**Inflammatory bowel disease.** Adalimumab is used in the management of Crohn's disease[1-4] (p.1697), including in patients who are intolerant of, or relapse on, infliximab treatment.[5-8] It has also been tried in the treatment of ulcerative colitis (p.1697).[9]


1. Hanauer SB, *et al.* Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology* 2006; **130:** 323–33.
2. Sandborn WJ, *et al.* Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut* 2007; **56:** 1232–9.
3. Colombel JF, *et al.* Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007; **132:** 52–65.
4. Plosker GL, Lyseng-Williamson KA. Adalimumab: in Crohn's disease. *BioDrugs* 2007; **21:** 125–32.
5. Sandborn WJ, *et al.* An open-label study of the human anti-TNF monoclonal antibody adalimumab in subjects with prior loss of response or intolerance to infliximab for Crohn's disease. *Am J Gastroenterol* 2004; **99:** 1984–9.
6. Papadakis KA, *et al.* Safety and efficacy of adalimumab (D2E7) in Crohn's disease patients with an attenuated response to infliximab. *Am J Gastroenterol* 2005; **100:** 75–9.
7. Peyrin-Biroulet L, *et al.* Adalimumab maintenance therapy for Crohn's disease with intolerance or lost response to infliximab: an open-label study. *Aliment Pharmacol Ther* 2007; **25:** 675–80.
8. Sandborn WJ, *et al.* Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. *Ann Intern Med* 2007; **146:** 829–38.
9. Peyrin-Biroulet L, *et al.* Adalimumab induction therapy for ulcerative colitis with intolerance or lost response to infliximab: an open-label study. *World J Gastroenterol* 2007; **13:** 2328–32.


**Psoriasis.** Adalimumab is used in the treatment of plaque psoriasis (p.1583).

References.


1. Gordon KB, *et al.* Clinical response to adalimumab treatment in patients with moderate to severe psoriasis: double-blind, randomized controlled trial and open-label extension study. *J Am Acad Dermatol* 2006; **55:** 598–606.
2. Papoutsaki M, *et al.* Adalimumab for severe psoriasis and psoriatic arthritis: an open-label study in 30 patients previously treated with other biologics. *J Am Acad Dermatol* 2007; **57:** 269–75.
3. Menter A, *et al.* Adalimumab therapy for moderate to severe psoriasis: a randomized, controlled phase III trial. *J Am Acad Dermatol* 2008; **58:** 106–15.
4. Revicki D, *et al.* Impact of adalimumab treatment on health-related quality of life and other patient-reported outcomes: results from a 16-week randomized controlled trial in patients with moderate to severe plaque psoriasis. *Br J Dermatol* 2008; **158:** 549–57.
5. Saurat J-H, *et al.* CHAMPION Study Investigators. Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis. *Br J Dermatol* 2008; **158:** 558–66.
6. NICE. Adalimumab for the treatment of adults with psoriasis: Technology Appraisal Guidance 146 (issued June 2008). Available at: http://www.nice.org.uk/nicemedia/pdf/TA146Guidance.pdf (accessed 25/07/08)


**Rheumatoid arthritis.** References to the use of adalimumab in rheumatoid arthritis (p.11).


1. den Broeder AA, *et al.* Long-term anti-tumour necrosis factor alpha monotherapy in rheumatoid arthritis: effect on radiological course and prognostic value of markers of cartilage turnover and endothelial activation. *Ann Rheum Dis* 2002; **61**: 311–18.
2. Rau R. Adalimumab (a fully human anti-tumour necrosis factor alpha monoclonal antibody) in the treatment of active rheumatoid arthritis: the initial results of five trials. *Ann Rheum Dis* 2002; **61** (suppl 2): 70–3.
3. Weinblatt ME, *et al.* Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum* 2003; **48:** 35–45.
4. Furst DE, *et al.* Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). *J Rheumatol* 2003; **30:** 2563–71.
5. van de Putte LB, *et al.* Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. *Ann Rheum Dis* 2004; **63:** 508–16.
6. Keystone EC, *et al.* Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum* 2004; **50:** 1400–11.
7. Wick MC, *et al.* Adalimumab (Humira) restores clinical response in patients with secondary loss of efficacy from infliximab (Remicade) or etanercept (Enbrel): results from the STURE registry at Karolinska University Hospital. *Scand J Rheumatol* 2005; **34:** 353–8.
8. Navarro-Sarabia F, *et al.* Adalimumab for treating rheumatoid arthritis. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 13/06/08).
9. Weinblatt ME, *et al.* Long term efficacy and safety of adalimumab plus methotrexate in patients with rheumatoid arthritis: ARMADA 4 year extended study. *Ann Rheum Dis* 2006; **65:** 753–9.
10. Breedveld FC, *et al.* The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* 2006; **54:** 26–37.
11. Heiberg MS, *et al.* Adalimumab and methotrexate is more effective than adalimumab alone in patients with established rheumatoid arthritis: results from a 6-month longitudinal, observational, multicentre study. *Ann Rheum Dis* 2006; **65:** 1379–83.
12. Cvetković RS, Scott LJ. Adalimumab: a review of its use in adult patients with rheumatoid arthritis. *BioDrugs* 2006; **20:** 293–311.
13. Burmester GR, *et al.* Adalimumab alone and in combination with disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis in clinical practice: the Research in Active Rheumatoid Arthritis (ReAct) trial. *Ann Rheum Dis* 2007; **66:** 732–9.
14. Bombardieri S, *et al.* Research in Active Rheumatoid Arthritis (ReAct) Study Group. Effectiveness of adalimumab for rheumatoid arthritis in patients with a history of TNF-antagonist therapy in clinical practice. *Rheumatology (Oxford)* 2007; **46:** 1191–9.
15. NICE. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis: Technology Appraisal Guidance 130 (issued October 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA130guidance.pdf (accessed 13/06/08)


**Spondyloarthropathies.** References to the use of adalimumab in ankylosing spondylitis and psoriatic arthritis (see Spondyloarthropathies, p.13).


