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SIDE-EFFECTS OF INDOMETHACIN

BY

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This paper reports side-effects on indomethacin in patients with rheumatic disorders, with particular reference to factors which may affect their frequency and severity.

Side-effects occur in three major groups; referable to the central nervous system, the gastrointestinal system, and the skin. Percy, Stephenson, and Thompson (1964) emphasized the psychic side-effects, including depression and hallucinations; epilepsy and coma have occurred (Thompson and Percy, 1966), and Robinson (1965) reported narcolepsy and suicide.

Rashes related to the administration of indomethacin include urticaria and purpura. Activation of latent infection was reported by Solomon (1966). In contrast, Robinson, Fitzpatrick, and Graessle (1965) reported increased resistance of mice and rats to bacterial infection when treated with indomethacin.

Acute gastrointestinal emergencies are well recognized (Dixon, Jones, Wanka, and Wood, 1963; Lövgren and Allander, 1964). Fluid retention is rare (Ballabio and Caruso, 1964).

Abnormal liver function tests have been recorded occasionally. Katz, Pearson, and Kennedy (1965), in a series of 97 patients, found two with raised serum alkaline phosphatase and SGOT (serum aspartate transaminase) levels, but pointed out that neither had control determinations. Bruckner and Randle (1965) noted raised serum alkaline phosphatase levels in three out of fourteen patients with rheumatoid arthritis; a transient rise in SGOT occurred in one. No controls were available.

Wanka, Jones, Wood, and Dixon (1964) estimated gastrointestinal bleeding during indomethacin therapy by means of erythrocytes labelled with radioactive chromium. The mean daily loss on aspirin was 5·9 ml. compared with 1·2 ml. on indomethacin. One of their patients developed progressive anaemia on indomethacin over a 4-month period and finally had a severe melaena. Robinson (1965) reported anaemia in 4 per cent. of 193 patients. In one patient seen by the authors, occult gastro-intestinal blood loss exceeded 25 ml. per day. The finding of occult blood in the stools has varied from 2 per cent. (Ballabio, Cirla, Girardi, Caruso, and Colombo, 1963) to 45 per cent. (Datey and Pandya, 1964).

Raised blood urea levels have been reported occasionally in patients on indomethacin (Michotte and Wauters, 1964; Ballabio and others, 1963; Thompson, 1964); in general the rise did not reach the upper limit of normal. The development of proteinuria with granular casts was noted in one patient by Bruckner and Randle (1965).

Rubens-Duval and Villiaumey (1964) recorded one instance of transient neutropenia and one of transient thrombocytopenia. An occasional decrease in circulating eosinophils was noted by Miehlke (1964). No abnormality has been detected in the bone marrow (Rothermich, 1964, 1966; Berman, 1965) and no irreversible changes in the peripheral blood count have so far been reported.

Sicuteri, Michelacci, and Anselmi (1964) demonstrated a vasoconstrictor effect, exerted preferentially on the cerebral circulation; in a patient with essential hypertension, a considerable prolonged rise in pressure was recorded.

Occasional deterioration in diabetic control has been reported as a result of indomethacin (Katz and others, 1965; Ballabio and others, 1963), but generally there is little effect on glucose tolerance. One of us (FDH) found no effect on diabetic balance when administering the drug to five diabetic patients, though one of these first developed diabetes mellitus while on indomethacin. Patients occasionally find difficulty in differentiating between hypoglycaemic attacks and the cerebral side-effects of indomethacin.

The administration of indomethacin by suppository

has certain therapeutic advantages, as in the relief of early morning stiffness. Systemic reactions, such as headache and giddiness, are less prominent and local rectal irritation is only an occasional, relatively unimportant problem (Holt and Hawkins, 1965; Woolf, 1965; Whitehouse and Hart, 1965).

Material

This analysis is based on results in 228 patients; 118 with rheumatoid arthritis, 32 with ankylosing spondylitis, 52 with osteo-arthrosis, and 26 with gout, details of whom have been reported previously (Hart and Boardman, 1965; Boardman and Hart, 1965). For this study, as long-term placebo studies were not practicable, the patients were divided into two groups for comparative purposes:

(1) 115 patients received a relatively high dosage of indomethacin tablets (mean 2·9 mg./kg./day; S.D. $\pm$ 1·5);

(2) 113 patients received a low dosage of indomethacin capsules (mean 1·1 mg./kg./day; S.D. $\pm$ 0·37).

