PAPERS AND ORIGINALS

Comparison of Aspirin and Benorylate in the Treatment of Rheumatoid Arthritis

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Summary

In a double-blind between-patient study of aspirin and benorylate carried out in 72 outpatients with rheumatoid arthritis, benorylate 4 g twice daily was shown to be an effective analgesic and anti-inflammatory drug, its effects being indistinguishable from those of aspirin 1·2 g four times daily. Compared with the pretreatment values both drugs produced a statistically significant improvement ($P < 0·01$) in functional grade, overall pain, articular index, and grip strength at the end of the first and second weeks. The overall incidence of side effects was less with benorylate, though this difference was not significant at the 5% level.

Introduction

Benorylate, a lipid soluble ester of acetylsalicylic acid and N-acetyl-*p*-aminophenol, has recently been synthesized and investigated as a treatment for rheumatoid arthritis (Cardoe, 1970; Sperryn *et al.*, 1971; Franke and Manz, 1972). It is tasteless, insoluble in water, and 80-90% is eventually excreted in the urine. Its rate of metabolism in animals and man is slower than that of its principal metabolites salicylic acid, acetylsalicylic acid, phenetsal, and N-acetyl-*p*-aminophenol (Rosner *et al.*, 1968; Robertson, 1971). The blood levels of salicylic acid in man produced after medication with benorylate two or four times daily are comparable (Robertson, 1971). Using a radioactive chromium technique, Cuddigan (1971) showed that 4 g of benorylate suspension twice daily produced a mean daily blood loss of 1·7 ml; by comparison, the same patients treated with soluble aspirin in a daily dose of 4·8 g had a mean daily blood loss of 5·1 ml.

In view of the potential advantage to patients with rheumatoid arthritis of a drug effective in a twice-daily dosage regimen which causes insignificant gastrointestinal bleeding, it was decided to undertake a study of benorylate suspension and soluble aspirin to compare the clinical efficacy of the two compounds.

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Patients and Methods

Outpatients of either sex aged 15 to 70 years who satisfied the American Rheumatism Association criteria for definite or classical rheumatoid arthritis (Ropes *et al.*, 1959) were selected from those attending the rheumatology clinics at Guy's and New Cross Hospitals. Patients were excluded if (*a*) they had received gold therapy in the year preceding the study or were receiving corticotrophin or antimalarial drugs; (*b*) gave a history of renal, hepatic, or cardiac dysfunction or were pregnant (a pregnancy test was performed before the start of treatment in premenopausal patients); or (*c*) gave a history of dyspepsia or intolerance to aspirin. Patients whose steroid regimen had not been altered for three months before the treatment period were not excluded.

An initial assessment was carried out 48 hours after stopping all drugs other than steroids. Informed consent was obtained, and it was explained to the patients they they were to receive one of two forms of therapy—either tablets to be dissolved in water (1·2 g four times a day of soluble aspirin) or a suspension (4 g twice daily of benorylate). They were asked not to discuss their treatment among themselves nor to let the examining physician know whether they were receiving the tablets or the suspension.

Patients were seen and assessed again by the same observer after 7 and 14 days' treatment; after each assessment the record cards were filed and not referred to again by the observer.

Analgesic effect was evaluated by means of a diurnal pain score; the patients were asked to record pain as nil (0), mild (1), moderate (2), or severe (3) at hourly intervals for 14 hours from 8 a.m. to 10 p.m. before starting the treatment and on the day immediately preceding attendance for reassessment. An identical scoring system was used for overall pain response. Severity of disease and functional grading were assessed according to the criteria of Steinbrocker *et al.* (1949). Grip strength was measured by means of a grip dynamometer attached to a sphygmomanometer with the cuff inflated to 30 mm Hg. Finger stiffness was measured with the apparatus of Ingpen and Hume Kendall (1968). After five preliminary drops 20 consecutive drops were timed and the average time for the right and left middle fingers

to fall through an arc of 10 degrees was obtained. Total ring size was measured by the method of Boardman and Hart (1967), and the articular index recorded by the technique described by Ritchie *et al.* (1968). As a check that the patients were taking the drugs during the period of study, blood samples were taken for estimation of salicylate level at each assessment.

Homogeneity of Treatment Groups.—The two treatment groups were found to be similar with respect to patient characteristics (Table I) and the initial subjective (Table II) and objective measurements (Table III).