1. Chew A-L, *et al.* Successful treatment of severe psoriasis and psoriatic arthritis with adalimumab. *Br J Dermatol* 2004; **151:** 492–6.
2. Mease PJ, *et al.* Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2005; **52:** 3279–89.
3. van der Heijde D, *et al.* Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2006; **54:** 2136–46.
4. van der Heijde D, *et al.* ATLAS Study Group. Efficacy and safety of adalimumab in patients with ankylosing spondylitis: results of a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2006; **54:** 2136–46.
5. Simpson D, Scott LJ. Adalimumab: in psoriatic arthritis. *Drugs* 2006; **66:** 1487–96.
6. Gladman DD, *et al.* Adalimumab improves joint-related and skin-related functional impairment in patients with psoriatic arthritis: patient-reported outcomes of the Adalimumab Effectiveness in Psoriatic Arthritis Trial. *Ann Rheum Dis* 2007; **66:** 163–8.
7. Gladman DD, *et al.* Adalimumab for long-term treatment of psoriatic arthritis: forty-eight week data from the adalimumab effectiveness in psoriatic arthritis trial. *Arthritis Rheum* 2007; **56:** 476–88.
8. Genovese MC, *et al.* M02-570 Study Group. Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy. *J Rheumatol* 2007; **34:** 1040–50. Correction. *ibid.*; 1439.
9. Davis JC, *et al.* Health-related quality of life outcomes in patients with active ankylosing spondylitis treated with adalimumab: results from a randomized controlled study. *Arthritis Rheum* 2007; **57:** 1050–7.
10. NICE. Adalimumab for the treatment of psoriatic arthritis: Technology Appraisal Guidance 125 (issued August 2007). Available at: http://www.nice.org.uk/nicemedia/pdf/TA125guidance.pdf (accessed 13/06/08)


**Uveitis.** Adalimumab has been tried with some success in the treatment of idiopathic uveitis (p.1515). Uveitis can also develop as a complication of other inflammatory disorders such as rheumatoid arthritis; treatment with adalimumab may improve ocular symptoms in addition to its effect on the primary disorder.

References.


1. Vazquez-Cobian LB, *et al.* Adalimumab therapy for childhood uveitis. *J Pediatr* 2006; **149:** 572–5.
2. Biester S, *et al.* Adalimumab in the therapy of uveitis in childhood. *Br J Ophthalmol* 2007; **91:** 319–24.


## Preparations

**Proprietary Preparations** (details are given in Part 3)

***Arg.:*** Humira; ***Austral.:*** Humira; ***Belg.:*** Humira; ***Braz.:*** Humira; ***Canad.:*** Humira; ***Chile:*** Humira; ***Cz.:*** Humira; ***Denm.:*** Humira; ***Fin.:*** Humira; ***Fr.:*** Humira; ***Ger.:*** Humira; ***Gr.:*** Humira; ***Hong Kong:*** Humira; ***Hung.:*** Humira; ***Irl.:*** Humira; ***Israel:*** Humira; ***Ital.:*** Humira; ***Malaysia:*** Humira; ***Mex.:*** Humira; ***Neth.:*** Humira; Trudexa; ***Norw.:*** Humira; ***NZ:*** Humira; ***Pol.:*** Humira; ***Port.:*** Humira; ***Singapore:*** Humira; ***Spain:*** Humira; ***Swed.:*** Humira; ***Switz.:*** Humira; ***UK:*** Humira; ***USA:*** Humira; ***Venez.:*** Humira.

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# Alfentanil Hydrochloride

*(BANM, USAN, rINNM)* ⊗

Alfentaniilihydrokloridi; Alfentanil, chlorhydrate d'; Alfentanil Hidroklorür; Alfentanil-hidroklorid; Alfentanil-hydrochlorid; Alfentanilhydroklorid; Alfentanili hydrochloridum; Alfentanilio hidrochloridas; Hidrocloruro de alfentanilo; R-39209. *N*-{1-[2-(4-Ethyl-5-oxo-2-tetrazolin-1-yl)ethyl]-4-(methoxymethyl)-4-piperidyl}propionanilide hydrochloride.

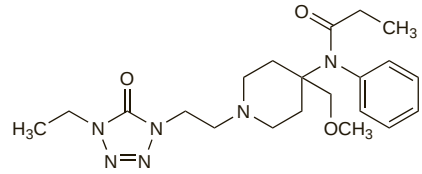
Альфентанила Гидрохлорид

$C_{21}H_{32}N_6O_3$,HCl = 453.0.

*CAS — 71195-58-9 (alfentanil); 69049-06-5 (anhydrous alfentanil hydrochloride); 70879-28-6 (alfentanil hydrochloride monohydrate).*

*ATC — N01AH02.*

*ATC Vet — QN01AH02.*



*(alfentanil)*

**Pharmacopoeias.** In *Eur.* (see p.vii) and *US.*

**Ph. Eur. 6.2** (Alfentanil Hydrochloride). A white or almost white powder. Freely soluble in water, in alcohol, and in methyl alcohol. Protect from light.

