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Brufen in Conditions Allied to, but Excluding Rheumatoid Arthritis and Osteoarthrosis – Open Study

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A CLINICAL TRIAL OF Brufen (ibuprofen-2-(4-iso-butyl phenyl) propionic acid) in conditions allied to, but excluding Rheumatoid Arthritis and Osteoarthrosis was undertaken at the Orthopaedic Department, University Hospital, during the period from January 1974 to October 1974. The patients attended the above department on an outpatient basis during this period. Those with proven rheumatoid arthritis were excluded, but all other allied conditions of joints and periarticular tissues where anti-rheumatic therapy was indicated were included in the trial.

Method

A group of fifteen patients were selected from those attending the outpatient department with recent complaints and mostly untreated by any effective anti-rheumatic therapy. The study was at first conducted by a Double-blind Cross-over technique using placebo capsules supplied by Boots Research Department. The technique involved giving the drug Ibuprofen 1200 milligrams in three divided doses daily for the first two weeks and a Placebo over the next two weeks in a group of patients, and then reversing the procedure in the same group of patients. After three months of this technique, the trial was changed in favour of Open study in a similar group of patients. Brufen capsules were administered orally. The treatment period in any one patient lasted from two weeks to two months, and in one patient for three months. The duration of treatment was dictated by the clinical response in a given patient.

The conditions treated were varied, but a common factor of pain in and around joints were chosen, and investigations that were carried out included Haemoglobin estimation, total and differential white cell count, erythrocyte sedimentation rate, serum uric acid, blood urea, faecal occult blood, and a complete urinalysis including glucose, and protein, cells and casts. Serum rheumatoid factor was tested by the Rose Waaler and Latex adhesion methods. The patients had a complete physical examination, including fundoscopic examination of the eyes. A pretreatment assessment of pain was made by the patients' subjectively into the following categories: very severe, severe, moderate, and slight. (The Practitioner)[1] Objective assessment included articular or periarticular swelling, tenderness, range of movements of the affected or neighbouring joints.

Brufen was initially given in doses of 200 milligrams, four times a day, but later the dose was increased to 400 milligrams three times a day, this being found to be the optimal dose for clinical effect. Follow-up of the patient was done at two-weekly intervals, up to two months for the purpose of the trial initially. Later on the trial period was extended to three months; the first month being the period of double-blind cross-over technique and the next two months being the period of open study. All the patients in the trial were re-examined after an interval of six-months from the end of the trial period to find out if they were taking any Brufen or other pain-relieving drugs, whether there was any re-currence of the original conditions and to record their subjective impression about the drug given to them. The patients did not keep any record of the pain, but were thoroughly questioned at each two-week period. It was felt that daily record keeping would subjectively make the patient too self-critical.

Pain is to some extent is a personal experience and a daily reminder was not considered proper. However, for subjective assessment of pain, the following criteria was offered to the patient (The Practitioner)[1]:–

Very severe:	Continuous severe pain, requiring pain-relieving drugs continuously.
Severe:	Pain present continuously, with periods of reduced intensity, but requiring continuous use of pain-relieving drugs.
Moderate:	Bouts of pain, bearable, but interfering with daily activity, and requiring pain-relieving drugs.
Mild:	Pain, which is not constant and bearable requiring only occasional use of pain-relieving drugs.
No pain:	Complete relief of pain, for an interval of six weeks after stoppage of drugs.

The objective assessment of pain was done by doctor and patients, as follows: Much better, Better, No Change, Worse and Much Worse. In addition clinical assessment of part affected in terms of tenderness, range of movement and inflammation was made at each visit. Laboratory investigations were repeated after an interval of one month to six weeks. Any additional therapy, during this period such as anti-rheumatic drugs and physiotherapy was also noted. Opthalmological examination was also repeated.

Results

The patient characteristics is given in Table I. The diagnoses is summarised in Table II. This included conditions like peri-arthritis of the shoulder, non-specific synovitis of the knee, non-specific articular pain in the hands including the thumb, Tennis elbow, and Cervical spondylosis and Poly-arthralgia with negative rheumatoid factor. The subjective assessment of pain by the patients, both before and after treatment is given in Table III. All the patients were objectively assessed by one doctor (author) and the results are given in Table IV. It will be seen from Table III that four patients were still in pain after six weeks, though mild, but three out of these were satisfied with daily Brufen of 800 milligrams in four divided doses. The doctor's grading of patients' pain as seen in Table IV compares well with that of the patients', especially in the severe and very severe grades, indicating thereby the milder nature of the drug in question. The side-effects were noticeably absent, except in two patients; patient number 2 complained of increased thirst and patient number II complained of an uneasy feeling in the 'stomach'. Blood sugar estimation in the former was within normal limits and occult faecal blood tested in the latter was negative. These two patients continued to tae the drug, after reassurance.