TABLE I—*Patient Characteristics in the Two Treatment Groups*

	Aspirin	Benorylate
Sex: Male	18	11
Sex: Female	16	24
Age (years). Mean ± S.E.	54 ± 2	51 ± 1
Weight (kg). Mean ± S.E.	67 ± 2	65 ± 2
Duration of disease (years). Mean ± S.E.	9·0 ± 2	7·5 ± 1
Severity of disease: Stage 1	1	0
Severity of disease: Stage 2	7	11
Severity of disease: Stage 3	25	23
Severity of disease: Stage 4	1	1
Erosions: Present	31	33
Erosions: Absent	3	2
Rheumatoid serology, differential agglutination titre, 1:32 or above	19	18

TABLE II—*Initial Assessment of Subjective Measurements*

	Aspirin	Benorylate
Overall pain level: 0 (none)	1	—
Overall pain level: 1 (mild)	12	14
Overall pain level: 2 (moderate)	14	16
Overall pain level: 3 (severe)	7	5
Diurnal pain score. Mean ± S.E.	24 ± 2	22 ± 2
Functional grade (Steinbrocker): 1	2	2
Functional grade (Steinbrocker): 2	19	26
Functional grade (Steinbrocker): 3	13	7
Functional grade (Steinbrocker): 4	—	—
Morning stiffness (hours): 0	11	11
Morning stiffness (hours): <1	4	8
Morning stiffness (hours): 1<4	16	10
Morning stiffness (hours): 4<8	1	3
Morning stiffness (hours): 8+	2	3

TABLE III—*Initial Assessment of Objective Measurements. (Mean ± S.E.)*

	Aspirin	Benorylate
Articular index	17 ± 2	15 ± 2
Grip strength (mm Hg): Right	160 ± 12	153 ± 11
Grip strength (mm Hg): Left	155 ± 12	147 ± 10
Total ring size (mm): Right	296 ± 5	294 ± 4
Total ring size (mm): Left	288 ± 5	289 ± 4
Finger stiffness (msec): Right	85 ± 2	89 ± 2
Finger stiffness (msec): Left	87 ± 1	86 ± 2
E.S.R. (mm/1st hour)	27 ± 3	31 ± 4

Results

Data from 69 of the 72 patients who entered the trial were available for analysis at the end of the first week and from 66 patients at the end of the second week. Three patients in the aspirin group withdrew from the trial—two because of lack of analgesic effect and one because of severe tinnitus—and a fourth patient was excluded from the analysis after he had been admitted to hospital with pneumonia. One patient in the benorylate group failed to keep her subsequent appointment and a second patient developed vomiting. The results of the subjective assessments are shown in Table IV and the objective measurements in Table V. It can be seen that there was a significant improvement in overall pain, functional grade, and articular index in both drug groups, although there was no significant difference between these groups. In the aspirin group there was a statistically significant improvement in the diurnal pain score, grip strength, finger stiffness, and ring size (Tables IV and V). In the benorylate group there was a statistically significant improvement in the diurnal pain score, grip strength, ring size, and morning stiffness (Tables IV and V).

TABLE IV—*Changes in Subjective Measurements at Each Assessment Period*

	Weeks of Treatment	Changes in Subjective Measurements: Aspirin	Changes in Subjective Measurements: Benorylate	Significance of Changes with Respect to Initial Value: Aspirin	Significance of Changes with Respect to Initial Value: Benorylate
Reduction in overall pain	1	39%	46%	P <0·01	P <0·01
Reduction in overall pain	2	48%	41%	P <0·01	P <0·01
Reduction in Diurnal pain score Mean ± S.E.	1	5 ± 2	5 ± 2	P <0·05	P <0·05
Reduction in Diurnal pain score Mean ± S.E.	2	6 ± 2	2 ± 2	P <0·01	P >0·05
Improvement in Functional grade	1	26%	35%	P <0·01	P <0·01
Improvement in Functional grade	2	41%	24%	P <0·01	P <0·01
Reduction in morning stiffness (hours) △ Mean ± S.E.	1	1·17 ± 0·87	1·61 ± 0·75	P >0·05	P <0·05
Reduction in morning stiffness (hours) △ Mean ± S.E.	2	1·08 ± 0·56	1·10 ± 0·69	P >0·05	P >0·05

N.B.: Difference between the treatments were found to be not significant (P >0·05)
△ of those who complained of initial morning stiffness.