**USP 31** (Alfentanil Hydrochloride). A white to almost white powder. Soluble in water; freely soluble in alcohol, in chloroform, and in methyl alcohol; sparingly soluble in acetone. Store in airtight containers.

## Dependence and Withdrawal

As for Opioid Analgesics, p.101.

## Adverse Effects and Treatment

As for Opioid Analgesics in general, p.102, and for Fentanyl, p.56.

**Effects on the cardiovascular system.** Sinus arrest had occurred[1] during intubation in 2 patients given alfentanil 30 micrograms/kg.


1. Maryniak JK, Bishop VA. Sinus arrest after alfentanil. *Br J Anaesth* 1987; **59:** 390–1.


**Effects on mental function.** Like fentanyl, alfentanil 7.5 or 15 micrograms/kg intravenously had no effect on memory in healthy subjects.[1] In another study impairment of memory for new facts did occur 2 hours after operation in patients anaesthetised with alfentanil 7.5 micrograms/kg, but not in those given fentanyl;[2] methohexital might have contributed to the impairment.


1. Scamman FL, *et al.* Ventilatory and mental effects of alfentanil and fentanyl. *Acta Anaesthesiol Scand* 1984; **28:** 63–7.
2. Kennedy DJ, Ogg TW. Alfentanil and memory function: a comparison with fentanyl for day case termination of pregnancy. *Anaesthesia* 1985; **40:** 537–40.


**Effects on the respiratory system.** Alfentanil, like other opioid agonists, causes dose-related respiratory depression; it is significant with doses of more than 1 mg. Recovery has been reported to be faster after alfentanil than after fentanyl (see p.56),[1,2] possibly reflecting the shorter elimination half-life of alfentanil. Even so, accumulation of alfentanil is possible with large doses over a prolonged period. Profound analgesia is accompanied by marked respiratory depression which may persist or recur postoperatively.

Sudden respiratory arrest usually within an hour after the end of alfentanil infusion has been reported in patients who initially appeared to have made a rapid recovery from anaesthesia;[3-5] all responded to treatment with naloxone. Close monitoring of respiration in the initial postoperative period was recommended and this was reinforced by the manufacturers;[6] factors such as hyperventilation and the use of opioid premedication might enhance or prolong the respiratory depressant effects of alfentanil.


1. Andrews CJH, *et al.* Ventilatory effects during and after continuous infusion of fentanyl or alfentanil. *Br J Anaesth* 1983; **55:** 211S–16S.
2. Scamman FL, *et al.* Ventilatory and mental effects of alfentanil and fentanyl. *Acta Anaesthesiol Scand* 1984; **28:** 63–7.
3. Sebel PS, *et al.* Respiratory depression after alfentanil infusion. *BMJ* 1984; **289:** 1581–2.
4. Krane BD, *et al.* Alfentanil and delayed respiratory depression: cases studies and review. *Anesth Analg* 1990; **70:** 557–61.
5. Sternlo JEG, Sandin RH. Recurrent respiratory depression after total intravenous anaesthesia with propofol and alfentanil. *Anaesthesia* 1998; **53:** 378–81.
6. Waldron HA, Cookson RF. Respiratory depression after alfentanil infusion. *BMJ* 1985; **290:** 319.


## Precautions

As for Opioid Analgesics in general, p.103.

**Children.** Alfentanil given to preterm infants undergoing paralysis and mechanical ventilation for respiratory distress syndrome resulted in a rapid and significant fall in heart rate and blood pressure, emphasising that proper evaluation of the pharmacological and clinical effects was necessary.[1]

The *BNFC* states that the half-life of alfentanil is prolonged in neonates and accumulation is likely with prolonged use; muscle rigidity may occur and the use of muscle relaxants may be required.


1. Marlow N, *et al.* Hazards of analgesia for newborn infants. *Arch Dis Child* 1988; **63:** 1293.


**The elderly.** EEG changes suggested that elderly patients had increased brain sensitivity to alfentanil,[1] and that lower doses might be indicated in older patients for pharmacodynamic rather

than pharmacokinetic reasons. See also under Pharmacokinetics, below.

1. Scott JC, Stanski DR. Decreased fentanyl and alfentanil dose requirements with age: a simultaneous pharmacokinetic and pharmacodynamic evaluation. *J Pharmacol Exp Ther* 1987; **240:** 159–66.

**Handling.** Avoid contact with the skin and the inhalation of particles of alfentanil hydrochloride.

**Inflammatory bowel disease.** Patients with Crohn's disease required higher doses of alfentanil than control patients[1] although there were no differences in alfentanil pharmacokinetics between the 2 groups of patients.

1. Gesink-van der Veer BJ, *et al.* Influence of Crohn's disease on the pharmacokinetics and pharmacodynamics of alfentanil. *Br J Anaesth* 1993; **71:** 827–34.

**Pregnancy.** UK licensed product information contra-indicates the use of alfentanil in labour, or before clamping of the cord during caesarean section, because placental transfer means there is a risk of neonatal respiratory depression.

## Interactions

For interactions associated with opioid analgesics, see p.103.

Drugs that depress the heart or increase vagal tone, such as beta blockers and anaesthetic drugs, may predispose patients given alfentanil to develop bradycardia and hypotension. Use of alfentanil with non-vagolytic neuromuscular blockers may produce bradycardia and possibly asystole.