Discussion

The purpose of the study was to assess the efficiency of Brufen (Ibuprofen) in terms of degree and duration of analgesic activity; anti-inflammatory effects and to ascertain the nature and incidence of adverse reactions in conditions allied to but excluding rheumatoid arthritis and osteo-arthrosis. Strict selection of patients, resulted in a total of only fifteen patients who could be given the drug with the certainty that they will take it regularly for the prescribed time. In view of this, the small number was not felt to invalidate the results obtained. In addition these patients attended the trial on an outpatient basis intentionally, in order to remove any "ameliorative effects that a hospital admission may produce". (Mills et al 1971)[2].

There is an immense amount of western literature reporting on clinical trials conducted with Ibuprofen, since 1967, but very little from this country itself. Its efficacy has been compared with other anti-rheumatic drugs like aspirin (Chalmers 1969)[4], (Jasani et al, 1967)[5], (J.B. Dick-Smith 1969)[9], indomethasin (Shridhar D. Deodhar et al, 1973)[7], phenyl-butazone (Cardoe N. 1969)[3], (Pavelka K. et al 1973)[8], Butacote (Regaldo R.G. and Fowler P.D. 1974)[6], Prednisolone (Shridhar D. Deodhar et al 1973)[7], and Ketoprofen (Sarah B. Mills 1973)[10], in the treatment of rheumatoid and non-rheumatoid conditions. The opinions stated are at best still controversial and inconclusive. That Ibuprofen does possess anti-inflammatory effects, there does not seem to be any doubt (Dick-Smith J.B. 1969)[9], but its pain relieving effects in conditions studied here is not very un-equivocally stated. Hence the justification for our trial, of the drug.

During the course of this trial, it was found that the objective assessment of anti-inflammatory response was not satisfactory. Grip-strength, joint tenderness and joint swelling were measured in all the patients where relevant. There was no dramatic alteration in these clinical features and it was felt that a subjective element of patient responsiveness is involved, especially in the former two signs. Although clinical indices of joint tenderness, joint 'dolorimeters', measurement of digital joint size, hand grip and various composite laboratory indices

Table I

Patient Characteristics

No.	Name	Age	Sex	Race	Diagnosis	Duration of Complaint	Previous Treatment
1)	L.L.P.	31 yrs.	M	Ch.	Articular pain in both hands, nausea on taking Indocid capsules.	three months	Indocid 25 mg three thrice daily.
2)	N.P.	50 yrs.	F	Ind.	Articular pain left thumb. metacarpo-phalangeal and inter-phalangeal joints.	four months	Paracetamol irregularly.
3)	R.A.	35 yrs.	M	Ind.	Traumatic synovitis right knee.	one month	Knee bandage and aspiration of the joint.
4)	C.C.K.	52 yrs.	M	Ch.	Right Tennis elbow and polyarthralgia.	one month	Physiotherapy only.
5)	J.L.	26 yrs.	F	Ind.	Non-specific synovitis both knees.	two years	Intra-articular Hydrocortisone.
6)	S.L.	47 yrs.	F	Ind.	Cervical spondylosis.	three months. previous episode four years ago.	Physiotherapy.
7)	J.L.	33 yrs.	F	Ind.	Cervical spondylosis.	two months	Paracetamol irregularly.
8)	J.J.	36 yrs.	F	Ind.	Cervical spondylosis.	four months	Intermitant neck traction.
9)	T.S.	26 yrs.	M	Ch.	Polyarthritis with negative rheumatic factor.	one month	– Nil –
10)	A.G.	55 yrs.	M	Ind.	Periarthritis right shoulder.	three months	Physiotherapy only.
11)	M.A.	20 yrs.	F	Ind.	Articular pain in both hands, rheumatic factor negative.	four months	Paracetamol irregularly.
12)	M.T.	40 yrs.	F	Ind.	Non-specific synovitis both knees.	two months	No treatment.
13)	S.B.	54 yrs.	F	Ind.	Periarthritis right shoulder; diabetic. post-mastectomy right side for Ca. Breast three years ago. X'Rays R. Shoulder negative.	six months	Physiotherapy, Paracetamol irregularly.
14)	A.P.	55 yrs.	F	Ind.	Polyarthritis with negative rheumatoid factor; pain both heels; Obese.	one year	Physiotherapy; one course of Butazolidine six months earlier caused anaemia.
15)	T.S.K.	18 yrs.	F	Ch.	Polyarthritis with negative rheumatoid factor; severe low-back pain.	three months	Bed-rest; aspirin Hospitalised for three months.

