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Naproxen in juvenile chronic polyarthritis

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SUMMARY Naproxen at 10 mg per kg body weight was compared with aspirin at 80 mg per kg body weight in children suffering from juvenile chronic polyarthritis. It was found to be as effective as aspirin, with certainly no more and possibly fewer gastrointestinal side effects. A long-term tolerance study up to 12 months confirmed that naproxen was a satisfactory nonsteroidal anti-inflammatory drug in the management of various types of juvenile chronic arthritis.

Naproxen is an effective alternative to aspirin in the management of rheumatoid arthritis (Hill *et al.*, 1974). While salicylates remain the drug of choice as the initial treatment of childhood arthritis (Ansell, 1975), in some patients they are either ineffective or not tolerated. Ibuprofen, given as a suspension, has been shown to be a possible alternative (Ansell, 1973). When naproxen suspension became available preliminary studies showed it to produce satisfactory blood levels, with a half-life similar to that given by the tablets in adults, thus permitting a twice daily regimen (Ansell *et al.*, 1975).

The present study was undertaken to investigate the use of naproxen as Naprosyn Suspension in juvenile chronic polyarthritis. It consists of 2 parts, first, a comparative study with aspirin lasting 2 months, and, secondly, a tolerance study on the use of naproxen in the clinic.

Patients and methods

CROSS-OVER STUDY

Twenty-three patients entered a double-blind cross-over study lasting eight weeks with two consecutive 4-week periods and random allocation for either naproxen or aspirin for the first period. All patients were suffering from seronegative juvenile chronic polyarthritis (Ansell and Bywaters, 1959), and their disease was sufficiently active to be considered in need of an anti-inflammatory analgesic agent. The duration of the disease ranged from less than 1 year to 14 years, but in over half the patients it had lasted 2 years or less. The age of the patients was from 5 to 16 years with a median of 11–12 years. On entry to the trial 14 patients were receiving salicylates; of these 3 were also receiving ibuprofen and 4 indomethacin. Of the remaining 9, 3 had not received regular anti-inflammatory medication, 3 were on ibuprofen, 1 on ibuprofen with indomethacin, 1 on alclofenac, and 1 on benorylate.

All these nonsteroidal anti-inflammatory drugs were discontinued after the initial assessment. Four patients were on maintenance gold, 2 on low-dose corticotrophin (Acthar gel), and 1 on penicillamine; these were continued unaltered throughout the study period. The dosages used were naproxen 10 mg per kg body weight per 24 hours given as a suspension in 2 divided doses, and soluble aspirin at 80 mg per kg per day given in 4 divided doses. Placebo suspension and tablets were given to make the study double-blind. Patients were assessed as follows: Functional grading (Taplow); joint involvement; grip strength; walking time over 22 yd (20 m); functional test; comparison with last visit (physician); laboratory tests (haemoglobin, full blood count, platelets, erythrocyte sedimentation rate, liver function tests, urea, urine analysis, stools for occult blood). Assessments were made on admission and at 2-weekly intervals. The side effects were elicited by indirect questioning or spontaneous complaints.

TOLERANCE STUDY OF NAPROSYN SUSPENSION

A further 30 children with various patterns of juvenile chronic arthritis received naproxen as the suspension at 10 mg per kg body weight per day either as their first nonsteroidal anti-inflammatory drug or instead of their usual analgesic anti-inflammatory drug. Three chose to continue after the above trial. These patients consisted of 22 with

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polyarthritis, 2 of whom also had systemic illness, 1 with pauciarticular disease, 2 with monarticular disease, 4 with juvenile ankylosing spondylitis, and 1 with seropositive juvenile rheumatoid arthritis. The parameters used for assessment were as previously described, but the assessments were carried out initially at 1 month and then at 2 or 3 monthly intervals. The initial aim was to maintain this therapy for 6 months, but this period has now been extended to 12 months.

Results

CROSS-OVER STUDY

Overall there was equal clinical efficacy with both drugs, with only slight differences noted (see Table 1). Statistical significance was tested by Student's *t* test and Wilcoxon's signed rank test. At 8 weeks a significant improvement had occurred in the left hand grip strength, walking time, and peg test when naproxen was taken after aspirin. Small decreases in haemoglobin occurred on both drugs, almost reaching statistical significance on aspirin at 8 weeks (P=0·06). The difference between the rise in ESR on naproxen at 4 weeks and the fall in ESR on aspirin at 6 weeks was significant (P=0·03). Side effects were relatively uncommon. Six patients complained of a total of 10 side effects while on aspirin. Only 1 side effect was reported on naproxen (Table 2).