The metabolism of alfentanil via the cytochrome P450 isoenzyme CYP3A4 may be reduced by potent inhibitors of this isoenzyme, resulting in a risk of prolonged or delayed respiratory depression. Reduced doses of alfentanil may be required if given with a CYP3A4 inhibitor such as cimetidine, diltiazem, erythromycin, fluconazole, itraconazole, ketoconazole, or ritonavir.

**Antibacterials.** The elimination half-life of alfentanil was increased and clearance decreased when given after a 7-day course of oral *erythromycin* in healthy subjects.[1] Prolonged respiratory depression has also occurred in a 32-year-old man given alfentanil during anaesthesia after three 1-g doses of erythromycin in the 24 hours before surgery.[2] In another study of healthy subjects, the clearance (three-compartment model) of alfentanil was reduced by 70% in those given oral *troleandomycin*.[3]

Other hepatic enzyme inhibitors and drugs interfering with hepatic blood flow might also affect the clearance of alfentanil.

1. Bartkowski RR, *et al.* Inhibition of alfentanil metabolism by erythromycin. *Clin Pharmacol Ther* 1989; **46:** 99–102.
2. Bartkowski RR, McDonnell TE. Prolonged alfentanil effect following erythromycin administration. *Anesthesiology* 1990; **73:** 566–8.
3. Kharasch ED, *et al.* The role of cytochrome P450 3A4 in alfentanil clearance: implications for interindividual variability in disposition and perioperative drug interactions. *Anesthesiology* 1997; **87:** 36–50.

**Antifungals.** Azole antifungals such as *fluconazole*, *ketoconazole*, or *voriconazole* can inhibit the metabolism of alfentanil. In a study,[1] giving alfentanil 1 hour after intravenous or oral fluconazole decreased the clearance of alfentanil by 60 and 55%, respectively and increased the mean half-life of alfentanil from 1.5 hours to 2.7 and 2.5 hours, respectively. Similarly, another study[2] found that giving alfentanil 1 hour after oral voriconazole decreased the clearance of alfentanil by 85% and increased the mean half-life of alfentanil to 6.6 hours.

1. Palkama VJ, *et al.* The effect of intravenous and oral fluconazole on the pharmacokinetics and pharmacodynamics of intravenous alfentanil. *Anesth Analg* 1998; **87:** 190–4.
2. Saari TI, *et al.* Voriconazole, but not terbinafine, markedly reduces alfentanil clearance and prolongs its half-life. *Clin Pharmacol Ther* 2006; **80:** 502–8.

## Pharmacokinetics

After parenteral doses alfentanil hydrochloride has a rapid onset and short duration of action. Alfentanil is about 90% protein bound and has a small volume of distribution. Its terminal elimination half-life is about 1 to 2 hours. It is metabolised in the liver; oxidative *N*- and *O*-dealkylation by the cytochrome P450 isoenzyme CYP3A4 leads to inactive metabolites, which are excreted in the urine. Alfentanil crosses the blood-brain barrier and the placenta and has been detected in colostrum.

◊ Alfentanil is less lipid-soluble than fentanyl, but more so than morphine. It is highly bound to plasma proteins, mainly to $\alpha_1$-acid glycoprotein. Decreased lipid solubility can be expected to limit penetration of the blood-brain barrier when compared with fentanyl, but the majority of unbound alfentanil is unionised and can rapidly gain access to the CNS. Alfentanil has a smaller volume of distribution than fentanyl and its elimination half-life is shorter. The manufacturers have given values for a three-compartment pharmacokinetic model with a distribution half-life of 0.4 to 3.1 minutes, a redistribution half-life of 4.6 to 21.6 minutes, and a terminal elimination half-life of 64.1 to 129.3 minutes after single bolus injections of 50 or 125 micrograms/kg. Accumulation is less likely than with fentanyl, but can occur after repeated or continuous dosage especially in patients with reduced clearance. The mean elimination half-life reported is usually about 90 minutes, but this is reduced in children and increased in the elderly and neonates, in hepatic impairment, in the obese, and during cardiopulmonary bypass (see below).

◊ Reviews.

1. Hull CJ. The pharmacokinetics of alfentanil in man. *Br J Anaesth* 1983; **55** (suppl 2): 157S–164S.
2. Mather LE. Clinical pharmacokinetics of fentanyl and its newer derivatives. *Clin Pharmacokinet* 1983; **8:** 422–46.
3. Davis PJ, Cook DR. Clinical pharmacokinetics of the newer intravenous anaesthetic agents. *Clin Pharmacokinet* 1986; **11:** 18–35.
4. Bodenham A, Park GR. Alfentanil infusions in patients requiring intensive care. *Clin Pharmacokinet* 1988; **15:** 216–26.
5. Scholz J, *et al.* Clinical pharmacokinetics of alfentanil, fentanyl and sufentanil. *Clin Pharmacokinet* 1996; **31:** 275–92.

**Administration.** ***CONTINUOUS INTRAVENOUS INFUSION.*** Small studies of alfentanil by continuous intravenous infusion[1-3] have found pharmacokinetic parameters to be similar to those after a single bolus injection, but with some conflicting results. In 29 patients undergoing orthopaedic surgery an initial bolus intravenous injection of alfentanil 50 micrograms/kg was followed by intravenous infusion of 1 microgram/kg per minute, continued for 44 to 445 minutes; a second bolus injection of 50 micrograms/kg was given immediately before incision and an additional bolus injection of 1 mg given if necessary.[4] The time course of the plasma-alfentanil concentration fitted a two-compartmental model in 26 patients. Terminal half-lives varied widely from 56 to 226 minutes (mean 106 minutes), the highest values being mainly in patients over 60 years. There was no significant correlation between pharmacokinetic parameters and the duration of the infusion or the total dose. Plasma clearance and volumes of distribution did not correlate significantly with body-weight although steady-state volume of distribution was enlarged with increasing age. The mean estimated steady-state concentration was 293 nanograms/mL (range 147 to 636 nanograms/mL).