Although there is some variation in the absorption of indomethacin tablets (Hodgkinson, 1963), the main difference between the two groups was considered to be one of dosage.

Method

All patients were seen in the out-patients clinic at monthly intervals. They were also seen within 14 days of any alteration in therapy. They were instructed to return at any time if side-effects developed. At each visit they were asked about untoward reactions generally, leading questions being avoided, except for a direct inquiry regarding the occurrence of dyspepsia. Patients received indomethacin and phenylbutazone or oxyphenbutazone at different times, the drugs never being prescribed together.

The mean period of administration of indomethacin was 15 weeks (range one dose only to 87 weeks), the total treatment amounting to 3,420 patient weeks. The length of treatment with the pyrazole agents varied from one dose to 326 weeks (mean 50 weeks), the total treatment amounting to 9,250 patient weeks. The average period of treatment in the high dosage indomethacin group was 12 weeks, and in the low dosage indomethacin group 18 weeks.

The nature, frequency, and severity of side-effects were recorded, the last in three grades; mild, moderate, and severe. Mild side-effects were noted by, but did not inconvenience, the patient. Moderately severe side-effects made the patient modify his daily activities and usually take a few hours' rest. Severe side-effects were incapacitating for a few hours, rest in bed being imperative and symptoms very unpleasant.

Patients suffering from side-effects described the reactions in their own words. The number of spontaneous complaints varied from one to four symptoms at one time, this being taken as an index of severity of the reaction. The dominant complaint, either headache or giddiness, was also noted. A record was kept of the interval between the start of treatment and the development of side-effects. Indomethacin-induced dyspepsia was compared with that caused by the pyrazoles (phenylbutazone and oxyphenbutazone).

Results

Side-effects occurred in 113 patients (49·5 per cent.), 181 spontaneous symptoms being recorded (Table I) in 71 (61·7 per cent.) of the 115 on high dosage and in 42 (37·1 per cent.) of the 113 on low dosage. This is a significant difference ($\chi^2 = 13·6$; $n = 1$; $P < 0·01$).

Of the 185 patients who received both indomethacin and a pyrazole derivative, 97 developed side-effects on indomethacin, of whom 40 were intolerant of phenylbutazone or oxyphenbutazone (40/97 = 41·2 per cent.). Among the 88 patients who tolerated indomethacin, sixteen were intolerant of the pyrazoles (16/88 = 9·9 per cent.). This is a significant difference ($\chi^2 = 10·50$; $n = 1$; $P < 0·01$).

TABLE I
ACTUAL COMPLAINTS AND INCIDENCE IN PATIENTS RECEIVING INDOMETHACIN

Side-effect	No. of Complaints
Headache	50
Giddiness	30
Dyspepsia	18
Muzziness	17
Nausea	15
Vomit	7
Diarrhoea	6
Drowsiness	6
Odd	5
Rash	4
Sensation of drunkeness	4
Faint	2
Ill	2
Legs odd	2
Costive	1
Drumming in ears	1
Doped	1
Loss of taste and smell	1
Swollen tongue	1
Depressed	1
Lassitude	1
Nightmares	1
Shaky	1
Mouth ulceration	1
Neck rigidity	1
Throbbing all over	1
Light-headedness	1
Total	181

The incidence of side-effects in relation to diagnosis and dosage is shown in Table II (opposite). It was about equal in cases of rheumatoid arthritis and ankylosing spondylitis in both dosage groups. In the low dosage group the incidence of side-effects in cases of gout was about the same as in cases of

TABLE II

SIDE EFFECTS, CHARACTERISTICS, DOSAGE, AND DIAGNOSIS IN 228 PATIENTS

Dosage			High	Low
Number of Patients			115	113
Total Patients with Side-effects	No.		71	42
	Per cent.		61·7	37·1
Side-effects (per cent.) related to Diagnosis in 228 Patients*	Rheumatoid Arthritis (118)		70·1	43·1
	Ankylosing Spondylitis (32)		71·4	45·45
	Osteo-arthrosis (52)		46·1	25·6
	Gout (26)		21·4	41·6
Severity of Side-effects (per cent.)	Severe		7·0	0
	Moderate		40·8	26·2
	Mild		52·1	73·8
Number of Spontaneous Complaints by Each Patient with Side-Effects (per cent.)	Four		4·2	0
	Three		15·4	7·14
	Two		32·3	16·6
	One		47·8	76·18
Dominant Complaint	Headache	No.	41	9
		Percentage of Those with Side-effects in the Group	57·6	21·4
	Giddiness	No.	21	22
		Percentage of Those with Side-effects in the Group	29·5	52·4

