*Alfentanil

*Specialist use only

Updated (minor change) November 2024

Class

Strong opioid analgesic.

Indications

Intra-operative analgesia; analgesia and procedure-related pain in mechanically ventilated patients on ICUs; †an alternative in cases of intolerance to other strong opioids, particularly in renal failure; [1] †procedure-related pain in non-ventilated patients; [2-4] †break-through pain. [5]

Contra-indications:

Do not administer concurrently with MAOIs or within 2 weeks of their discontinuation. Generally, none absolute if titrated carefully against a patient's pain (see also **Strong opioids**).

Pharmacology

Alfentanil is a synthetic lipophilic μ-opioid receptor agonist in the same class as **fentanyl** and **sufentanil** (see **Strong opioids, Table 1**). Compared with these, it has a more rapid onset of action and time to peak effect, and a shorter duration of action (Table 1). Its potency is approximately one quarter to one tenth that of **fentanyl** [6] (and 10–20 times more than parenteral **morphine**).

Alfentanil is less lipophilic than **fentanyl** and is 90% bound to mainly α_1-acid glycoprotein.[7] However, because most of the unbound alfentanil is un-ionized, it rapidly enters the CNS. Alfentanil is metabolized in the liver by CYP3A4 to inactive metabolites that are excreted in the urine. Alfentanil can accumulate with chronic administration, particularly in the elderly and the obese, and even with only mild hepatic impairment.[8,9] Renal impairment does not significantly alter the clearance of alfentanil, and, consequently, alfentanil is used at some centres when a parenteral opioid is required in severely reduced renal function or ESRF. Lower doses may be sufficient because of changes in protein binding (see **Renal impairment**).[1] However, unless the volume is prohibitive, **fentanyl** is generally recommended as the first-line parenteral opioid in ESRF at the end of life (see **Renal impairment**).[1]

It has been suggested that analgesic tolerance occurs rapidly with alfentanil,[10] but this has been refuted.[11] However, tolerance does not seem to be a problem in palliative care.[12]

Because alfentanil is available in a more concentrated form (500microgram/mL) than **fentanyl** (50microgram/mL), a smaller equivalent dose volume is needed, and this facilitates administration by CSCI or SL. For similar reasons, in countries where alfentanil is not available, **sufentanil** is used instead (Table 1 and Box A).[13]

Alfentanil has been used successfully by short-term PCA, CSCI or SL for procedure-related pain, e.g. dressing changes in burns or trauma patients.[2,4,14] It has also been used SL and nasally for break-through pain, including severe intractable angina in inoperable coronary artery disease.[5,15,16] In an audit in one centre of patients already on regular strong opioids, about three-quarters benefited from SL alfentanil in doses of 560–1,680microgram (4–12 sprays of alfentanil 140microgram/0.14mL spray; titrated as necessary). Pain relief was seen within 10min.[17] However, such use has diminished since **transmucosal fentanyl** products have become available.

Spinal administration of lipophilic opioids remains controversial because of the rapid clearance into the systemic circulation (see **Spinal analgesia**).[18]

Opioid withdrawal symptoms can occur when switching from **morphine** (or other less lipophilic/less potent opioid) to CSCI alfentanil.[19] These manifest with symptoms like gastric flu and last for a few days; p.r.n. doses of the original opioid will relieve troublesome symptoms.

Table 1 Pharmacokinetics of single IV doses of fentanils [20–22]

	Alfentanil	*Sufentanil*	*Fentanyl*
Onset of action (min)	0.75 [a]	1	1.5 [b]
Time to peak effect (min)	1.5	2.5	4.5
Plasma halflife (min)	95	165	220
Duration of action (min)	30 [a]	60	60

a. if given IM, onset slower (<5min), and duration of action longer (60min)

b. if given IM, onset slower (7-15min), and duration of action longer (1-2h).

Box A Sufentanil injection (not UK)

A lipophilic opioid with a strong affinity for the μ-opioid receptor. Time to onset of action and to peak effect is mid-way between that of alfentanil and fentanyl (Table 1). [21]

Sufentanil is about 7.5–10 times more potent than fentanyl, [23,24] and this allows a smaller volume to be given by injection. Divide the parenteral dose of fentanyl by 10 to obtain an easy-to-calculate starting dose.