Four patients did not entirely complete the medication in accordance with the protocol. Two patients did not complete the 28 days on aspirin because of abnormal results in liver function tests, while a third withdrew because of vomiting. One patient had vague but persistent abdominal pain and indigestion throughout the 8 weeks and withdrew during the naproxen period (Table 3). These patients were seen a few days early and were analysed as completing the trial. The physicians' assessment at the end of the study suggested that naproxen was better than aspirin in 9 patients, that both drugs were equal in 9 patients, while aspirin was better than naproxen in 5 patients (Table 4).

Table 2 *Side effects*

	Naproxen		*Aspirin*	
	No. of times reported	*No. of patients reporting*	*No. of times reported*	*No. of patients reporting*
Depression	0	0	1	1
Tinnitus	0	0	1	1
Nausea	0	0	2	2
Vomiting	0	0	2	2
Lassitude	0	0	1	1
Abdominal pain	2	1	1	1
Abnormal liver function tests	0	0	2	2

Table 3 *Trial withdrawals*

Therapy	*Reason*
Aspirin	Abnormal liver function tests, nausea, tinnitus, lassitude
Aspirin	Abnormal liver function tests
Aspirin	Vomiting
Naproxen	Abdominal pain

Table 4 *Medication preference at end of trial*

Naproxen much better	*Naproxen better*	*Both periods equal*	*Aspirin better*	*Aspirin much better*
0	9	9	4	1

Difference not significant.

Table 1 *Assessment of patients*

Group I Change±SD	*Admission*	*Naproxen*		*Aspirin*	
		2 wk	*4 wk*	*6 wk*	*8 wk*
Joint involvement (0–25)	3·30±2·83	+0·40±2·27	−0·20±1·99	−0·40±1·78	+0·20±4·71
Grip strength L	175±87	8·9±34·1	2·7±35·5	7·5±29·2	4·5±34·5
(mmHg) R	179±77	5·4±48·8	13·5±55·3	14·5±47·5	12·4±52·5
Walking time (secs)	49·8±70·0	−12·2±39·1	−17·0±45·4	−20·1±50·8	−11·9±51·5
Function Test time (secs)	42·1±24·9	4·4±6·3	−0·5±4·5	−4·0±12·6	−6·1±9·2
Group II Change±SD	*Admission*	*Aspirin*		*Naproxen*	
		2 wk	*4 wk*	*6 wk*	*8 wk*
Joint involvement (0–25)	5·38±2·57	−0·46±2·07	−1·58±2·11*	−1·61±2·10*	−2·00±2·20**
Grip strength L	175±85	−0·8±18·1	17·3±40·7	19·2±47·4	22·0±59·5*
(mmHg) R	182±76	−14·2±34·2	3·2±19·5	6·8±19·8	3·9±24·4
Walking time (secs)	28·0±20·2	−3·2±9·8	−3·8±9·8	−5·7±12·5**	−6·2±13·4*
Function Test time (secs)	37·1±20·2	−0·4±4·1	−2·6±4·2	−3·7±6·4	−5·3±6·3*

* P<0·05. ** P<0.01.

TOLERANCE STUDY

Nineteen patients have completed 1 year of therapy without untoward side effects. One patient developed a rash and discontinued therapy at 1 month. One stopped at 9 months because of nausea and another at 11 months because of vomiting (Table 5). At the dosage employed naproxen did not control the fever in 2 with serious systemic illness, 1 of whom subsequently had to have corticotrophin added to the regimen and ultimately has required penicillamine for continuing joint activity, with the other being controlled with indomethacin and high doses of aspirin.

Discussion

Naproxen at a dose of 10 mg per kg body weight was found to be as effective as soluble aspirin at 80 mg per kg body weight in controlling joint symptoms in chronic arthritis of childhood.

Table 5 *Side effects in tolerance study*

	No. of times reported	*When reported*
Rash	1	1 month
Nausea	1	9 months
Vomiting	1	11 months

Side effects were relatively infrequent and mild. As an 8-week comparison does not allow an adequate assessment of the tolerance and side effects of a new drug, a longer tolerance study was continued. This suggests that side effects do not become particularly obvious during a follow-up period up to 1 year. In both studies they were similar to those seen with adults, that is, gastrointestinal disturbances and rash. In the tolerance study naproxen did not control the fever of the 2 patients who had both systemic illness and arthritis.

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