PAPERS AND SHORT REPORTS

Benoxaprofen: side-effect profile in 300 patients

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Abstract

Out of 300 patients who had taken benoxaprofen for a mean of 6·4 months, 196 (65·3%) reported side effects, resulting in 104 patients (34·6%) having the drug withdrawn. Out of 42 patients aged over 70, 35 (83·3%) had side effects and 29 (69·0%) had the drug withdrawn because of them.

Cutaneous side effects accounted for 180 (69·5%) of all 259 side effects reported. The commonest cutaneous side effect was photosensitivity, which occurred in 86 patients (28·6%). Photosensitivity, which occurred in half of the patients treated in the summer, resulted in withdrawal of benoxaprofen in 26 (30·2%) of the patients who experienced it. Onycholysis was observed in 38 patients (12·6%) and was frequently unnoticed by patients. The overall incidence of gastric side effects was 12·6% (38 patients), and the figure rose to 40·5% (17 cases) in patients over 70. During treatment with benoxaprofen one patient developed an active duodenal ulcer but no cases of major gastrointestinal haemorrhage occurred. Multiple subepidermal cysts (milia) were observed in 16 patients, who had been treated for a mean of 10·8 months.

These findings show that benoxaprofen is a potent phototoxic drug and that the manufacturers' recommended dosage of 600 mg daily is associated with an unacceptable incidence of side effects in the elderly.

Introduction

Benoxaprofen is a non-steroidal anti-inflammatory drug and was introduced into clinical practice in May 1980. Its pharmacological profile suggests a different mode of action from other such drugs.[1] The long plasma half life of 30-35 hours means that it can be given once daily.[2] Well-controlled clinical studies have shown benoxaprofen to be effective in treating rheumatoid arthritis,[3] osteoarthritis,[4] and ankylosing spondylitis.[5]

Clinicians have a bewildering choice of over 20 non-steroidal anti-inflammatory agents to prescribe. It is not possible to produce a league table of the efficacy and toxicity of these drugs owing to the conflicting results of clinical trials.[6] Nevertheless, a non-steroidal anti-inflammatory agent that may be given once daily is convenient, especially in the elderly.

Our experience of treating 300 patients with benoxaprofen provided an opportunity to assess the incidence of clinical side effects of this new drug.

Patients and methods

Three-hundred patients who attended rheumatology clinics between May 1980 and May 1981 began benoxaprofen if the clinician thought that they needed a non-steroidal anti-inflammatory drug. Table I shows their age and sex distribution, the diagnoses, and the durations of disease. All were white, and most had rheumatoid arthritis.

The daily dosage of benoxaprofen was 600 mg in 292 patients, 900 mg in five. Benoxaprofen was increased from 600 mg to 900 mg daily in seven patients and decreased from 600 mg to 300 mg daily in three, the changes being based on clinical response. By December 1981 the mean duration of exposure to benoxaprofen was 6·4 months (range 2 days to 19 months). Fifty patients had received benoxaprofen for more than a year and 113 patients for six to 11 months. We therefore had a cumulative total of over 160 patient-years.

In addition to benoxaprofen, 44 patients with rheumatoid arthritis were taking suppressive agents—prednisolone (25 patients), penicillamine (14), and gold (5). These drugs were continued with occasional dosage modification depending on clinical requirements. Twenty-three patients were receiving an additional non-steroidal anti-inflammatory agent to benoxaprofen—indomethacin (6 patients), flurbiprofen (8), naproxen (3), ibuprofen (3), fenclofenac (2), and fenoprofen (1).

At each visit patients were questioned about new symptoms. Possible side effects were recorded if the clinician thought that they might be drug related. Specific inquiry was made about gastric symptoms, photosensitivity reactions, and nail changes. The reasons for withdrawing benoxaprofen were also recorded.

