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INDOMETHACIN TREATMENT IN OSTEOARTHRITIS OF THE HIP JOINT

Does the Treatment Interfere with the Natural Course of the Disease?

HELGE RØNNINGEN & NORVALD LANGELAND

Sophies Minde Orthopaedic Hospital, University of Oslo, Oslo, Norway

The course of osteoarthritis in 294 hips of 186 patients was evaluated by examining their radiographs. The development of the disease in patients treated with indomethacin was compared with that in a control material. In the indomethacin group the disease progressed more frequently and in one parameter the progress was more severe. The results support previous reports indicating that indomethacin might have a deleterious effect on osteoarthritic hip joints. Some possible explanations for this adverse effect of indomethacin treatment are discussed.

Key words: hip joint, indomethacin, osteoarthritis

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In most patients osteoarthritis of the hip joints is a chronic disease, lasting for decades without dramatic changes. Rapid disintegration of the joint such as collapse of the femoral head occurs, but has been considered to be rare (Murray 1976, Storey 1968). In the last 10 years this phenomenon has been observed in a number of patients. Many of them had been treated with indomethacin, and this left the impression that there might be a relationship between treatment with indomethacin and a rapid disintegration of osteoarthritic hip joints (Foss Hauge 1975).

The present paper deals with a review of the radiographs of patients treated as in-patients in Sophies Minde Orthopaedic Hospital during 1970. In order to investigate a possible relationship between indomethacin treatment and a rapid deterioration of osteoarthritic hip joints, the progress in a group treated with indomethacin was compared with that in a control group.

MATERIAL AND METHODS

Radiographs of all patients admitted to the hospital because of osteoarthritis of the hip joint in 1970 were reviewed. The radiographs, anteroposterior projections had been taken with the patient lying supine with his patellae in the frontal plane. The patients had been admitted for a radiographic examination of their hips prior to their actual admission to the hospital in 1970. Films taken between the years 1965 and 1975 were studied. The earliest and most recent radiographs taken between these time limits were used for the assessment of the severity and progress of the radiographic changes. The radiographic changes were assessed by an orthopedic surgeon without knowledge of the treatment given to the patient.

A modification of the method of Danielsson (1964) was used to quantify the radiographic changes. In Danielsson's method the term "structure" includes hyperdensity (sclerosis), cystic changes and destruction of the joint. These parameters were assessed separately in the present study. Changes in the trabecular structure of the femoral head and neck were assessed by the

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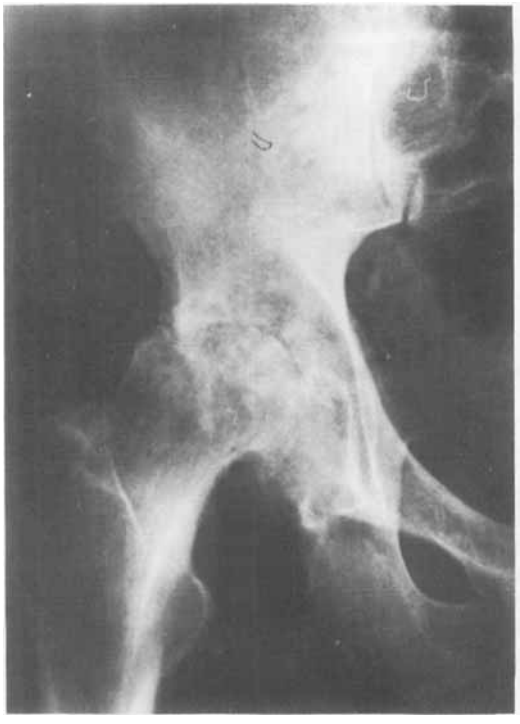

Figure 1. Radiograph of the right hip of a 56-year-old male showing multiple but small cysts in acetabulum, femoral head and neck. The trabecular structure in the head and neck is indistinct giving a "cloudy" appearance. Classified with index figure 2 for bone structure (see Table 1).

parameter "bone structure", which is further detailed in Table 1 and Figure 1. The width of the joint space was measured in millimeters at the line where the vertical axis through the center of the femoral head passes through the joint.

All data from the radiographs have been expressed in index figures ranging from 0 to 3 (0 to 2 for bone structure) as the severity of the changes increased (Table 1). The sum of the index figures ranging from 0 to 17 is the "score" for the actual hip, increasing from 0 to 17 as the severity increases. In the present study the parameters altered bone structure, cystic changes and destruction will be given special attention.

The patients were divided into two groups. The "indomethacin group" includes all patients treated with indomethacin. Untreated patients and patients treated with other antiphlogistica or analgesics were included in the "control group". None of the patients in the "indomethacin group" had received steriod therapy. It was not possible to assess the exact dosage administered to the patients in the "indomethacin group". Osteoarthritis with unknown etiology was classified as primary, and those presenting etiological factors such as acetabular dysplasia, luxations or fractures, etc., were classified as secondary.

