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RESPONSE OF PATHOLOGICAL ISCHAEMIC MUSCLE PAIN TO ANALGESICS

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1 Twenty-four patients suffering from severe pain due to chronic occlusive arterial disease of the legs were given oral doses of indoprofen (200 mg), ibuprofen (300 mg) and placebo.

2 Differences in pain intensity scored on a five-point scale were taken as measurement of pain relief.

3 This double-blind, cross-over trial showed that indoprofen had significantly greater analgesic effect than placebo and reference drug.

4 From a methodological point of view there are many arguments on favour of pathological ischaemic pain as a test for clinical assessment of analgesics.

Introduction

Since Lewis, Pickering & Rothschild (1931) experimental ischaemic muscle pain has been suggested and used for testing analgesics in man. One of the most thoroughly investigated methods, the submaximum-effort tourniquet technique (Smith & Beecher 1969) gave results which however could not be confirmed by others (Moore, Weissman, Thomas & Whitman, 1971; Adler & Lomazzi, 1974; Adler Gervasi, Holzer & Hermeler, (1974). Taking into account these conflicting results, pathological ischaemic pain was used to study analgesic activity of two non-steroidal antiinflammatory drugs, indoprofen (Nannini, Giraldi, Molgora, Biasoli, Spinelli, Logemann, Dradi, Zanni, Buttinoni & Tommasini, 1973; Buttinoni, Cuttica, Franceschini, Mandelli, Orsini, Passerini, Turba & Tommasini, 1973) and ibuprofen (Lewis, 1975; Martindale, 1977) given orally in single doses, compared with placebo. Ibuprofen has been already examined as an analgesic in a non arthritic disorder i.e. episiotomy pain (Bloomfield, Barden & Mitchell, 1974).

Methods

In-patients suffering from severe rest pain due to chronic atherosclerotic obliterant disease of the legs were admitted to the trial, to which they gave their free informed consent. The main criteria for exclusion were non collaborative or unreliable subjects, morphine dependence, concomitant analgesic treatment, surgical procedure compulsive, liver and/or renal failure, concomitant gastro-intestinal haemorrhage, history of or concomitant peptic ulcer.

Thirty-one patients entered the trial which began in October 1974 and ended in May 1977. Seven cases were dropped due to deviations from the protocol.

Twenty-four subjects completed the trial and their experimental data were judged suitable for analysis. The main characteristics of this sample are reported in Table 1.

Single oral doses of indoprofen (200 mg), ibuprofen (300 mg) and placebo were given as sealed hard gelatine capsules identical in shape, size and colour. The content was a powder mixture for both indoprofen and placebo (excipients of the indoprofen dosage form) and a powder obtained by grinding commercially available coated tablets (Brufen®) for ibuprofen. A small amount of fresh water was given with the capsules to make them easier to swallow and to speed up drug bioavailability.

Drugs were administered according to a double-blind, cross-over design, using two complete balanced 3×3 latin squares with four replications.

Doses were given at intervals of about 24 h when patients requested analgesic treatment. No other drugs were allowed which might possibly have interfered with test drugs.

Patients were asked to rate their pain on a five-point scale from 0 = no pain to 4 = very severe pain. They were always questioned by the same investigator just before treatment and 15 and 30 min and 1, 2, 3, 4 and 6 h after medication.

Adverse reactions freely reported by patients and those observed by the investigator were recorded.

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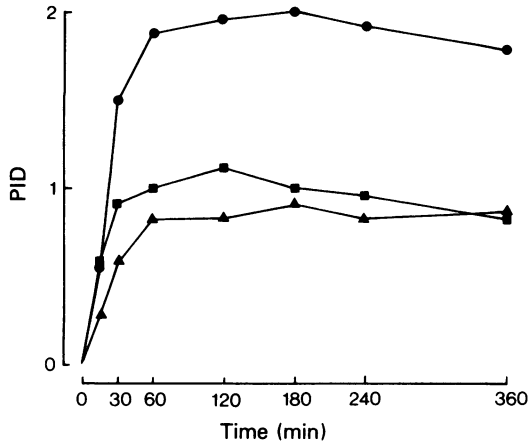

Figure 1 Pain intensity differences after single oral doses of indoprofen (200 mg, ●), ibuprofen (300 mg, ■) and placebo (▲) given to twenty-four patients with pathological ischaemic muscle pain.

Statistical analyses

Pain scores transformed according to Fisher & Yates (1963) were analyzed using a four-way mixed model analysis of variance; three factors (treatments, times and periods) were taken as fixed and one factor (patients) as random factor (Ostle, 1963). Analysis of variance on sums of pain intensity differences (SPID) and peaks of pain intensity differences (peak PID) was done to evaluate the effect of sequences, periods, adjusted and not adjusted treatment and residuals according to Cochran & Cox model (Cochran & Cox, 1968). Single contrasts between treatments were performed by Duncan test (Duncan, 1955).

