usually occurring within the first 2 weeks of therapy, and particularly in women and in patients with seronegative rheumatoid arthritis or psoriatic arthritis. Disorders such as epidermal necrolysis, erythema multiforme, and Stevens-Johnson syndrome have also been reported. A small number of patients who develop rash may go on to develop a severe illness characterised by pulmonary eosinophilia or allergic alveolitis. Treatment with fenbufen should be stopped immediately if a rash appears.

Breast feeding. UK licensed product information advises that fenbufen should be avoided in breast-feeding mothers, because of the presence of its metabolites in breast milk.

Effects on the blood. Haemolytic anaemia[1] and aplastic anaemia[2] have been reported in patients receiving fenbufen.

1. Martland T, Stone WD. Haemolytic anaemia associated with fenbufen. *BMJ* 1988; **297:** 921.
2. Andrews R, Russell N. Aplastic anaemia associated with a non-steroidal anti-inflammatory drug: relapse after exposure to another such drug. *BMJ* 1990; **301:** 38.

Effects on the lungs. In January 1989 the UK CSM reported that it had received 7 reports of a suspected association between rash and an allergic interstitial lung disorder in patients receiving fenbufen.[1] In 5 patients, the lung disorder was diagnosed as pulmonary eosinophilia; in the 2 other patients the pulmonary component of the reaction was described as allergic alveolitis. Several of these reactions have been reported in the literature.[2,3]

1. CSM. Fenbufen, rash and pulmonary eosinophilia. *Current Problems 24* 1989. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024431&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)
2. Swinburn CR. Alveolitis and haemolytic anaemia induced by azapropazone. *BMJ* 1987; **294:** 375.
3. Burton GH. Rash and pulmonary eosinophilia associated with fenbufen. *BMJ* 1990; **300:** 82–3.

Effects on the skin. In September 1988 the UK CSM reported[1] that it was still receiving large numbers of reports of adverse reactions to fenbufen when such reports were expected to have declined. Fenbufen was the most commonly reported suspect drug in 1986 and 1987. At the time of the report more than 6000 such reports had been received, 80% concerning mucocutaneous reactions and most involving a generalised florid erythematous rash, often with pruritus. There were 178 reports of erythema multiforme, 30 of Stevens-Johnson syndrome, and 2 fatalities.

1. CSM. Fenbufen and mucocutaneous reactions. *Current Problems 23* 1988. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024430&RevisionSelectionMethod=LatestReleased (accessed 01/11/07)

Hypersensitivity. See under Effects on the Lungs (above).

Interactions

For interactions associated with NSAIDs, see p.99.

Use of fenbufen with aspirin may result in decreased serum concentrations of fenbufen and its metabolites.

Pharmacokinetics

Fenbufen is absorbed from the gastrointestinal tract after oral use and peak plasma concentrations are reached in about 70 minutes. Fenbufen is over 99% bound to plasma proteins. It is metabolised in the liver to the active metabolites, biphenylacetic acid and 4-hydroxy-biphenylbutyric acid. Fenbufen and its metabolites are reported to have plasma half-lives of about 10 to 17 hours and are mainly eliminated as conjugates in the urine. Metabolites of fenbufen have been detected in breast milk in small amounts.

Uses and Administration

Fenbufen, a propionic acid derivative, is an NSAID (p.99). It is given for the relief of pain and inflammation associated with musculoskeletal and joint disorders such as rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis in oral doses of 900 mg daily; the dose may be either 450 mg in the morning and evening or 300 mg in the morning with 600 mg in the evening.

Preparations

BP 2008: Fenbufen Capsules; Fenbufen Tablets.

Proprietary Preparations (details are given in Part 3)
Austria: Lederfen†; ***Indon.:*** Cybufen; ***Irl.:*** Lederfen; ***Port.:*** Basifen; Reugast†; ***Thai.:*** Cepal; Cinopal†; ***Turk.:*** Cinopal; ***UK:*** Lederfen.

