been sufficiently selective in their action and their overall interference in cellular metabolism has had a deleterious effect on the proliferative phase. *E.g.* the influence of corticosteroids on exsudation of fibrin and on fibroblastic activity which slows down the rate of healing (*Dougherty* 1954) is well known. *Sandberg & Steinhardt* (1964) have found that the retarding influence of steroids on wound-healing depends on the inhibition of an enzyme, histidinedecarboxylas. With the introduction of non-steroid compounds such as phenylbutazone, (Butazolidin®), oxyphenbutazone (Tanderil®) and indomethacin (Indomee®) it has been proved in experimental investigations that the proliferative phase is undisturbed (*Winter* 1964; *Brunius & Zederfelt* 1965) and that the painproducing destructive phase with oedema is combated (*Winter* 1964).

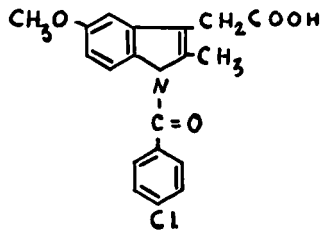
Problem

The origin of low back pain with sciatic irradiation is obscure and many explanations have been forwarded. The common and most accepted cause is the pressure a herniated intervertebral disc exerts on the nerve root. But mechanical factors are not the only painproducing agents and chemical, degenerative and autoimmune reactions either primary or secondary to ruptures in the disc substance have to be considered (*Hirsch* 1965). They all form part of the inflammatory reaction and no doubt a nerve root can be interfered with by the sole products of an inflammatory development without the intervertebral disc material necessarily appearing as a herniation (*Hirsch* 1965, *Nachemson* 1965).

This study has therefore been carried out to assay the effect of—indomethacin (Indomee®)—in patients with an acute attack of sciatica.

Properties of Indomethacin (Indomee®)

Indomethacin is 1-(p-chlorbenzoyl)-5-methoxy-2-methyl-indole-3-acetic acid. It has formula of $C_{19}H_{16}NO_4CL$ and a molecular weight of 357,8.



It is relatively insoluble in water but is soluble in the common organic solvents (*Shen et al.* 1963). Experimental studies (*Winter* 1964) show very active antiinflammatory properties. In inhibition tests on granulation tissue in rats indomethacin was 85 times more active than phenylbutazone and 4 times as active as hydrocortisone. Its inhibiting action on oedema has also been recorded in animal studies and it was 30 and 20 times as active as salicylates and phenylbutazone respectively but only twice as efficient as hydrocortisone (*Winter et al.* 1963).

The analgesic effect has also been tested in clinical trials (*Jacobs* 1965) and 50 mg indomethacin has the same effect as 600 mg salicylic acid (*Wanka, Jones, Wood & Dixon* 1964, *Percy, Stephenson & Thomson* 1964).

Side-effects have been reported such as headache, dizziness, rashes and dyspepsia. In 1964 Lövgren and Allander reported several cases of peptic ulceration and haemorrhage, two of which had a fatal outcome. *Wanka et al.* (1964) have also reported on cases with gastric bleeding and ulcers. Since the drug no longer has been administered as tablets but in capsules gastric side-effects have almost completely disappeared. Besides, these can be alleviated by taking the drug with meals.

Headache is as a rule transient (*Hart & Boardman* 1963) and dependent on the dosage. Hepatic, renal and haematological complications have not been reported.

Indomethacin was originally introduced as an antirheumatic drug. As its antiphlogistic properties became more known the range of indications widened to include most conditions with pain secondary to tissue reactions of inflammatory type. Thus inflammatory reactions in periarticular structures have appeared to be a good target for

treatment with indimethacin (*Jacobs* 1965). The dosage recommended is 75 mg–100 mg per day divided into three or four doses.

METHOD

The trial was a blind inter-patient comparison, patients receiving a course of 50 capsules of either indomethacin or placebo. The indomethacin was administered as capsules containing 25 mg of the drug, a total of 75 mg being taken each day in three divided doses. The placebo was administered in identical capsules three times daily.

Neither doctor, nurse or patient were aware of which treatment was given as the bottles in which the capsules were dispensed only had a number on the label the code of which was known only to the manufacturer.