* No. of patients with each diagnosis given in brackets.

arthritis and spondylitis, and was much lower in those with osteoarthrosis (25·6 per cent.). In the high dosage group it was also lower in those with osteo-arthrosis, but very much lower in those with gout (21·4 per cent.).

The grade of severity of side-effects is also shown in Table II. In the 71 patients on a high dosage, the reaction was mild in 37 (52·1 per cent.), moderate in 29 (40·8 per cent.), and severe in five (7·0 per cent.). In the 42 patients on a low dosage, it was mild in 31 (73·8 per cent.), moderate in eleven (26·2 per cent.), and severe in none. This is a statistically significant difference ($\chi^2 = 4·5$; $n = 1$; $0·05 < P < 0·02$).

The number of spontaneous complaints recorded in Table II shows that, of the 71 patients on high dosage, 34 (47·8 per cent.) had only one spontaneous complaint, 23 (32·3 per cent.), complained of two symptoms, eleven (15·4 per cent.) of three, and three (4·2 per cent.) of four. Of the 42 patients on low dosage, 32 (76·2 per cent.) complained of one symptom, seven (16·6 per cent.), of two, and three (7·1 per cent.) of three. At the lower dosage, therefore, the majority of side-effects consisted of a single complaint, usually giddiness.

In the high dosage group, the dominant complaint was headache (Table II), which occurred in 41 (57·6 per cent.) of the 71 patients with side-effects, giddiness being recorded in 21 (29·5 per cent.). In the low dosage group, headache was dominant in only nine (21·4 per cent.) of the 42 patients with side-effects, giddiness being recorded in 22 (52·4 per cent.). The difference is significant ($\chi^2 = 10·5$; $n = 1$; $P < 0·01$).

Side-effects developed within 48 hours in 78 patients (69 per cent.), between 48 hrs and 28 days in 28 patients, and after 28 days in seven patients.

In six patients, in whom early, transient side-effects developed, it was possible to continue with indomethacin. Most, however, experienced further side-effects after more prolonged therapy.

Abdominal pain or discomfort related to indomethacin occurred in eighteen of 228 patients (7·8 per cent.). A pyrazole derivative had been taken by seventeen of the eighteen and fourteen of these had consequent dyspepsia (82·3 per cent.). In contrast, of the 210 patients who did not have dyspepsia on indomethacin, 168 had received a pyrazole and 26 of them had had associated dyspepsia (15·4 per cent.). Dyspepsia occurred in seven of the 115 (6 per cent.) patients in the high dosage group and in eleven of the 113 (9·7 per cent.) in the low dosage group; the difference is not significant ($\chi^2 = 0·6$; $n = 1$; $0·9 > P > 0·8$).

Dyspepsia was noted within the first month of treatment in thirteen patients, in one it occurred intermittently, and in four it developed after more prolonged therapy.

Discussion

There are significantly more non-dyspeptic side-effects in the high dosage group. Dyspepsia occurs with similar frequency in both groups, which confirms its independence of dosage. This explains the relative increase in importance of dyspepsia, in that it constitutes 26·2 per cent. of all side-effects in the low dosage group and 9·8 per cent. in the high dosage group. High dosage is also associated with

increased severity of side-effects and in the number of spontaneous complaints relating to each undesirable reaction. The dominant complaint at low dosage is muzziness or giddiness; at high dosage it is headache. The reciprocal relationship between headache and giddiness at high and low dosage suggests that these symptoms are the result of a common reaction of the central nervous system to indomethacin, the intensity of which varies according to dosage.

There is a significant increase of side-effects in patients in whom the previous administration of phenylbutazone or oxyphenbutazone had been associated with untoward reactions. In particular, 80 per cent. with dyspepsia while taking indomethacin gave a history of having suffered similarly while taking the pyrazoles, as against 15 per cent. of those who tolerated indomethacin. The interrelationship of the two drugs in causing dyspepsia is not unexpected, but it is surprising that the dissimilar, non-dyspeptic side-effects tend to occur in the same patients when taking these chemically unrelated drugs. It is unlikely that this is entirely the result of selection or placebo reaction. Relevant factors may include the severity of the disease rather than its nature, and the fact that the drugs share certain pharmacological properties.