The Wilcoxon test was applied to evaluate statistical significance and differences.

Table 1. Scheme used for evaluation of the radiographic severity of the coxarthrosis

	Index figure
Joint space	
5 mm	0
3–4 mm	1
1–2 mm	2
0 mm	3
Sclerosis	
No sclerosis	0
Acetabulum or caput (Hyperdensity)	1
Acetabulum and caput	2
Severe sclerosis	3
Osteophytes	
None	0
Visible medial or lateral	1
Visible medial and lateral	2
Bulky masses	3
Cysts	
None	0
Single cysts, acetabulum or caput	1
Single cyst, acetabulum and caput. Two or more cysts one side of the joint	2
Multiple cysts	3
Bone structure	
Normal	0
Loss of trabecular structure in caput (giving a "cloudy appearance")	1
Totally destroyed trabecular structure in caput and collum	2
Destruction	
Normal shape of caput and acetabulum	0
Flattening of caput	1
Advanced destruction caput and/or acetabulum	2
Grossly destroyed joint	3

Table 2. Survey of the patient material. The median age refers to the first examination. The distribution between cases with primary and secondary osteoarthritis is given as the percentage with primary osteoarthritis

	Indomethacin group				Control group				Total			
	Number		Median age	Per cent primary	Number		Median age	Per cent primary	Number		Median age	Per cent primary
	Patients	Hips			Patients	Hips			Patients	Hips		
Males	18	33	61.5	61	51	82	59.5	55	69	115	60.6	57
Females	40	67	63.2	24	77	112	60.4	21	117	179	61.3	22
Total	58	100	62.7	36	128	194	60.2	36	186	294	61.0	36

RESULTS

Tables 2, 3 and 4 give some characteristics of the series. Table 2 presents a survey of the patient material. Radiographs of 294 hips (186 patients) were examined. The male: female ratio was about 1:2 in both groups. There was no significant difference in the median age of the patients in the two groups, and there was an equal distribution with respect to primary and secondary osteoarthritis. In the indomethacin group the median at the commencement of joint pain was 58.6 (range 41–70) years for the patients with primary, and 58.4 (range 12–72) years for those with secondary osteoarthritis. In the control group this was 58.9 (range 17–69) years for primary and 49.4 (range 10–71) years for secondary osteoarthritis. The differences were not significant. Table 3 shows the severity of the radiographic changes at the first examination and that most patients presented a rather severe osteoarthritis at the first examination. The observation time was 2.9 ± 2.0 (s.d.) years in the indomethacin group and 3.1 ± 2.2 (s.d.) years in the control group.

Tables 4 and 5 give the results of the parameters reflecting deterioration of the hip joints, i.e., altered bone structure, cystic changes and destruction. The groups did not differ significantly as regards the three selected parameters at the first examination.

Table 3. Severity at the first examination. Total score ± s.d. is given. The hips are divided into subgroups with respect to the patients' sex and type of osteoarthritis

	Indomethacin group		Control group	
	Primary	Secondary	Primary	Secondary
Males	7.8 ± 3.5	6.6 ± 3.3	5.7 ± 4.5	5.8 ± 4.4
Females	7.3 ± 4.5	6.8 ± 3.6	6.9 ± 3.8	6.9 ± 4.4
Total	7.6 ± 3.9	6.7 ± 3.5	6.1 ± 4.2	6.5 ± 4.5

Table 4. Presence of cysts, altered bone structure and destruction at the first examination

	Cysts		Altered bone structure		Destruction	
	Per cent of hips	Mean index	Per cent of hips	Mean index	Per cent of hips	Mean index
Indomethacin group	78	2.2 ± 0.6	22	1.2 ± 0.4	17	1.2 ± 0.4
Control group	71	2.2 ± 0.7	22	1.4 ± 0.5	18	1.7 ± 0.6

Table 5. Progress of cysts, altered bone structure and destruction during the observation period

	Cysts		Altered bone structure		Destruction	
	Per cent with progress	Mean progress	Per cent with progress	Mean progress	Per cent with progress	Mean progress
Indomethacin group	40*	1.3 ± 0.6	30*	1.2 ± 0.4	31*	1.5 ± 0.6
Control group	26	1.3 ± 0.6	8	1.1 ± 0.3	6	1.0 ± 0.0

* Significantly different from control group ($2\alpha < 0.05$)

Table 6. Hips with progression in cystic changes, altered bone structure or destruction during the observation period. Observation time, mean age and score at the first examination are indicated

	Number	Mean age Years ± s.d.	Mean score ± s.d.	Mean observation time Years ± s.d.
Indomethacin group	59	61.9 ± 6.8	7.6 ± 3.1	3.1 ± 2.1
Control group	64	58.3 ± 12.2	5.3 ± 3.8	3.8 ± 2.2

Table 5 shows the percentage of the hips with progression in the above parameters during the observation period. Progression was significantly more frequent in the indomethacin group than in the control group ($2\alpha < 0.05$). Furthermore, in the indomethacin treated hips that progressed, a more severe destruction was found ($2\alpha < 0.05$). Progression was equally frequent in females and males.