1. Fragen RJ, *et al.* Pharmacokinetics of the infusion of alfentanil in man. *Br J Anaesth* 1983; **55:** 1077–81.
2. Shafer A, *et al.* Pharmacokinetics and pharmacodynamics of alfentanil infusions during general anesthesia. *Anesth Analg* 1986; **65:** 1021–8.
3. Reitz JA, *et al.* The pharmacokinetics of alfentanil in gynecologic surgical patients. *J Clin Pharmacol* 1986; **26:** 60–4.
4. van Beem H, *et al.* Pharmacokinetics of alfentanil during and after a fixed rate infusion. *Br J Anaesth* 1989; **62:** 610–15.

***INTRAMUSCULAR.*** See The Elderly, below.

**Burns.** The volume of distribution and total clearance of alfentanil were reduced and its elimination half-life prolonged in patients with burns.[1] This was due, in part, to raised concentrations of $\alpha_1$-acid glycoprotein leading to increased protein binding.

1. Macfie AG, *et al.* Disposition of alfentanil in burns patients. *Br J Anaesth* 1992; **69:** 447–50.

**Cardiopulmonary bypass.** The elimination half-life of alfentanil increased from 72 minutes before cardiopulmonary bypass to 195 minutes afterwards in 5 patients.[1] This was attributed to an increase in volume of distribution, based in part on a dilution-induced decrease in plasma protein binding. Others[2,3] found that on starting cardiopulmonary bypass total serum concentrations of alfentanil were halved, mainly because of dilution of $\alpha_1$-acid glycoprotein and an increase in unbound alfentanil.

1. Hug CC, *et al.* Alfentanil pharmacokinetics in patients before and after cardiopulmonary bypass. *Anesth Analg* 1983; **62:** 266.
2. Kumar K, *et al.* The effect of cardiopulmonary bypass on plasma protein binding of alfentanil. *Eur J Clin Pharmacol* 1988; **35:** 47–52.
3. Hynynen M, *et al.* Plasma concentration and protein binding of alfentanil during high-dose infusion for cardiac surgery. *Br J Anaesth* 1994; **72**: 571–6.

**Children.** Alfentanil has been shown to have a shorter elimination half-life (about 40 minutes) and a smaller volume of distribution in children than in adults.[1] However, the half-life of alfentanil is prolonged in neonates. See also Hepatic Impairment, below.

1. Meistelman C, *et al.* A comparison of alfentanil pharmacokinetics in children and adults. *Anesthesiology* 1987; **66:** 13–16.

**The elderly.** Plasma clearance of alfentanil after a single intravenous dose of 50 micrograms/kg was reduced in patients more than 65 years old when compared with that in healthy young adults.[1] Mean elimination half-life was 137 minutes in the elderly and 83 minutes in the young adults. Volumes of distribution were similar and it was considered that reduced clearance might be due to decreased hepatic metabolism in the elderly. In a study in male patients the terminal elimination half-life of alfentanil increased with age, although clearance was not significantly affected.[2] In patients given alfentanil 1 microgram/kg per minute by continuous intravenous infusion during orthopaedic surgery,[3] terminal half-life increased linearly with age in those older than 40 years and steady-state volume of distribution was enlarged with increasing age; clearance did not correlate significantly with age and was thought to be more variable during a continuous infusion in long-term surgery than after a single bolus injection. Others have reported[4] that the effects of age on alfentanil pharmacokinetics are dependent on gender. In this study total plasma clearance decreased and terminal half-life increased with increasing age in women, but not in men. It has been suggested that this effect in women may be more dependent on menopausal status than on age.[5]

In a study[6] in elderly patients plasma concentrations of alfentanil were greater and the maximum concentration occurred earlier when alfentanil was injected into the deltoid muscle compared with injection into the gluteal muscle.

1. Helmers H, *et al.* Alfentanil kinetics in the elderly. *Clin Pharmacol Ther* 1984; **36:** 239–43.
2. Scott JC, Stanski DR. Decreased fentanyl and alfentanil dose requirements with age: a simultaneous pharmacokinetic and pharmacodynamic evaluation. *J Pharmacol Exp Ther* 1987; **240:** 159–66.
3. van Beem H, *et al.* Pharmacokinetics of alfentanil during and after a fixed rate infusion. *Br J Anaesth* 1989; **62:** 610–15.
4. Lemmens HJM, *et al.* Influence of age on the pharmacokinetics of alfentanil: gender dependence. *Clin Pharmacokinet* 1990; **19:** 416–22.
5. Rubio A, Cox C. Sex, age and alfentanil pharmacokinetics. *Clin Pharmacokinet* 1991; **21:** 81.
6. Virkkilä M, *et al.* Pharmacokinetics and effects of i.m. alfentanil as premedication for day-case ophthalmic surgery in elderly patients. *Br J Anaesth* 1993; **71:** 507–11.