The incidence of side-effects is similar in cases of rheumatoid arthritis and ankylosing spondylitis (Table II), but it is lower in cases of osteo-arthrosis, though the difference is not significant. The incidence of side-effects in cases of gout is about the same as in rheumatoid arthritis and ankylosing spondylitis for the low dosage group. The incidence in cases of gout was very much lower in the high dosage group, but the small number of gouty patients probably accounts for the discrepancy. The lower incidence of side-effects in cases of osteo-arthrosis was noted by Thompson and Percy (1966). Rothermich (1966) found that more than 50 per cent. of all patients had side-effects while taking indomethacin, a higher incidence than reported here on low dosage. Although he emphasized that he was using high dosage, his incidence of side-effects is lower than that seen in this study in patients with rheumatoid arthritis and ankylosing spondylitis in the high dosage group.

There is evidence that side-effects decrease with increasing age (Table III), but the difference does not reach statistical significance ($\chi^2 = 7{\cdot}0$; $n = 5$; $0{\cdot}3 > P > 0{\cdot}2$). The lower incidence of side-effects in osteo-arthrosis may be related to the greater mean age of the patients. The 27 patients above 55 years of age included six (22 per cent.) with side-effects, compared with four (33 per cent.) out of twelve aged less than 55 years. An analysis of the results in the patients with gout revealed that, allowing for dosage, those who suffered from side-effects were generally younger.

Side-effects occurred with significantly greater frequency in females (55·5 per cent.) than in males (40·8 per cent.) ($\chi^2 = 4{\cdot}12$; $n = 1$; $0{\cdot}05 > P > 0{\cdot}02$). Treadwell, Sever, Savage, and Copeman (1964) found a similar difference between the sexes in patients on long-term corticosteroids and corticotrophin.

The reason for the early occurrence of non-dyspeptic side-effects in this series is their dependence on dosage. Dyspepsia may occur at any time, often after a long period of treatment. There has so far been no increase in incidence of side-effects in relation to the duration of therapy.

Predisposing factors included head injury, the precipitation of a rash by alcohol, and giddiness in a patient with Menière's disease.

In the absence of control groups, it is difficult to differentiate between rare, true, side-effects and the chance occurrence of unrelated incidents. Short-term double-blind trials tend to emphasize placebo reactions. In this paper comparison was made at two dosage levels during long-term administration of indomethacin.

Summary and Conclusions

(1) Side-effects in patients treated with indomethacin at two dosage levels are compared and the literature briefly reviewed.

(2) Side-effects occurred in 37·1 per cent. of patients receiving a low dosage of 1·1 mg./kg./day in capsules. They occurred in 41-45 per cent. of cases of

TABLE III
SIDE-EFFECTS AND AGE OF PATIENTS

Age (yrs)	Number of Patients with Side-effects	Total Number Treated	Number with Side-effects as Percentage of Total
20–29	7	10	70
30–39	9	17	52·9
40–49	27	42	64·3
50–59	37	79	46·8
60–69	26	59	44·1
70–79	7	21	33·3

rheumatoid arthritis, ankylosing spondylitis, and gout, and in 25 per cent. of cases of osteo-arthrosis. The incidence of dyspepsia was 8 per cent. The incidence of side-effects had been 61·7 per cent. before the reduction from 2·9 mg./kg./day to the lower dosage.

(3) High dosage was associated with more severe, polysymptomatic reactions, headache being the dominant complaint. On low dosage, reactions frequently consisted of single, relatively mild symptoms, the most usual complaint being giddiness. On the low dosage, over 75 per cent. of all reactions consisted of mild transient giddiness or muzziness. Side-effects in this series were transient, resolving on reduction or withdrawal of the drug.

(4) Side-effects were more common in patients with a history of previous pyrazole intolerance, in particular dyspepsia, and more common in females than in males.

(5) Side-effects were less common in osteo-arthrosis than in rheumatoid arthritis, ankylosing spondylitis, and gout. This is probably because the frequency decreases with increasing age.