Only patients with true sciatica *i.e.* low-back pain with irradiation down either leg were selected excepting six patients in whom the irradiation was not as constant but the back pain very severe. The duration of symptoms did not exceed three weeks. All but five patients were hospitalized and their reactions were read on day 1–5 and thereafter at weekly intervals up to at the most three months. As indomethacin is said to institute its effect wihin 24–48 hours (*Ward* 1964) it might have been sufficient with definite readings after this time but for the sake of completeness it was felt more appropriate to carry on the observations and make a conclusive registration after 14 days.

As in many cases sciatica may be a self-limited disease within this time the daily registration and final observation were, however, thought necessary to evaluate any possible radical influence the administered drug might have.

No other drugs as sedatives, hypnotics or supplementary analgesics were administered. No physiotherapy was given. The patients as a rule remained in bed for a few days and were allowed to move around freely.

The following criteria were measured initially and on subsequent registrations. All observations were made by the author.

Subjective evaluation of pain. The patient were asked daily about the intensity of pain and the relief was registered as complete, fair or none using a score system with initial pain and no recovery recorded as 3 points; lessened pain = fair relief = 2 points; no pain = complete relief = 1 point.

Irradiation of pain. The patients were asked daily if any change in irradiation was noted in either intensity or spread.

Alteration in straight-leg raising test. The test was performed daily. The difference before and after treatment was expressed in degrees and final registration was made after 14 days.

Other neurologic signs.

MATERIAL

The total number of patients amounted to fifty.

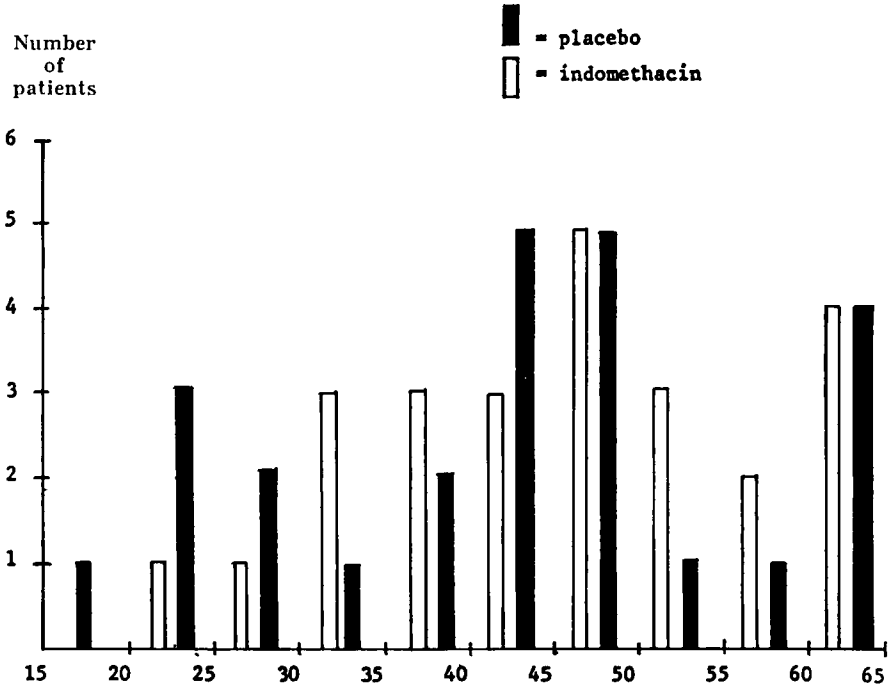
After decodification and division into indomethacin and placebogroups the distribution was as follows, Table 1.

The age distribution is seen in Table 2 and corresponds well with the distribution of lumbago and irradiating pain as reported elsewhere (*Hirsch* 1965).

Table 1. Distribution of patients in treatment groups after decodification.

Sex	Indomethacin	Placebo
Male	13	13
Female	12	12

Table 2. Distribution of age and treatment of material.



Duration of symptoms before treatment is seen in Table 3.

Table 3. Duration of symptoms.

Time	Indomethacin		Placebo		Total
	Male	Female	Male	Female	
One week	4	3	7	3	17
Two weeks	7	9	4	8	28
Three weeks	2	–	2	1	5

Side affected is seen in Table 4.

Table 4. Localisation of pain.