Table 6 refers to the hips that progressed during the observation time. Mean score at the first examination was insignificantly lower in the controls showing progression than in the indomethacin treated hips. Mean observation time and age of the patients correspond to these factors in the groups as a whole.

DISCUSSION

Evaluated according to the method described, deterioration of osteoarthritic hip joints occurred more frequently among indomethacin treated patients than in the control group. In one parameter, destruction, the deterioration was also more severe. No significant difference in the severity of the osteoarthritis at the first examination could be detected (Table 3). In addition, the patients' ages, sex distibution and observation time were only insignificantly different in the two groups; thus the groups should be statistically comparable.

As indomethacin was first introduced in Norway in 1964, none of the patients in the

indomethacin group had received indomethacin for a long period of time at the first examination. Unfortunately exact information about dosages of indomethacin was not available in all cases, but none of the patients, where the dosage was known, had received doses exceeding those recommended by the producer.

As indomethacin treatment was the only known variable between the two groups, the investigation supports the theory of a relationship between indomethacin treatment and a rapid deterioration of osteoarthritic hip joints.

Coke (1967), Arora (1968), Allen & Murray (1971), Murray (1976), Milner (1973) and Foss Hauge (1975) have reported several cases which have been interpreted as examples of a relationship between indomethacin treatment and a rapid progression of osteoarthritis.

Solomon (1973) reported similar destruction in osteoarthritic hip joints as "new events" during treatment with non-steroid anti-inflammatory drugs, though he paid no special attention to indomethacin. He performed further investigations on the extirpated femoral heads with examination of cut surface, slab radiographs and histology. Many of the heads, and especially those with changes attributable to non-steriod anti-inflammatory drugs, were found to have microscopic fragmentation of the bony trabeculae giving the appearance of a jammed marrow space. In the present study loss of trabecular structure in the subchondral bone seems to be a characteristic feature in "indomethacin joint destruction" as well as disappearance of normal joint contours and multiple small cysts. Hyperdensity is comparatively rare. The loss of trabecular structure could be a parallel to the "jammed marrow spaces" described by Solomon (1973). According to him the drug-induced arthropathy presented features consistent with necrosis of the femoral head. Storey (1968) reporting 14 cases with collapsing osteoarthritic hip joints, concluded that the collapse had been a complication of degenerative joint disease, caused either by an avascular necrosis or an osteoporosis predisposing to microfractures in the femoral heads. Watson (1976) proposed that osteoporosis leading to microfractures contributes to a rapid disintegration of the hips in these elderly patients. The radiographs examined in the present study exhibited features commonly seen in femoral head necrosis, but histological examination has not been carried out. As the hips presented well established degenerative disease at the first examination, necrosis could not in any way be the primary event. If the theory of osteoporosis as a predisposing factor is the correct one, predominance of females would be expected among the patients showing progression. This could not be detected in the present study.

Why indomethacin in some cases may produce a rapid joint destruction remains unknown. Two theories have been put forward; the one that indomethacin as an anti-inflammatory agent produces disturbances in bone metabolism and the other that the pain relieving effect makes the patient "overuse" his joint and by increased wear the joint is destroyed. The first theory seems to be the more reliable. Minor necrosis of bone may be a pathogenetic feature of osteoarthritis, either as a primary event or secondary to microfractures. Normally this necrosis or these fractures are followed by bone repair. Bone repair starts with an inflammation. Indomethacin inhibits this inflammation, probably through inhibition of prostaglandin synthetase (Vane 1971, Floman et al. 1977). Because of this inhibition bone repair will be inhibited or delayed as well. Repair of necrotic areas or microfractures will thus be affected and severe joint destruction may be the outcome. If this theory is correct, a similar effect is to be expected from treatment with other anti-inflammatory agents, although at present indomethacin seems to be the most potent of these agents.

Recently Rö et al. (1976) found that in-

domethacin delayed fracture healing in rats, and Sudmann (1975) reported an inhibition by indomethacin of new bone formation in the rabbit ear chamber. An experimental investigation in rats concluded that indomethacin delayed formation of new bone in the extraction cavity following tooth extraction (Huusko et al. 1975). The doses used in these animal studies may have been too high to be clinically relevant, but their results support the theory that indomethacin interferes with bone metabolism, leading to delayed bone repair.

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Correspondence to: Helge Rønningen, Sophies Minde Ortopedisk Hospital, Trondheimsvn. 132, Oslo 5 Norway.