**Hepatic impairment.** Total plasma clearance and protein binding of alfentanil were decreased in patients with alcoholic cirrhosis when compared with control subjects. Elimination half-life was prolonged from 90 to 219 minutes in the cirrhotic patients following a single intravenous dose of 50 micrograms/kg and was attributed in part to alterations in binding sites of $\alpha_1$-acid glycoprotein.[1] There might be different effects on alfentanil disposition in patients with non-alcoholic cirrhosis or other liver disorders.[2] The pharmacokinetics of alfentanil were apparently not affected in children with cholestatic hepatic disease whereas clearance was reduced postoperatively in 3 patients who had undergone liver transplantation.[3]

1. Ferrier C, *et al.* Alfentanil pharmacokinetics in patients with cirrhosis. *Anesthesiology* 1985; **62:** 480–4.
2. Bower S, *et al.* Effects of different hepatic pathologies on disposition of alfentanil in anaesthetized patients. *Br J Anaesth* 1992; **68:** 462–5.
3. Davis PJ, *et al.* Effects of cholestatic hepatic disease and chronic renal failure on alfentanil pharmacokinetics in children. *Anesth Analg* 1989; **68:** 579–83.

**Obesity.** The pharmacokinetics of alfentanil are reportedly altered in obesity.[1] Elimination half-life was 172 minutes in 6 obese patients compared with 92 minutes in 7 who were not obese. Plasma clearance of alfentanil was also decreased, although others[2] found that obesity had no effect on clearance, but it did have a direct relationship with the volume of the central compartment.

1. Bentley JB, *et al.* Obesity and alfentanil pharmacokinetics. *Anesth Analg* 1983; **62:** 251.
2. Maitre PO, *et al.* Population pharmacokinetics of alfentanil: the average dose-plasma concentration relationship and interindividual variability in patients. *Anesthesiology* 1987; **66:** 3–12.

**Renal impairment.** The pharmacokinetics of alfentanil were not affected significantly in adults[1] or children[2] with chronic renal failure. In another study[3] increased volume of distribution of alfentanil at steady state was associated with decreased plasma protein binding in patients with chronic renal failure.

1. Van Peer A, *et al.* Alfentanil kinetics in renal insufficiency. *Eur J Clin Pharmacol* 1986; **30:** 245–7.
2. Davis PJ, *et al.* Effects of cholestatic hepatic disease and chronic renal failure on alfentanil pharmacokinetics in children. *Anesth Analg* 1989; **68:** 579–83.
3. Chauvin M, *et al.* Pharmacokinetics of alfentanil in chronic renal failure. *Anesth Analg* 1987; **66:** 53–6.

## Uses and Administration

Alfentanil is a short-acting opioid analgesic (p.104) related to fentanyl (p.58).

Alfentanil is used in surgical procedures as an analgesic and adjunct to general anaesthetics or as a primary anaesthetic. It is also used as an analgesic and respiratory depressant in the management of mechanically ventilated patients under intensive care.

Alfentanil is given intravenously as the hydrochloride although doses are expressed in terms of the base. Alfentanil hydrochloride 108.8 micrograms is equivalent to about 100 micrograms of alfentanil. A peak effect may be seen within 1.5 to 2 minutes of an injection and analgesia can be expected to last for up to 10 minutes; dose supplements are therefore required if it is to be used for more prolonged surgical procedures. It may be given by continuous intravenous infusion in ventilated patients.

The dosage of alfentanil used depends on whether the patient has spontaneous respiration or assisted ventilation and on the expected duration of anaesthesia. Doses are adjusted according to the needs of the patient. Children may require higher or more frequent doses than adults, whereas the elderly or debilitated patients may require lower or less frequent doses. Obese patients may require doses based on their ideal (lean) bodyweight.

When used as an adjunct in the **maintenance of general anaesthesia** the initial licensed dose in the UK is as follows:

- in patients with *spontaneous respiration*, up to 500 micrograms may be given slowly over about 30 seconds with supplementary doses of 250 micrograms
- *ventilated* patients may be given 30 to 50 micrograms/kg with supplements of 15 micrograms/kg. When given by infusion to ventilated patients there is an initial loading dose of 50 to 100 micrograms/kg given as a bolus or by infusion over 10 minutes, followed by infusion at a rate of 0.5 to 1 microgram/kg per minute

Typical doses that have been used in the USA are as follows:

- for *short surgical procedures of less than 1 hour* in patients with spontaneous respiration or assisted ventilation, the dose is 8 to 20 micrograms/kg; this may be followed by supplementary doses of 3 to 5 micrograms/kg every 5 to 20 minutes or an infusion of 0.5 to 1 microgram/kg per minute. Alternatively patients with assisted or controlled ventilation may be given an initial dose of 20 to 50 micrograms/kg, followed by supplementary doses of 5 to 15 micrograms/kg every 5 to 20 minutes
- in *general surgical procedures* in patients with assisted or controlled ventilation, an initial dose of 50 to 75 micrograms/kg may be followed by an infusion of 0.5 to 3 micrograms/kg per minute. If alfentanil has been given in anaesthetic doses (see below) for the induction of anaesthesia, infusion rates may need to be reduced by 30 to 50% during the first hour of maintenance

Maintenance infusions of alfentanil should be stopped 10 to 30 minutes before the anticipated end of surgery.

For details of doses in children, see below.

The dose for the **induction of anaesthesia** in patients with assisted ventilation undergoing procedures of at least 45 minutes is 130 to 245 micrograms/kg, followed by an inhalation anaesthetic or maintenance doses of alfentanil of 0.5 to 1.5 micrograms/kg per minute.