TABLE V—*Changes in Objective Measurements at Each Assessment Period*

	Weeks of Treatment	Changes in Objective Measurements Mean ± S.E.: Aspirin	Changes in Objective Measurements Mean ± S.E.: Benorylate	Significance of Changes with respect to Initial Value: Aspirin	Significance of Changes with respect to Initial Value: Benorylate
Articular index	1	−4 ± 1	−4 ± 1	P <0·01	P <0·01
Articular index	2	−5 ± 1	−4 ± 1	P <0·01	P <0·01
Grip strength (mm Hg) Right	1	+25 ± 5	+19 ± 5	P <0·01	P <0·01
Grip strength (mm Hg) Right	2	+25 ± 5	+18 ± 6	P <0·01	P <0·01
Grip strength (mm Hg) Left	1	+25 ± 5	+20 ± 5	P <0·01	P <0·01
Grip strength (mm Hg) Left	2	+28 ± 6	+15 ± 5	P <0·01	P <0·01
Total ring size (mm) Right	1	−3 ± 1	−2 ± 1	P <0·05	P >0·05
Total ring size (mm) Right	2	−4 ± 1	−3 ± 1	P <0·01	P <0·01
Total ring size (mm) Left	1	−1 ± 1	−2 ± 1	P >0·05	P >0·05
Total ring size (mm) Left	2	−3 ± 1	−3 ± 1	P <0·01	P <0·05
Finger stiffness (msec) Right	1	−4 ± 1	−2 ± 2	P <0·01	P >0·05
Finger stiffness (msec) Right	2	−3 ± 1	−6 ± 3	P >0·05	P >0·05
Finger stiffness (msec) Left	1	−3 ± 1	+2 ± 4	P <0·05	P >0·05
Finger stiffness (msec) Left	2	−4 ± 2	−1 ± 2	P <0·05	P >0·05
E.S.R. (mm/1st hour)	1	−6 ± 2	−1 ± 3	P <0·05	P >0·05
E.S.R. (mm/1st hour)	2	−2 ± 2	−3 ± 3	P >0·05	P >0·05

N.B.: A positive sign indicates an increase in the variable. A negative sign indicates a decrease in the variable.
Differences between the treatment groups were found not to be significant at each assessment (P >0·05).

During the first week of treatment 57% of the patients in the aspirin group complained of side effects, compared with 44% on the benorylate group (P >0·05); after two weeks 41% of the patients in the aspirin group complained of side effects and 29% in the benorylate group (P >0·05). The side effects are listed in Table VI, and in both groups tinnitus and deafness were most common. All the patients had detectable salicylate levels in their plasma at both assessment periods, although there was wide intersubject variation in the levels achieved.

TABLE VI—*Distribution of Side Effects*

Treatment	Weeks of Treatment	No. of Complaints of: A	B	C	D	E	F	G	H	Total No. of Complaints	No. of Patients with Complaints
Aspirin	1	10	7	3	4	3	2	—	6	35	20
Aspirin	2	4	5	3	—	1	—	—	2	15	13
Benorylate	1	8	5	3	1	2	5	2	3	29	16
Benorylate	2	1	—	3	1	2	2	1	2	12	10

A = Tinnitus. B = Deafness. C = Nausea, Biliousness. D = Flatulence, epigastric pain, or discomfort. E = Lethargy, tiredness. F = Increased bowel action or diarrhoea. G = Muzziness. H = Other (includes headache, constipation, etc.).

Discussion

This study was designed to assess the value of a new drug, benorylate, in the treatment of rheumatoid arthritis and to compare it with aspirin in a standard high-dose anti-inflammatory regimen. The dissimilar presentation of the drugs and the fact that benorylate can be given twice daily posed problems with the double-blind design. Cromie (1963) stated that it is inadvisable to make gross alterations to the formulations of trial drugs because of the possibility of altering bio-availability. Double-blind conditions were achieved by ensuring that neither the patient nor the assessor were aware of the nature of the preparations being administered.

There is still no single reliable assessment for monitoring drug response in rheumatoid arthritis and a number of assessments are used (Dudley Hart and Huskisson, 1972). In this trial a diurnal pain score was used in addition to the other standard measurements, and it was found that both drugs produced a statistically significant reduction in the pain level. The measurement of finger stiffness has previously been correlated with morning stiffness (Ingpen, 1968), and a similar correlation was found with the aspirin group in the present study. The lack of correlation in the benorylate group may have been due to the small number of patients (12) completing this assessment.

The results of the study have shown that both drugs produced a statistically significant improvement in the clinical response but that there was no detectable difference between the two drugs: side effects occurred more often in the aspirin group but the difference was not significant and in both groups were less common in the second week of treatment.