Results

Of the 300 patients, 196 reported side effects (table II); 60 patients reported more than one side effect. Patients with rheumatoid arthritis

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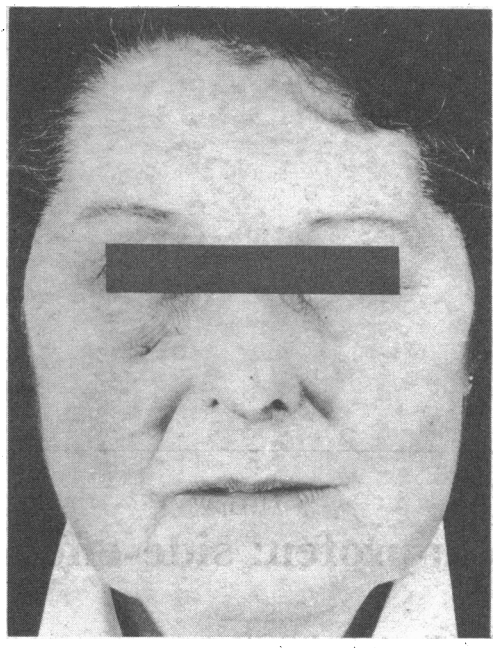
were more liable to develop side effects than patients with osteoarthritis.

Side effects occurred in 35 (83·3%) of the 42 patients aged over 70 and in 161 (62·4%) of the 258 patients aged under 70. Of the 23 patients with rheumatoid arthritis who were taking benoxaprofen in combination with another non-steroidal anti-inflammatory drug, 17 (73·9%) reported side effects. Side effects also occurred in 20 (45·5%) of the 44 patients taking the drug combined with a suppressive agent.

Most of the side effects were cutaneous (table III), and table IV shows the various types. The photosensitivity reaction, which was described as a severe burning sensation occurring within a few minutes of exposure to direct sunlight, was reported by 86 patients (28·6%). Photosensitivity occurred in 79 (30·6%) of the 258 patients aged under 70 and in 7 (16·6%) of the 42 aged over 70. Between June and September photosensitivity occurred in 83 out of 166 patients taking benoxaprofen. Severity diminished as patients developed a suntan and the reaction did not persist once benoxaprofen was stopped.

Onycholysis was observed in 38 patients (12·6%) as a gradual separation of the nail from the nail bed. Clinically onycholysis did not affect more than half of the nail and was often unnoticed by patients. Fingernails were more often affected than toenails. In no case was there complete loss of nails. Onycholysis improved in some patients who continued with benoxaprofen, and we thought that onycholysis was less evident in winter. Photosensitivity occurred in 18 of the 38 patients with onycholysis; and out of 79 patients with photosensitivity, 22 had onycholysis.

Seven patients reported an increased rate of nail growth, three of whom had onycholysis. Rashes were mild, transient, and did not vary with season. Stevens-Johnson syndrome was not observed.



Typical case of milia (multiple subepidermal cysts) observed during treatment with benoxaprofen.

TABLE I—*Distribution of patients studied*

Diagnosis	No of patients	Men	Women	Mean age in years (range)	Mean duration of disease in years (range)
Rheumatoid arthritis	237	65	172	57 (18–80)	9·8 (0·5–40)
Osteoarthritis	21	4	17	68 (47–86)	5·3 (1–20)
Paget's disease*	16	5	11	67 (50–78)	12·6 (1·5–30)
Psoriatic arthritis	10	2	8	47 (35–63)	3·6 (0·25–5)
Ankylosing spondylitis	8	7	1	47 (31–70)	17·6 (4–30)
Miscellaneous†	8	1	7	54 (39–67)	4·1 (0·16–27)
Total	300	84	216	54·9 (18–86)	9·5 (0·16–40)

*Six patients had coexistent rheumatoid arthritis.
†Painful shoulder (3), mixed connective-tissue disease (2), polymyalgia rheumatica (1), back pain (1), Behçet's disease (1).