Ind.: Indian
Ch. : Chinese

have all proven useful in assessing new anti-inflammatory and anti-rheumatic drugs, none has proved superior to simple demonstration of pain-relief. (Shridhar D. Deodhar and Carson Dick W. et al 1973)[7]. A satisfactory assessment of pain-relief could be made in all our patients and this is the index used in this study. Additional treatment in the form of short-wave diathermy, wax baths and active assisted movements were given where indicated, as physiotherapeutic measures.

One of the problems faced during the period of double-blind cross-over technique was that, many patients had recurrence of pain while on placebo and declined the offer of further supply of medicines. Once a patient's confidence in the

Table II

Diagnosis	Number of Patients
Articular pain in Hand including metacarpo-phalangeal joint of Thumb.	3
Tennis elbow with polyarthralgia.	1
Periarthritis shoulder.	2
Cervical Spondylosis.	3
Polyarthritis without rheumatoid factor.	3
Non-specific synovitis of the Knee.	3
TOTAL	15

Table III

Patients' assessment of pain before treatment and after treatment

Grade of Pain	Before Treatment	At Four Weeks	At Six Weeks
Very severe	3 patients	3 patients	1 patient
Severe	3 patients	3 patients	2 patients
Moderate	9 patients	2 patients	2 patients
Slight	—	—	3 patients
TOTAL	15 patients	8 patients	8 patients

Three patients at the end of three months still had slight pain; but were satisfied with daily Brufen of One Tablet (200 milligram per tablet) four times a day.

Table IV

Doctor's assessment of patients' pain taking into consideration the findings on clinical examination and interrogation

Grade of Pain	Before Treatment	At Four Weeks	At Six Weeks
Very severe	3 patients	2 patients	1 patient
Severe	3 patients	2 patients	1 patient
Moderate	6 patients	2 patients	—
Slight	3 patients	—	—
TOTAL	15 patients	6 patients	2 patients

At the end of six weeks two patients in the very severe and severe categories still had slight pain, and were on a maintenance dose of Brufen one tablet (200 milligrams) four times a day.

efficacy of a drug was shaken, it is never easily restored. This was the reason for the abandonment of the double-blind cross-over technique and institution of an Open Study. With respect to the dosage of Brufen, initially an attempt was made to co-relate pain relief with the amount of drug. The optimal clinical effect was obtained between dosages of 1200 milligrams to 1600 milligrams of Brufen, in four divided doses daily.

The main value of the drug Ibuprofen, was observed to be good relief of 'moderate' pain. Patients with 'severe' pain did not get a satisfactory response. In these patients additional treatment with another analgesic drug was required, in full dosage. Once the severity was lessened, Brufen reduced further pain. The time at which optimal effect of the drug began to be noticed was about two weeks, reaching full effect of pain relief in three weeks. In those, who still had pain, exhibition of the drug produced an effect up to six weeks, after which the drug had to be discontinued. Curiously, after an interval of two weeks, when Brufen is again taken, pain relief was better. Other than a subjective phenomenon it is difficult to explain this feature. The best feature of this drug is in respect of side-effects, which are virtually negligible. In this series, one patient complained of increased thirst and another complained of an uneasy abdominal sensation. Blood sugar in the former was normal and faecal blood in the latter negative. Several previous workers with this drug have similarly commented upon the side-effects, but tended to question the therapeutic efficiency. (Owen-Smith and Burry, 1972)[11]. It is interesting to note, that long after the trial has ended, we still get some patients requesting "those tablets you used to give before"!

Summary

In conclusion, it is felt that, despite a plethora of anti-rheumatic drugs available, some of which are undoubtedly effective, Ibuprofen is a valuable, pain-relieving drug in moderately painful non-rheumatoid articular and periarticular conditions. The optimal dose appears to be 1200 milligrams in four divided doses daily and satisfactory clinical response takes at least two weeks. The complete absence of side-effects makes this the drug of choice in long-term therapy.

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