In the UK, *ventilated* patients in **intensive care** may be given alfentanil initially at an infusion rate of 2 mg/hour or a loading dose of 5 mg may be given in divided doses over 10 minutes or more slowly if hypotension or bradycardia occur. Thereafter a suitable rate of infusion should be determined for each patient (rates of 0.5 to 10 mg/hour have been used); patients should be carefully monitored and the duration of treatment should not generally exceed 4 days. During continuous infusion additional bolus injections of 0.5 to 1 mg may be given if required to provide analgesia for short painful procedures that may be carried out in intensive care.

Alfentanil is also used as an analgesic in patients with *spontaneous respiration* receiving monitored anaesthesia care; in the USA, an initial dose of 3 to 8 micrograms/kg may be followed by supplementary doses of 3 to 5 micrograms/kg every 5 to 20 minutes or an infusion of 0.25 to 1 microgram/kg per minute.

**Administration.** Alfentanil is usually given by intravenous injection or infusion, but has also been given intramuscularly,[1,2] intrathecally,[3] or epidurally (see Pain, below).

1. Arendt-Nielsen L, *et al.* Analgesic efficacy of im alfentanil. *Br J Anaesth* 1990; **65:** 164–8.
2. Virkkilä M, *et al.* Pharmacokinetics and effects of i.m. alfentanil as premedication for day-case ophthalmic surgery in elderly patients. *Br J Anaesth* 1993; **71:** 507–11.
3. Hughes DA, Hill DA. Intrathecal alfentanil with and without bupivacaine for analgesia in labour. *Anaesthesia* 2000; **55:** 1116–21.

**Administration in children.** Alfentanil is licensed in the UK for use in ventilated children during surgical procedures as an analgesic and adjunct to general anaesthetics or as a primary anaesthetic. When used as an adjunct in the **maintenance of general anaesthesia** licensed product information states that ventilated children may be given the usual intravenous *injection* doses as for ventilated adults (see above). However, the *BNFC* suggests that neonates may be given 5 to 20 micrograms/kg initially and children aged from 1 month to 18 years, 10 to 20 micrograms/kg initially; supplementary doses of up to 10 micrograms/kg may be given. When given by *infusion* the *BNF* states that ventilated children may be given the usual doses as for ventilated adults (see above); the *BNFC* suggests that usual adult doses may be given to those aged as young as 1 month. The *BNFC* also suggests that neonates may be given an initial loading dose of 10 to 50 micrograms/kg over 10 minutes followed by infusion at a rate of 0.5 to 1 microgram/kg per minute.

**Anaesthesia.** Alfentanil, like fentanyl (p.59), appears to produce fewer circulatory changes than morphine and may be preferred for anaesthetic use, especially in cardiovascular surgery. It is generally considered to have a shorter duration of action than fentanyl. It has been used with propofol to facilitate intubation, and for total intravenous anaesthesia.

For a discussion of the drugs used to facilitate intubation and of opioids such as alfentanil used to control the pressor response and the rise of intra-ocular pressure associated with intubation, see Anaesthesia, p.1900. For reference to a study indicating that pretreatment with alfentanil can reduce the pain associated with injection of propofol, see p.1791.

***CAESAREAN SECTION.*** UK licensed product information contraindicates the use of alfentanil before clamping the cord during caesarean section because of the risk of respiratory depression in the neonate. A study of alfentanil 30 micrograms/kg in women undergoing caesarean section was abandoned after massive respiratory depression had occurred in 4 of 5 neonates.[1] Another study[2] in patients undergoing elective caesarean section found that although maternal haemodynamic responses to intubation were minimised when alfentanil 10 micrograms/kg was given intravenously immediately before induction, neonates in the alfentanil group had lower Apgar scores compared with those in the placebo group.

However, alfentanil has been used successfully to minimise haemodynamic responses to intubation and surgery in patients with severe cardiovascular disorders undergoing caesarean section.[3,4] A baby delivered after the successful use of alfentanil 35 micrograms/kg in a mother with severe aortic stenosis[3] was apnoeic and unresponsive with poor muscle tone; the baby responded rapidly to naloxone. Alfentanil 10 micrograms/kg immediately before induction attenuated the cardiovascular response to intubation in patients with severe pregnancy-induced hypertension[4] and was considered a suitable alternative to fentanyl 2.5 micrograms/kg; no effect on neonatal mortality could be attributed to anaesthetic technique. However, it has been suggested that the use of smaller doses of alfentanil of 7.5 micrograms/kg with magnesium sulfate 30 mg/kg may provide better cardiovascular control.[5]

1. Leuwer M, *et al.* Pharmacokinetics and pharmacodynamics of an equipotent fentanyl and alfentanil dose in mother and infant during caesarean section. *Br J Anaesth* 1990; **64:** 398P–9P.
2. Gin T, *et al.* Alfentanil given immediately before the induction of anesthesia for elective cesarean delivery. *Anesth Analg* 2000; **90:** 1167–72.
3. Redfern N, *et al.* Alfentanil for caesarean section complicated by severe aortic stenosis: a case report. *Br J Anaesth* 1987; **59:** 1309–12.
4. Rout CC, Rocke DA. Effects of alfentanil and fentanyl on induction of anaesthesia in patients with severe pregnancy-induced hypertension. *Br J Anaesth* 1990; **65:** 468–74.
5. Ashton WB, *et al.* Attenuation of the pressor response to tracheal intubation by magnesium sulphate with and without alfentanil in hypertensive proteinuric patients undergoing caesarean section. *Br J Anaesth* 1991; **67:** 741–7.