Sex	Lumbago-ischias sin.		Lumbago-ischias dx.		Lumbago ac.	
	Indo-methacin	Placebo	Indo-methacin	Placebo	Indo-methacin	Placebo
Male	4	8	6	4	3	1
Female	3	6	9	4	–	2
Total	7	14	15	8	3	3

Straight-leg raising test before treatment in seen in Table 5.

Table 5. Straight-leg raising before treatment.

Straight-leg raising test	Indomethacin		Placebo		Total
	Male	Female	Male	Female	
Negative	7	7	6	9	29
Positive 10–40°	3	1	1	1	6
Positive 40–80°	3	4	6	2	15

RESULTS

It very soon became evident that decrease in pain was a slow process and that recordings would gain in reliability if measurements were made at slightly longer intervals. After seven days of treatment the subjective relief of pain was as follows, see Table 6.

At the conclusive registration after 14 days the evaluation of pain was as seen in Table 7.

Table 6. Subjective evaluation of pain after 7 days' treatment.

Relief of pain	Indomethacin		Total	Placebo		Total
	Male	Female		Male	Female	
Complete	5	2	7	5	4	9
Fair	4	4	8	4	5	9
None	4	6	10	4	3	7

Table 7. Subjective evaluation of pain after 14 days' treatment.

Relief of pain	Indomethacin		Total	Placebo		Total
	Male	Female		Male	Female	
Complete	9	5	14	7	9	16
Fair	–	1	1	2	–	2
None	4	6	10	4	3	7

Of the 17 patients with no relief 3 were later operated on for a herniated disc in the indomethacin group and 2 in the placebo group. These 5 patients still have complete relief of pain from 3 to 1 months after surgery.

The remaining 12 who had not experienced any relief of pain after 14 days were further checked for 3 months. Of these 10 had received physiotherapy and taken muscle relaxants and analgesics of various kinds. 5 had complete relief of pain. 5 still suffered constant but very mild pain which was alleviated by rest and light analgesics. 2 still suffered from such severe pain that admission for myelography was considered.

Straight-Leg Raising Test

Indomethacin group: After 14 days 4 were normalised. 7 remained as before treatment. Crossed straight-leg raising pain was not observed.

Placebo group: Of 10 positive 3 patients were normalised. In one patient crossed straight-leg raising pain was present prior to the treatment. After 14 days therapy it remained. Those patients who were later operated for herniated disc from both groups had positive straight-leg raïsing tests of 40°–80°.

Reflexes

Indomethacin group: At initial examination no areflexia was registered in any case. At final registration after treatment no change was noted.

Placebo group: At initial examination one patient responded with no reflexes at all. All the remaining had normal reflexes. At the conclusion of treatment the patient with areflexia still retained this. She did not belong to the group in which eventually operation was performed. No change in reflexes was observed in the remaining patients after treatment.

Sensitivity

Indomethacin group: Normal sensitivity was encountered in all but two. These had reduced sensitivity for pain along the outside of the lower leg. After treatment the loss of sensitivity remained. They were later operated for herniated disc in the level L.IV–L.V. The sensitivity was not influenced by the treatment in the remaining patients of this group.

Placebo group: Before treatment 5 patients had reduction of sensitivity. In 3 this corresponded to the radiation of the L.V root and in 2 the S.I root. Two of the former were operated for a herniated disc at the L.IV–L.V level. Normal sensitivity was encountered in the remaining patients in this group before and after treatment.

Big Toe Paresis

Indomethacin group: Three patients had a big toe paresis before as well as after treatment. Of these two were operated for herniated disc at the L.IV–L.V level. The remaining patient had no paresis either before or after treatment.

Placebo group: One patient initially had a paresis which remained after treatment. This patient was later operated for herniated disc at the L.IV–L.V level. No paresis was observed in the remainder of this group.

Table 8. Results of treatment on different signs.

Signs	Indomethacin treatment		Placebo treatment	
	before	after	before	after
Straight-leg raising				
Negative	14	18	15	18
Positive 10–40°	4	1	2	1
Positive 40–80°	7	6	8	6
Reflexes				
No absence	25	25	24	24
Absence	–	–	1	1
Sensitivity				
Normal	23	23	20	20
Reduced	2	2	5	5
Big too paresis				
Not present	22	22	24	24
Present	3	3	1	1

Side-Effects

In 13 patients headache, nausea and giddiness were observed which in all instances appeared within some 24 hours after initiation of treatment. To secure that the side-effects could be ascribed to the given preparation its administration was withdrawn for a few days and then reinstituted after disappearance of the side-effects. They returned in all 13 patients within 12 hours after the second course of administration. The side-effects were distributed as is seen in Table 9.