Results

Raw pain scores, SPID and peak PID values are reported in Table 2. PID values at the fixed intervals are shown in Figure 1. Results of statistical analysis of the comparisons drugs *v* placebo and indoprofen *v* ibuprofen are shown in Table 3.

Table 1 Caselist of patients suffering from occlusive diseases of the arteries of the legs treated with single oral doses of indoprofen (I), ibuprofen (IB) and placebo (P).

					Lesion			*Treatment*		
Case number	*Age (years)*	*Sex*	*Weight (kg)*	*Height (cm)*	*Leg(s) R=right L=left*	*Grading for severity**	*Basal pain score*	*1st*	*2nd*	*3rd*
1	52	M	56	166	R & L	III	3	I	IB	P
2	67	M	56	168	L	III	4	IB	P	I
3	62	M	64	174	R & L	III	4	P	I	IB
4	64	M	72	175	R	III	4	I	P	IB
5	72	F	55	160	R & L; gangrene toes	IV	4	IB	I	P
6	77	M	64	176	R & L	III	3	P	IB	I
7	68	M	54	164	R & L	III	3	I	IB	P
8	54	M	68	173	R & L	III	3	IB	P	I
9	66	M	78	172	R	III	3	P	I	IB
10	65	M	61	165	L; gangrene toes	IV	4	I	P	IB
11	63	F	66	165	R & L; gangrene toes	IV	3	IB	I	P
12	52	M	55	166	R & L; gangrene toes	IV	3	P	IB	I
13	83	M	75	180	R & L; gangrene toes	IV	3	I	IB	P
14	54	M	68	172	R & L; gangrene toes	IV	3	P	I	IB
15	70	M	84	178	R; gangrene toes	IV	3	P	IB	I
16	78	M	81	178	R	III	3	IB	I	P
17	77	M	63	168	R & L	III	3	IB	P	I
18	72	M	60	170	L; gangrene toes	IV	4	I	P	IB
19	65	M	68	173	R & L	III	2	I	IB	P
20	47	M	70	170	R & L	III	3	IB	P	I
21	70	M	58	168	L; gangrene toes	IV	3	P	I	IB
22	70	M	52	164	R & L	III	3	I	P	IB
23	67	M	65	168	R & L	III	3	IB	I	P
24	59	M	70	170	R; gangrene toes	IV	3	P	IB	I

*According to Van der Stricht (1975).

Pain scores

The comparison between treatments showed significant differences for the contrasts indoprofen *v* placebo and indoprofen *v* ibuprofen but not for the contrast ibuprofen *v* placebo. Similar results were obtained for the interaction treatments × times.

SPID and peak PID

Indoprofen was always significantly more active than placebo and ibuprofen except for the contrast indoprofen *v* ibuprofen pertaining to SPID 2 h values. Ibuprofen was never significantly different from placebo.

In the analysis of variance either the effects of sequency and periods or the adjusted and unadjusted residual effects were not significant.

No adverse reactions were found.

Discussion

The idea that pathological rather than laboratory pain is the best bench for testing analgesics is widely shared.

Ischaemic pain arising from chronic atherosclerotic occlusive disease is well known as a cardinal clinical symptom (Arcangeli, Digiesi, Ronchi, Dorigo & Bartoli, 1976) but its biochemical mechanisms are not clearly understood. Available data are briefly set out here.

Induced ischaemia in skeletal muscles leads to severe pain on exercising the ischaemic muscles, possibly due to increased availability of bradykinin (Lim, 1968), which has also been suggested as responsible for the pain of angina pectoris (Burch & De Pasquale, 1963). Dog ischaemic muscle synthesizes and releases prostaglandins (Herbaczyńska-Cedro, Staszewska-Barczak & Janczewska, 1974) as does rabbit ischaemic heart (Minkes, Douglas & Needleman, 1973). Bradykinin induces release of prostaglandins by rabbit heart (Needleman, Key, Denny, Isakson & Marshall, 1975) and dog spleen (Ferreira, Moncada & Vane, 1973). In the latter experiment the release was blocked by infusion of indomethacin.

Paucity of data prevents us knowing exactly what happens in patients with chronic arterial occlusive disease. However on the basis of the above reports the mechanism of pain and its relief by non-steroidal anti-inflammatory drugs could be explained as follows. Chronic ischaemia leads to a local increase of bradykinin and prostaglandins. According to Ferreira *et al.* (1973) drugs which inhibit prostaglandin synthesis exert their analgesic effect mostly peripherically by blocking the local production of prostaglandins which sensitize pain chemoreceptors to the pain-producing activity of bradykinin.