***PHAEOCHROMOCYTOMA.*** Alfentanil does not release histamine and was of value in the anaesthetic management of patients with phaeochromocytoma.[1] It has a very rapid onset of action, good vasodilating properties, and a relatively short elimination half-life. These patients are often very somnolent for the first 48 hours after surgery and postoperative opioid dosage requirements may be less than expected. Alfentanil infusion continued into the postoperative period allows careful titration of dosage.

1. Hull CJ. Phaeochromocytoma: diagnosis, preoperative preparation and anaesthetic management. *Br J Anaesth* 1986; **58:** 1453–68.

**Pain.** ***POSTOPERATIVE ANALGESIA.*** Continuous on-demand epidural infusions of alfentanil 200 micrograms/hour or fentanyl 20 micrograms/hour provided comparable analgesia to morphine 200 micrograms/hour in the early postoperative period;[1] alfentanil (16 minutes) and fentanyl (13 minutes) had the advantage of more rapid onset of analgesia than morphine (44 minutes). However, some considered that there was no overall advantage of epidural over intravenous alfentanil either as patient-controlled analgesia[2] or by continuous infusion.[3]

1. Chrubasik J, *et al.* Relative analgesic potency of epidural fentanyl, alfentanil, and morphine in treatment of postoperative pain. *Anesthesiology* 1988; **68:** 929–33.
2. Chauvin M, *et al.* Equivalence of postoperative analgesia with patient-controlled intravenous or epidural alfentanil. *Anesth Analg* 1993; **76:** 1251–8.
3. van den Nieuwenhuyzen MCO, *et al.* Epidural vs intravenous infusion of alfentanil in the management of postoperative pain following laparotomies. *Acta Anaesthesiol Scand* 1996; **40:** 1112–18.

## Preparations

***USP 31:*** Alfentanil Injection.

**Proprietary Preparations** (details are given in Part 3)
***Arg.:*** Brevafen; ***Austral.:*** Rapifen; ***Austria:*** Rapifen; ***Belg.:*** Rapifen; ***Braz.:*** Alfast; Rapifen; ***Canad.:*** Alfenta; ***Chile:*** Rapifen; ***Cz.:*** Rapifen; ***Denm.:*** Rapifen; ***Fin.:*** Rapifen; ***Fr.:*** Rapifen; ***Ger.:*** Rapifen; ***Gr.:*** Rapifen; ***Hong Kong:*** Rapifen; ***Hung.:*** Rapifen; ***Irl.:*** Rapifen; ***Israel:*** Rapifen; ***Ital.:*** Fentalim; ***Malaysia:*** Rapifen†; ***Mex.:*** Rapifen; ***Neth.:*** Rapifen; ***Norw.:*** Rapifen; ***NZ:*** Rapifen; ***S.Afr.:*** Rapifen; ***Spain:*** Fanaxal; Limifen; ***Swed.:*** Rapifen; ***Switz.:*** Rapifen; ***Turk.:*** Rapifen; ***UK:*** Rapifen; ***USA:*** Alfenta; ***Venez.:*** Rapifen.

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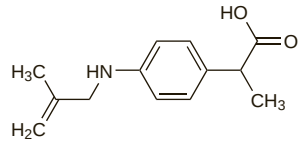
## Alminoprofen *(rINN)*

Alminoprofène; Alminoprofeno; Alminoprofenum. 4-[(2-Methylallyl)amino]hydratropic acid.

Альминопрофен

$C_{13}H_{17}NO_2$ = 219.3.
*CAS — 39718-89-3.*
*ATC — M01AE16.*
*ATC Vet — QM01AE16.*



### Profile
Alminoprofen, a propionic acid derivative related to ibuprofen (p.64), is an NSAID (p.96). It has been used in inflammatory and rheumatic disorders in oral doses of up to 900 mg daily.

### Preparations
**Proprietary Preparations** (details are given in Part 3)
***Fr.:*** Minalfene.

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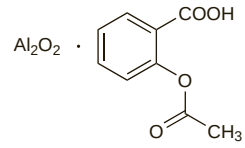
## Aloxiprin *(BAN, rINN)*

Acetilsalicilato de polioxoaluminio; Aloksipriini; Aloxiprina; Aloxiprine; Aloxiprinum.

Алоксиприн

*CAS — 9014-67-9.*
*ATC — B01AC15; N02BA02.*
*ATC Vet — QB01AC15; QN02BA02.*



**Pharmacopoeias.** In *Br.*
**BP 2008** (Aloxiprin). A polymeric condensation product of aluminium oxide and aspirin. A fine, white or slightly pink powder, odourless or almost odourless. It contains not less than 7.5% and not more than 8.5% of aluminium and not less than 79.0% and not more than 87.4% of total salicylates, calculated as aspirin, $C_9H_8O_4$, both calculated with reference to the dried substance. Practically insoluble in water, in alcohol, and in ether; slightly soluble in chloroform.

### Profile
Aloxiprin, a polymeric condensation product of aluminium oxide and aspirin, has actions similar to those of aspirin (p.20); aloxiprin 600 mg is equivalent to about 500 mg of aspirin. Aloxiprin has been used as an analgesic and anti-inflammatory in musculoskeletal and joint disorders. It has also been used in the treatment and prevention of thromboembolic disorders.

### Preparations
***BP 2008:*** Aloxiprin Tablets.

**Proprietary Preparations** (details are given in Part 3)
***Cz.:*** Superpyrin.

**Multi-ingredient:** ***UK:*** Askit.