Table 9. Side-effects of administered preparations.

Side-effect	Indomethacin		Total	Placebo		Total
	Male	Female		Male	Female	
Headache	–	4	4	1	1	2
Nausea	–	4	4	–	2	2
Giddiness	–	–	–	–	1	1

COMMENT

Mechanical factors no doubt have a great importance in the pathogenesis of low back pain and sciatica. As mentioned above, however, chemical, degenerative and perhaps autoimmune processes are concomitant and may augment the role of mechanical factors in the mechanism which primarily elicits pain. In 1958 Olsson came to the conclusion based on thorough animal experiments that large herniations of discs need not necessarily evoke symptoms but rather that a dynamic factor is responsible for the symptomatology and that this is an exponent for an inflammatory reaction. For this reason he believed that the activity of the inflammatory reaction had to be combated as a therapeutic measure more than the removal of protruding disc tissue.

In a study based on observations at operation for lumbago in humans *Lindahl & Rexed* (1959) showed that a pronounced fibrosis was present around the nerve root which supplied the segment from which the symptomatology originated. *Nachemson* (1966) has investigated in a double blind trial the effect of oxyphenbutazone (Tanderil®) at operation for herniated discs with special reference to various factors such as hemoglobin, leukocytes, thrombocytes, postoperative pain and haemorrhage during operation. He found that oxyphenbutazone had a significantly reducing effect on haemorrhage.

With the above observations in mind it therefore appears logical to

moderate the reaction around a nerve root which is the centre for irritation with ensuing pain. In this investigation however, the results indicate that the effect of the antiphlogistic drug used has been minimal.

SUMMARY

In a simple blind rial an antiphlogistic drug, indomethacin (indome®) was tried in comparison with placebo in cases of low-back pain and sciatica. Fifty patients were treated all of whom were hospitalised in an Orthopaedic Department. There was no greater difference in alleviation of pain between the two groups after fourteen days treatment. Complete alleviation of pain was observed in 14 patients in the indomethacingroup and in 16 in the placebo group. The treatment had no influence on the straight-leg raising test, reflex anomalies, loss of sensitivity or big toe extensor paresis.

In this investigation it was thus not possible to demonstrate any obvious effect of indomethacin treatment in cases of low back pain and sciatica.

RESUME

A titre de simple essai, on a comparé dans des cas de douleurs lombaires et de sciatiques un médicament antiphlogistique, l'indomethacine (Indome®) au placebo. 50 malades ont été mis en traitement, tous ayant été hospitalisés dans un Service d'orthopédie. Il n'y a pas eu grande différence par rapport au soulagement de la douleur après quinze jours de traitement chez les deux groupes. La suppression complète des douleurs a été constatée chez 14 malades du groupe indométhacine et chez 16 du groupe placebo. Le traitement n'a eu aucun effet sur le test de la jambe levée tendue, les anomalies des réflexes, la perte de sensibilité ou la parésie de l'extenseur du gros orteil.

Au cours de cette enquête, il n'a pas été possible de constater un effet quelconque du traitement à l'indométhacine dans les cas de douleurs lombaires et de sciatiques.

ZUSAMMENFASSUNG

In einem einfachen Blindversuch wurde eine antiphlogistische Droge, Indomethacin (Indome®) im Vergleich mit Placebo bei Fällen von Lumbago und Ischias ausprobiert. Fünfzig Patienten, die alle an eine orthopädische Abteilung aufgenommen worden waren, wurden be-

handelt. Man fandt keinen grösseren Unterschied in der Erleichterung der Schmerzen nach einer Behandlung von vierzehn Tagen. Vollständige Erleichterung der Schmerzen wurde bei 14 Patienten der Indomethazingruppe und bei 16 in der Placebogruppe gefunden. Kein Einfluss der Behandlung auf die Probe der Hebung des gestrackten Beines, auf Reflexanomalien, Verlust der Sensibilitet oder Parese des Extensor der Grosszehe konnte beobachtet werden.

In dieser Untersuchung war es daher nicht möglich irgendeine deutliche Wirkung der Indomethazinbehandlung in Fällen von Lumbago oder Ischias nachzuweisen.

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