Fenoprofen Calcium *(BANM, USAN, rINNM)*

Calcii Fenoprofenum; Fénoprofène Calcique; Fenoprofeno cálcico; Lilly-69323; Lilly-53858 (fenoprofen); Lilly-61169 (fenoprofen sodium). Calcium (±)-2-(3-phenoxyphenyl)propionate dihydrate.

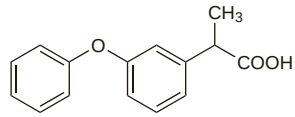
Кальций Фенопрофен

$(C_{15}H_{13}O_3)_2Ca,2H_2O$ = 558.6.

CAS — 31879-05-7 (fenoprofen); 34597-40-5 (anhydrous fenoprofen calcium); 53746-45-5 (fenoprofen calcium dihydrate).

ATC — M01AE04.

ATC Vet — QM01AE04.



(fenoprofen)

Pharmacopoeias. In *Br.*, *Chin.*, and *US.*
BP 2008 (Fenoprofen Calcium). A white or almost white odourless or almost odourless crystalline powder. Slightly soluble in water and in chloroform; soluble in alcohol.
USP 31 (Fenoprofen Calcium). A white crystalline powder. Slightly soluble in water, in methyl alcohol, and in n-hexanol; practically insoluble in chloroform. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Dysuria, cystitis, haematuria, interstitial nephritis, and acute renal insufficiency have been reported with fenoprofen. Nephrotic syndrome, which may be preceded by fever, rash, arthralgia, oliguria, azotaemia, and anuria, has also occurred. Upper respiratory-tract infection and nasopharyngitis have been reported. There have been reports of severe hepatic reactions, including jaundice and fatal hepatitis.

Breast feeding. Fenoprofen is distributed into breast milk although the amount is considered by the *BNF* to be too small to be harmful to a breast-fed infant. In contrast, licensed product information does not recommend its use since safety has not been established.

Effects on the blood. Haematological adverse effects including agranulocytosis,[1] aplastic anaemia,[2] and thrombocytopenia[3,4] have been reported in patients taking fenoprofen; licensed product information also reports haemolytic anaemia.

1. Simon SD, Kosmin M. Fenoprofen and agranulocytosis. *N Engl J Med* 1978; **299:** 490.
2. Ashraf M, *et al.* Aplastic anaemia associated with fenoprofen. *BMJ* 1982; 284: 1301–2.
3. Simpson RE, *et al.* Acute thrombocytopenia associated with fenoprofen. *N Engl J Med* 1978; **298:** 629–30.
4. Katz ME, Wang P. Fenoprofen-associated thrombocytopenia. *Ann Intern Med* 1980; **92:** 262.

Effects on the liver. Cholestatic jaundice and hepatitis developed in a 68-year-old woman after receiving fenoprofen 600 mg four times daily for 7 weeks. Subsequent use of naproxen and indometacin did not result in hepatotoxicity.[1] However, there has been a report of cross-hepatotoxicity between fenoprofen and naproxen.[2]

1. Stennett DJ, *et al.* Fenoprofen-induced hepatotoxicity. *Am J Hosp Pharm* 1978; **35:** 901.
2. Andrejak M, *et al.* Cross hepatotoxicity between non-steroidal anti-inflammatory drugs. *BMJ* 1987; **295:** 180–1.

Effects on the skin. Toxic epidermal necrolysis was associated with fenoprofen in 2 patients.[1]

1. Stotts JS, *et al.* Fenoprofen-induced toxic epidermal necrolysis. *J Am Acad Dermatol* 1988; **18:** 755–7.

Overdosage. A report of coma, respiratory depression, hypotension, and metabolic acidosis in a patient who had ingested between 24 and 36 g of fenoprofen.[1] The patient responded to gastric lavage and activated charcoal and intensive supportive care.

1. Kolodzik JM, *et al.* Nonsteroidal anti-inflammatory drugs and coma: a case report of fenoprofen overdose. *Ann Emerg Med* 1990; **19:** 378–81.

Interactions

For interactions associated with NSAIDs, see p.99.