In conclusion, this study has confirmed the efficacy of benorylate in rheumatoid arthritis and has shown that the twice-daily administration is as effective as the administration of aspirin four times daily. This convenience of administration together with the absence of gastrointestinal bleeding suggest that benorylate is a suitable alternative treatment for rheumatoid arthritis.

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References

Boardman, P. L., and Hart, F. D. (1967). *British Medical Journal*, 4, 264.
Cardoe, N. (1970). *Clinical Trials Journal*, 7, 313.
Cromie, B. W. (1963). *Lancet*, 2, 994.
Cuddigan, J. H. P. (1971). VII European Rheumatology Congress. Abstract No. 45/7.
Franke, M., and Manz, G. (1972). *Current Therapeutic Research*, 14, 113
Hart, F. D., and Huskisson, E. C. (1972). *Lancet*, 1, 28.
Ingpen, M. L. (1968). *Annals of Physical Medicine*, 9, 322.
Ingpen, M. L., and Hume Kendall, P. (1968). *Annals of Physical Medicine*, 9, 203.
Ritchie, D. M., *et al.* (1968). *Quarterly Journal of Medicine*, 147, 393.
Robertson, A. (1971). VII European Rheumatology Congress. Abstract No. 45/4.
Ropes, M. W., Bennett, G. A., Cobb, C., Jacox, R., and Jessar, R. A. (1959). *Annals of Rheumatic Diseases*, 18, 49.
Rosner, I., Malhie, P.. and Mottot, G. (1968). *Thérapie*, 23, 525.
Sperryn, P. N., Nicholson, P. A., Parsons, V., and Hamilton, E. B. D. (1971). VII European Rheumatology Congress. Abstract No. 45/3.
Steinbrocker, O., Traeger, C. H., and Batterman, R. C. (1949). *Journal of the American Medical Association*, 140, 659.

Reported Influenza in Pregnancy and Subsequent Cancer in the Child

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Summary

A longitudinal study of 1,959 infants born in the first week of March 1958 to mothers who were reported to have had influenza during pregnancy revealed an incidence of cancer of 4·1 per 1,000 compared with only 0·8 per 1,000 among the 14,791 infants of mothers who had not had influenza.

This increase was caused by cases of leukaemia and other neoplasms of lymphatic and haematopoietic tissue (I.C.D. 200-209) (P <0·0001).

Data from the reports of the Registrar General for England and Wales were used to estimate the number of infants born in each year from 1955 to 1964 who subsequently died of cancer before 5 years of age. The rates for each year were compared with an estimate of the prevalence of influenza during the preceding winter. After allowing for the overall trend in the cancer death rate, a highly significant correlation was shown with deaths attributed to causes classified as I.C.D. 200-209 (P <0·005), but not with deaths attributed to other cancers. The increase in the risk of developing these neoplasms among children whose mothers had influenza is estimated to be not less than fourfold. Even so the risk remains small (3 to 4 per 1,000).

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Introduction

Ever since the classic papers of the Oxford Survey of Childhood Cancers (Stewart, Webb, and Hewitt, 1958; Stewart, 1961) implicating abdominal *x*-ray examination during pregnancy with the development of cancer in the child, it has been thought feasible to postulate an association between cancer in childhood and events that occurred in utero. This possibility has been thrown into prominence recently by the striking study of Herbst, Ulfelder, and Poskanzer (1971) which provided evidence for an association between the rare adenocarcinoma of the vagina presenting in the late teens and early twenties and maternal stilboestrol therapy during pregnancy.

In the first report of the Oxford survey concerning childhood deaths from cancer in England and Wales over a two-year period, Stewart *et al.* (1958) showed an excess of the mothers of the children with cancer reporting a viral infection during pregnancy compared with the control mothers. More recently a neonatal leukaemia death has been reported with a history of the mother having had an influenza-like illness early in the second trimester (Miller, Newstead, and Young, 1969).

The first part of the present study was initially undertaken in an effort to ascertain the effects of maternal illness during pregnancy on the subsequent outcome of the pregnancy and the future health of the child. To our knowledge no previous study has looked longitudinally at the possibility of maternal infection in pregnancy being related to the subsequent development of childhood cancer. The second part of the study constitutes an attempt to confirm the positive findings by determining whether there is any correlation between the number of births of children who are destined to die of cancer and preceding epidemics of influenza.