TABLE II—*Occurrence of side effects according to disease*

Diagnosis	Total No of patients	No (%) with side effects	No of side effects
Rheumatoid arthritis	237	165 (69·6)	213
Osteoarthritis	21	11 (52·4)	19
Others*	42	20 (47·6)	27
Total	300	196 (65·3)	259

*Paget's disease (16), psoriatic arthritis (10), ankylosing spondylitis (8), painful shoulder (3), mixed connective-tissue disease (2), polymyalgia rheumatica (1), back pain (1), Behçet's disease (1).

TABLE III—*Type of side effect**

	Cutaneous	Gastro-intestinal	Central nervous system	Miscel-laneous	Total
No of patients	136	55	8	8	207
No of side effects	180	63	8	8	259

*Twelve patients had two types of side effects, and one had three types of side effects.

Facial milia (multiple subepidermal cysts; see figure) were observed in 16 patients (5·3%). These lesions were not present before benoxaprofen and were observed after a mean of 10·8 months (range 5-18 months) of treatment. Milia occurred in 11 patients with rheumatoid arthritis (one of whom was taking gold), two with osteoarthritis, two with Paget's disease, and one with polymyalgia rheumatica (who was also taking 10 mg prednisolone daily). The male to female ratio was 7:9. Nine patients who developed milia had had photosensitivity. Histologically a typical lesion showed "an epidermoid cyst compatible with the clinical diagnosis of milia."

The most florid example of milia occurred in the patient who was also taking prednisolone.

Three women with rheumatoid arthritis reported an increase in facial and forearm hair while taking benoxaprofen 600 mg daily. They were taking no other drugs. Examination confirmed a growth of downy hair at these sites, which was not in androgenic distribution.

Gastric symptoms were the most frequently reported gastrointestinal side effect (table V) and occurred in 38 patients (12·6%). The incidence of gastric side effects rose to 40·5% (17 cases) in patients over 70 and was 8·1% (21 cases) in patients under 70. Among patients over 70 the incidence of gastric side effects was 70% (7 out of 10 cases) in those with osteoarthritis and 30·7% (8 out of 26) in those with rheumatoid arthritis.

TABLE IV—*Cutaneous side effects**

	Photosensitivity	Onycholysis	Rash	Milia	Increased nail growth	Pruritus	Hypertrichosis	Total
No (%) reported	86 (47·7)	38 (21·1)	26 (14·4)	16 (8·8)	7 (3·8)	4 (2·2)	3 (1·6)	180

*Side effects occurred in 136 out of 300 patients; 35 patients had more than one side effect.

TABLE V—*Gastrointestinal side effects**

	Gastric†	Diarrhoea	Abdominal pain	Anorexia	Mouth ulcers	Taste change	Total
No (%) reported	44 (69·8)	7 (11·1)	6 (9·5)	2 (3·2)	2 (3·2)	2 (3·2)	63

*Side effects occurred in 55 out of 300 patients; eight patients had more than one side effect.
†Refers to nausea, vomiting, heartburn, and epigastric pain.

No patient had a major gastrointestinal haemorrhage. A 72-year-old woman with a seven-year history of rheumatoid arthritis treated with 10 mg prednisolone daily for six years developed an acute duodenal ulcer after taking benoxaprofen 600 mg daily for five months. Four years previously she had undergone surgery for a perforated duodendal ulcer at another hospital. Other side effects reported were faintness and dizziness (three), headache (three), depression and lethargy (two), feeling ill (three), palpitations (one), epistaxis (one), blurred vision (one), urinary urgency (one), and gynaecomastia (one).

A 36-year-old man with rheumatoid arthritis developed gynaecomastia after taking benoxaprofen 600 mg daily for three months; the condition took four months to disappear once benoxaprofen had been stopped. His only other drug treatment was flurbiprofen 100 mg daily.