Aspirin is reported to reduce plasma concentrations of fenoprofen.

Antiepileptics. *Phenobarbital* might increase the rate of metabolism of fenoprofen.[1] US licensed product information suggests that dosage adjustment of fenoprofen may be required when given with phenobarbital.

1. Helleberg L, *et al.* A pharmacokinetic interaction in man between phenobarbitone and fenoprofen, a new anti-inflammatory agent. *Br J Clin Pharmacol* 1974; **1:** 371–4.

Pharmacokinetics

Fenoprofen is readily absorbed from the gastrointestinal tract; bioavailability is about 85% but food and milk may reduce the rate and extent of absorption. Peak plasma concentrations occur 1 to 2 hours after a dose. The plasma half-life is about 3 hours. Fenoprofen is 99% bound to plasma proteins. About 90% of a dose is excreted in the urine in 24 hours, chiefly as the glucuronide and the glucuronide of hydroxylated fenoprofen. Fenoprofen is distributed into breast milk.

Uses and Administration

Fenoprofen, a propionic acid derivative, is an NSAID (p.99) used in the management of mild to moderate pain and for the relief of pain and inflammation associated with disorders such as osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. It is given as the calcium salt although doses are expressed in terms of the base; fenoprofen calcium (dihydrate) 1.2 g is equivalent to about 1 g of fenoprofen. A usual oral dose is the equivalent of 300 to 600 mg of fenoprofen three or four times daily, adjusted thereafter according to response. In the USA, lower doses of 200 mg every 4 to 6 hours are recommended for mild to moderate pain. It has been recommended that the total daily dose should not exceed 3 g (UK) or 3.2 g (USA).

Preparations

BP 2008: Fenoprofen Tablets;
USP 31: Fenoprofen Calcium Capsules; Fenoprofen Calcium Tablets.

Proprietary Preparations (details are given in Part 3)
Braz.: Trandor†; ***Canad.:*** Nalfon†; ***Denm.:*** Nalfon†; ***Fr.:*** Nalgesic; ***Gr.:*** Expron†; ***Mex.:*** Nalfon†; ***S.Afr.:*** Fenopron†; ***UK:*** Fenopron; ***USA:*** Nalfon; ***Venez.:*** Fenopron†.

Fentanyl *(BAN, rINN)* ⊗

Fentanil; Fentanilis; Fentanilo; Fentanylum; Fentanyyli. *N*-(1-Phenethyl-4-piperidyl) propionanilide.

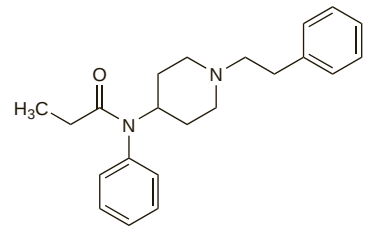
Фентанил

$C_{22}H_{28}N_2O$ = 336.5.

CAS — 437-38-7.

ATC — N01AH01; N02AB03.

ATC Vet — QN01AH01; QN02AB03.



NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of fentanyl:
Apache; China girl; China town; China white; Dance fever; Fentanest; Friend; Goodfellas; Great bear; He-man; Jackpot; King ivory; Murder 8; Poison; Tango & Cash; TNT; T.N.T.

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Fentanyl). A white or almost white polymorphic powder. Practically insoluble in water; freely soluble in alcohol and in methyl alcohol. Protect from light.

Fentanyl Citrate *(BANM, USAN, rINNM)* ⊗

Citrato de fentanilo; Fentanil-citrát; Fentanilio citratas; Fentanyl, citrate de; Fentanylcitrat; Fentanyl-citrát; Fentanyli citras; Fentanylu cytrynian; Fentanyylisitraatti; McN-JR-4263-49; Phentanyl Citrate; R-4263. *N*-(1-Phenethyl-4-piperidyl)propionanilide dihydrogen citrate.

Фентанила Цитрат

$C_{22}H_{28}N_2O,C_6H_8O_7$ = 528.6.

CAS — 990-73-8.