(6) There is little evidence of hepatic or renal toxicity in the literature and none of irreversible bone marrow depression, but indomethacin should be administered with great caution, if at all, to patients with a history of psychiatric illness, uraemia, or recent peptic ulceration.

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Effets secondaires de l'indométhacine
Étude comparative et revue de la littérature

RÉSUMÉ

(1) On compare les effets secondaires observés avec l'indométhacine avec deux dosages différents et on fait une brève revue de la littérature.

(2) On observa des effets secondaires dans 37 pour cent des cas chez 113 sujets recevant une dose faible de 1,1 mg. par kg. et par jour sous forme de capsules. On les observa dans 41 à 45 pour cent des cas d'arthrite rhumatismale, de spondylarthrite ankylosante et de goutte et dans 25 pour cent des cas d'ostéo-arthrose. La fréquence de la dyspepsie fut de 8 pour cent. La fréquence des effets secondaires fut de 61 pour cent chez 115 malades recevant une dose plus forte de 2,9 mg. par kg. et par jour sous forme de comprimés.

(3) L'administration à dose plus forte s'accompagna de réactions plurisymptomatiques plus accentuées, la céphalée prédominant. Avec les doses faibles, les réactions consistèrent fréquemment en des symptômes isolés relativement bénins, le plus commun étant les vertiges. A la dose basse plus de 75 pour cent de toutes les réactions consistèrent en sensations de vertige ou de malaise, légères et transitoires. Les effets secondaires dans cette série furent transitoires, disparaissant lors de l'arrêt du traitement ou de la réduction des doses.

(4) Les effets secondaires furent plus fréquents chez les sujets présentant des antécédents d'intolérance aux pyrazolés en particulier de dyspepsie et ils furent plus fréquents chez les femmes que chez les hommes.

(5) Les effets secondaires furent moins fréquents dans les cas d'ostéoarthrose que dans les cas d'arthrite rhumatismale, de spondylarthrite ankylosante et de goutte. Cela est probablement dû à une diminution de leur fréquence avec l'âge.

(6) On n'a guère fait mention dans la littérature de cas de toxicité hépatique ou rénale et jamais rapporté d'aplasie médullaire irréversible, mais l'indométhacine devrait être administrée avec grande prudence ou même pas du tout aux malades présentant des antécédents d'affection psychiatrique, d'urémie ou d'ulcère gastro-duodénal récent.

Efectos secundarios de la indometacina
Estudio comparativo y revista de la literatura

SUMARIO

(1) Se compararon los efectos secundarios en pacientes tratados con dos dosificaciones diferentes de indometacina y se revisó brevemente la literatura.

(2) Se observaron efectos secundarios en un 37 por ciento de un total de 113 sujetos que recibieron una dosis baja de 1,1 mg. por kg. al día en cápsulas, Ocurrieron estos efectos en un 41–45 por ciento de casos de artritis reumatoide, espondilitis anquilosante y gota, y en un 25 por ciento de casos de osteoartrosis. La incidencia de dispepsia fué de un 8 por ciento. La frecuencia de efectos secundarios fué de un 61 por ciento de un total de 115 sujetos que recibieron la dosis fuerte de 2,9 mg. por kg. al día en comprimidos.

(3) La dosis fuerte se vió asociada con reacciones más graves y polisintomáticas, siendo la cefalalgia el síntoma predominante. Con la dosis baja, las reacciones consistieron frecuentemente en síntomas aislados y relativemente benignos, siendo el mareo la queja más frecuente, ocurriendo en un 75 por ciento de todas las reacciones, siendo temporal y desapareciendo con la reducción o el retiro de la droga.

(4) Los efectos secundarios fueron más frecuentes en sujetos con antecendentes de intolerancia a los derivados del pirazol, particularmente la dispepsia y más comunes en mujeres.

(5) Los efectos secundarios fueron menos frecuentes en casos de osteoartrosis que en los de artritis reumatoide, de espondilartritis anquilosante y de gota. Esto probablemente se debe a que la frecuencia disminuye con la edad.

(6) Se menciona muy poco en la literatura la toxicidad hepática o renal y no se nombra la depresión irreversible de la médula ósea. Sin embargo la indometacina debe ser administrada con gran cuidado o incluso denegada a casos con antecendentes de enfermedad psiquiátrica, uremia o úlcera péptica reciente.