Benoxaprofen was stopped in 104 patients (34·6%) because of side effects. The mean duration of benoxaprofen in these patients was 4·9 months (range 2 days to 15 months). In patients over 70 the proportion withdrawn because of side effects rose to 69·0% (29 out of 42) compared with 29·1% (75 out of 258) of patients aged under 70. Of all 180 cutaneous and 63 gastrointestinal side effects recorded, 99 (55·0%) and 21 (33·3%), respectively, resulted in withdrawal of benoxaprofen. The severity of the photosensitivity reaction resulted in 26 (30·2%) of the 86 patients stopping benoxaprofen. Gastric side effects resulted in withdrawal of 24 (10·1%) of the 237 patients with rheumatoid arthritis, one of whom had a duodenal ulcer, and of eight of the 21 patients with osteoarthritis.

At the time of this report benoxaprofen had been stopped in 104 patients owing to side effects; 102 patients were still taking benoxaprofen; 93 patients had been either discharged or lost to follow-up; and one patient had died from carcinoma of the pancreas.

Discussion

The purpose of this study was to assess the type and incidence of side effects and also the withdrawal rate due to benoxaprofen. We did not assess the efficacy of benoxaprofen, which has been established by controlled clinical trials.[3-5] In this type of long-term study the incidence of side effects may be artificially high owing to coincidental non-drug-related medical conditions. In clinical trials side effects have been reported in 15% of patients with rheumatoid arthritis taking placebo.[7]

In our series an incidence of side effects in 65·3% of patients due to benoxaprofen and a withdrawal rate of 34·6% due to side effects were higher than reported for other non-steroidal anti-inflammatory drugs. The incidence of side effects in a long-term study of flurbiprofen was 52·5%, and the withdrawal rate due to side effects was 18·8%.[8] The higher incidence of side effects due to benoxaprofen was due to the unique photosensitivity reaction and also onycholysis.

In elderly patients who require a non-steroidal anti-inflammatory agent benoxaprofen is convenient as it can be taken once daily. Our experience in 42 patients aged over 70 taking 600 mg benoxaprofen daily showed an unacceptable incidence of side effects (83·3%), which resulted in withdrawal of benoxaprofen in 29 patients (69·0%). This finding could relate to high plasma benoxaprofen concentrations and prolonged excretion half life observed in the elderly.[9] It remains to be determined whether a lower dose of benoxaprofen in the elderly will be better tolerated while remaining effective.

The combination of two non-steroidal anti-inflammatory agents is not generally considered to be advantageous.[10] There may, however, be theoretical advantages in combining benoxaprofen, which may act by altering monocyte migration,[1] with another non-steroidal anti-inflammatory drug that acts by inhibiting prostaglandin synthetase activity. Our results show that combining benoxaprofen with another such drug resulted in a very high incidence (73·9%) of side effects and a withdrawal rate of 34·8% because of side effects.

That photosensitivity occurred during the summer in 83 out of 166 patients taking benoxaprofen indicates that the drug is a potent photosensitiser. The severity of the reaction was such that 26 patients had to stop taking benoxaprofen. This incidence of photosensitivity (50·0%) was much higher than the 9% incidence reported in North America.[11] This may, however, have been partly due to the fact that all of our patients were white, though the proportion of dark-skinned patients in the North American study was not stated. Skin complexion is the determining factor as regards the probability of developing photosensitivity. The lower incidence of photosensitivity in the elderly in our series might have been due to less exposure to the sun.

Benoxaprofen photosensitisation is due to a phototoxic reaction, as the photochemically induced skin response is without an immunological basis. Evidence suggests that the photoreactive molecule is benoxaprofen rather than a metabolite.[12] Photosensitivity occurs within a couple of days of taking 600 mg doses, and the reaction is transient. The reaction is due to both ultraviolet A and ultraviolet B rays.[13] The role of sunscreens, which should protect against ultraviolet A and ultraviolet B, in preventing benoxaprofen photosensitivity needs to be established in clinical practice.