Indoprofen has been found to have a strong inhibiting effect on prostaglandin release in animal experiments (Ku, Signor & Eakins, 1976; Ceserani, Ferrari, Goldaniga, Moro & Buttinoni, 1977; Stygles,

Table 2 Mean values and s.e. mean of pain scores, sums of pain intensity differences (SPID) and peaks of pain intensity differences (Peak PID) in twenty-four patients given single oral doses of indoprofen (200 mg), ibuprofen (300 mg) and placebo.

	Pain scores after single oral doses (min)								*SPID within*		*Peak*
Treatment	*0*	*15*	*30*	*60*	*120*	*180*	*240*	*360*	*2 h*	*6 h*	*PID*
Indoprofen	3.21	2.67	1.71	1.33	1.25	1.21	1.29	1.42	5.88	15.75	2.13
	0.10	0.13	0.24	0.27	0.26	0.29	0.31	0.31	0.75	4.61	0.26
Ibuprofen	3.08	2.50	2.17	2.08	1.96	2.08	2.12	2.25	3.63	6.83	1.33
	0.08	0.22	0.21	0.23	0.26	0.25	0.25	0.23	0.84	1.60	0.28
Placebo	3.08	2.79	2.50	2.25	2.25	2.17	2.25	2.21	2.54	5.17	1.29
	0.08	0.15	0.15	0.18	0.21	0.23	0.22	0.21	0.56	1.15	0.23

Table 3 Results of the statistical analysis; values of *P*.

Contrast	*Pain scores*	*SPID within 2 h*	*SPID within 6 h*	*Peak PID*
Indoprofen *v* Placebo	<0.01	<0.05	<0.01	<0.05
Ibuprofen *v* Placebo	>0.05	>0.05	>0.05	>0.05
Indoprofen *v* Ibuprofen	<0.05	>0.05	<0.05	<0.05

Similar results were obtained for the interaction 'single contrast × times'.

Newton & Hook 1977) and *in vitro* (Patrono, 1976 personal communication) and *in vivo* human studies (Caruso, Moro, Patrono, Sacchetti, Tamassia & Tosolini, 1979; Di Munno, Bombardieri & Patrono, 1978).

Ibuprofen is also reported to inhibit prostaglandin biosynthesis *in vitro* (Fjalland, 1976; Crook, Collins, Bacon & Chan, 1976).

Indoprofen displays its analgesic effect in different forms of pathological non-ischaemic pain when given orally (cancer, Fuccella, Conti, Corvi, Mandelli, Randelli & Stefanelli, 1975; Ventafridda, Martino, Mandelli & Emanueli, 1975; post-episiotomic, Fuccella, Corvi, Gorini, Mandelli, Mascellani, Nobili, Pedronetto, Ragni & Vandelli, 1977; osteoarthrosis, Marcolongo, Mandelli, Magni & Sacchetti, 1977), and intravenously (biliary colic, Sacchetti, Caputo, Mandelli, Fornari & Magni, 1977; acute gouty arthritis, Caruso, Fumagalli, Marcolongo & Sacchetti, 1977).

In the present trial only indoprofen had significantly greater effect than placebo. However single oral doses of indoprofen and ibuprofen were given in the amounts contained in one commercially available tablet, i.e. Flosint® Carlo Erba (200 mg) and Brufen® Boots (300 mg). The same dose of ibuprofen (300 mg) turned out more effective than placebo in episiotomy pain but not different from ibuprofen 900 mg (Bloomfield *et al.*, 1974). The present study suggests that a single oral dose of 300 mg of ibuprofen is too small for relieving severe pathological ischaemic muscle pain.

This study gave additional information about the response to placebo. The effect of placebo was only slight as is sometimes found when (a) pain is severe but not acute, (b) patients are accustomed to taking strong analgesics and (c) subjects have already taken part in clinical pharmacological trials. All three conditions were present in this study and the placebo results are in keeping with reports by other investigators and by us in other papers (Marcolongo *et al.*, 1977; Sacchetti *et al.*, 1977).

Severe chronic pain in chronic arterial occlusive disease has been suggested by the FDA Guidelines (1971) along with cancer pain and pain in musculoskeletal disease, as a model for testing analgesics. It is rarely used however (Taylor, 1971), possibly because laboratory ischaemic techniques in man diverted the attention of clinical pharmacologists from the pathological ischaemic pain. In addition suitable patients are not always easily available and clinical trials can be time consuming and prolonged.

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