The observation that oncycholysis occurred in 12·6% of patients treated with benoxaprofen is similar to other reports.[11] The onycholysis was similar to that induced by demeclocycline,[14] which is also phototoxic. Our anecdotal evidence suggests that benoxaprofen onycholysis is in part related to exposure to sunlight. Nevertheless, several cases of onycholysis were observed in toenails that had not been exposed to sunlight. If benoxaprofen onycholysis is due solely to photosensitivity it should be preventable by the application of an opaque nail varnish. Seven patients reported an increased rate of nail growth while taking benoxaprofen, three of whom had onycholysis. The rate of nail growth is increased in idiopathic onycholysis.[15] It has yet to be determined whether benoxaprofen can increase the rate of nail growth.

Milia are quite common at all ages and may occur after sunbathing and also in areas of chronic corticosteroid-induced atrophy.[16] We are unaware of published reports of the association of milia with benoxaprofen, which occurred in 16 of our patients (5·3%). Milia were in part related to the duration of exposure to benoxaprofen, as all cases occurred after five months of treatment (mean 10·8 months).

Hypertrichosis, which occurred in three patients, has not been reported in association with benoxaprofen. The hypertrichosis may have been unrelated to benoxaprofen, though we could not identify another cause. The patients were taking no other drugs. Drug-induced hypertrichosis is a frequent complication of treatment with minoxidil[17] and has also been reported in association with cortisone and penicillamine.[16]

The incidence of gastric side effects associated with benoxaprofen (12·6%) was similar to that in a study of 1681 patients and comparable to that with ibuprofen.[11] It has been estimated that the incidence of peptic ulceration during treatment with benoxaprofen is one per 200 patient-years.[11] Short-term studies show that benoxaprofen produces less gastrointestinal microbleeding that other non-steroidal anti-inflammatory drugs.[18] The elderly may, however, be more susceptible to major gastrointestinal haemorrhage associated with benoxaprofen.[19]

Our results suggest that in the elderly a dose of 600 mg daily is associated with an unacceptable incidence of gastric side effects. It is not clear why elderly patients with osteoarthritis were more prone to gastric side effects than patients with rheumatoid arthritis. Tyson and Glynne reported that in patients over 60 with osteoarthritis benoxaprofen caused more gastric side effects than did ibuprofen, whereas in patients under 60 the reverse was true.[4]

Compared with other non-steroidal anti-inflammatory agents benoxaprofen has a unique side-effect profile. It remains to be established whether benoxaprofen has the disease-modifying properties that were claimed at the enthusiastic launch of the drug.[19]

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Addendum

Since the submission of our paper six cases have been reported with hypertrichosis and accelerated nail growth associated with benoxaprofen,[21] one of whom also had milia.[22]

References

1 Meacock SCR, Kitchen EA, Dawson W. Effects of benoxaprofen and some other non steroidal anti-inflammatory drugs on leucocyte migration. *European Journal of Rheumatology and Inflammation* 1979;**3**:23-8.

2 Smith GL, Goulbourn RA, Burt RAP, *et al.* Preliminary studies of absorption and excretion of benoxaprofen in man. *Br J Clin Pharmacol* 1977;**4**:585-90.

3 Atkinson MH, Brown TA, Robinson HS, Willkens RF. Crossover comparison of benoxaprofen and naproxen in rheumatoid arthritis. *J Rheumatol* 1980;**7**,suppl 6:109-15.

4 Tyson VCH, Glynne A. A comparative study of benoxaprofen and ibuprofen in osteoarthritis in general practice. *J Rheumatol* 1980;**7**, suppl 6:132-8.

5 Bird HA, Rhind VM, Pickup ME, Wright V. A comparative study of benoxaprofen and indomethacin in ankylosing spondylitis. *J Rheumatol* 1980;**7**,suppl 6:139-42.

6 Anonymous. Choosing a non-steroidal anti-inflammatory drug. *Drug Ther Bull* 1981;**19**:53.

7 Huskisson EC. Diclofenac sodium. In: *Clinics in rheumatic diseases.* London: W B Saunders Co Ltd, 1979:427-64.

8 Sheldrake FE, Webber JM, Marsh BD. A long term assessment of flurbiprofen. *Curr Med Res Opin* 1977;**5**:106-16.

9 Hamdy RC, Murnane B, Perera N, Woodcock K, Koch IM. The pharmacokinetics of benoxaprofen in elderly subjects. *European Journal of Rheumatology and Inflammation* 1982;**5**:69-75.

10 Huskisson EC. Anti-inflammatory drugs. *Semin Arthritis Rheum* 1977;**7**: 1-20.

11 Mikulaschek WM. Long term safety of benoxaprofen. *J Rheumatol* 1980; **7**,suppl 6:100-7.

12 Kligman AM, Kaidbey KH. Phototoxicity to benoxaprofen. *European Journal of Rheumatology and Inflammation* 1982;**5**:124-37.

13 Fenton DA, Wilkinson JD, English JS. Photosensitisation to benoxaprofen not due to ultraviolet A alone. *Lancet* 1981;ii:1230-1.

14 Orentreich N, Harber LC, Tromovitch TA. Photosensitivity and photo-onycholysis due to demethylchlortetracycline. *Arch Dermatol* 1961;**83**: 68-75.

15 Dawber RPR, Samman PD, Bottoms E. Fingernail growth in idiopathic and psoriatic onycholysis. *Br J Dermatol* 1971;**85**:558-60.

16 Rook A, Wilkinson DS, Ebling FJD, eds. *Textbook of dermatology.* 3rd ed. Oxford: Blackwell Scientific, 1979:2160-1.

17 Burton JL, Marshall A. Hypertrichosis due to minoxidil. *Br J Dermatol* 1979;**101**:593-5.

18 Ridolfo AS, Crabtree RE, Johnson DW, Rockhold FW. Gastro-intestinal microbleeding: comparisons between benoxaprofen and other non-steroidal anti-inflammatory agents. *J Rheumatol* 1980;**7**,suppl 6:36-46.

19 Stewart IC. Gastrointestinal haemorrhage and benoxaprofen. *Br Med J* 1982;**284**:163-4.

20 Tucker A. Drug brings "new era" in treatment of arthritis. *The Guardian* 1980;October 15:2.

21 Fenton DA, English JS, Wilkinson JD. Reversal of male pattern baldness, hypertrichosis and accelerated hair and nail growth in patients receiving benoxaprofen. *Br Med J* 1982;**284**:1228-9.

22 Fenton DA. Milia, increased nail growth and hypertrichosis following treatment with benoxaprofen. *J R Soc Med* 1982;**75**:229.

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Side effects of benoxaprofen

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Abstract

A study was made of adverse dermatological reactions to the non-steroidal anti-inflammatory agent benoxaprofen. Photosensitivity was seen in several patients, confined to wavelengths less than 340 nm. Other cutaneous side effects were erythema multiforme, the Stevens-Johnson syndrome, milia, and onycholysis. One case of pancytopenia and toxic epidermal necrolysis was reported.

Patients were not rechallenged with the drug, but these reactions appear to be true side effects of benoxaprofen.

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Introduction

Benoxaprofen (Opren, Dista) is a non-steroidal anti-inflammatory agent derived from propionic acid that has been on general release for over a year, during which time it has produced several unusual dermatological side effects. To alert practitioners of their unusual nature we record here the side effects seen in patients referred to our two departments, which serve a population of about 700 000.

Studies and results

PHOTOSENSITIVITY

Initial trials of benoxaprofen[1] reported a 10% incidence of photosensitivity rashes. Since many patients complained of burning, itching, or redness when in sunlight while taking the drug we investigated this in six consecutive patients with rheumatic disorders who were to receive treatment with benoxaprofen. These studies were carried out using an irradiation monochromator before and at least one week after benoxaprofen 600 mg was taken at night. Each patient lay prone, and a liquid-filled light guide conducted the radiation from the exit slit of the monochromator to the patient's back, an anatomical site