Example
Fentanyl 1,000microgram/24h CSCI (i.e. 20mL of 50microgram/mL)
→ sufentanil 100microgram/24h CSCI (i.e. 2mL of 50microgram/mL).

Sufentanil can be administered SC, IV or spinally. [25] By CSCI, it is compatible with other commonly prescribed drugs. [26]

The injection formulation has been given intranasally (using an atomizer) for, e.g. moderate–severe acute trauma pain, break-through cancer pain; [27,28] specific 15microgram and 30microgram SL tablet formulations have been developed for use in postoperative pain (as part of a PCA system) and moderate–severe acute pain. [29,30]

Accumulates in fat tissue when given continuously; [31] monitor carefully when switching to another opioid.

Is not dependent on renal function for elimination, and is thus useful in renal impairment.

Cautions

Hepatic or renal impairment (also see **Renal impairment** and **Hepatic impairment**).

Drug interactions

Concurrent treatment with ≥2 CNS depressants (e.g. benzodiazepines, gabapentinoids, opioids) increases the risk of respiratory depression, particularly in susceptible groups, e.g. the elderly and those with renal or hepatic impairment. [32]

Alfentanil is metabolized by CYP3A4. Caution is required with concurrent use of drugs that inhibit or induce these enzymes (see **Variability in response to drugs, Table 8**). Reports of interactions where closer monitoring ± dose adjustment are required are listed in Box B. [33]

Box B Interactions between alfentanil and other drugs involving CYP450 [a]

Plasma concentrations of alfentanil *increased* by

Aprepitant [b]

Azoles, e.g. fluconazole, itraconazole, voriconazole

Cimetidine

Diltiazem

Macrolides, e.g. clarithromycin, erythromycin

Plasma concentrations of alfentanil *decreased* by

Apalutamide [c]

Aprepitant [b]

Enzalutamide

Carbamazepine [c]

Fosphenytoin [c]

Phenobarbital [c]

Phenytoin [c]

Rifampicin

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a. not an exhaustive list; limited to drugs most likely to be encountered in palliative care and excludes anticancer, antiviral, HIV and immunosuppressive drugs (seek specialist advice)

b. aprepitant can increase the exposure to CYP3A4 substrates in the short-term and then reduce their exposure within 2 weeks

c. based on theoretical extrapolation.

Undesirable effects

See **Strong opioids**.

Dose and use

Patients using opioids must be monitored for undesirable effects, particularly nausea and vomiting, and constipation. Depending on individual circumstances, an anti-emetic should be prescribed for regular or p.r.n. use (see **QCG: Nausea and vomiting**) and, routinely, a laxative prescribed (see **QCG: Opioid-induced constipation**).

Opioids can impair driving ability, and patients should be counselled accordingly (see **Drugs and fitness to drive**).

†Procedure-related pain (see **QCG: Procedure-related pain**)

- give 250–500microgram alfentanil SL (using the 500microgram/mL injection formulation) or SC/IV.

CSCI as an alternative to morphine

Used mostly for patients with severe renal impairment/ESRF in whom there is evidence of **morphine** neurotoxicity (see **Strong opioids**), or when volume restrictions prevent the use of **fentanyl**.

For general considerations when switching opioids, see **Appendix 2**. Given the shorter duration of action of alfentanil, it is difficult to give a single precise dose conversion ratio. However, the following are safe practical conversion ratios:

- PO **morphine** to CSCI alfentanil: give one thirtieth of the 24h dose, e.g. **morphine** 60mg/24h PO = alfentanil 2mg/24h CSCI
- CSCI **morphine** to CSCI alfentanil: give one fifteenth of the 24h dose, e.g. **morphine** 30mg/24h = alfentanil 2mg/24h
- CSCI **diamorphine** to CSCI alfentanil: give one tenth of the 24h dose, e.g. **diamorphine** 30mg/24h = alfentanil 3mg/24h.

Conventionally, p.r.n. SC doses of alfentanil are 1/10–1/6 of the total 24h CSCI dose. Because of the short duration of action of alfentanil (≤30min), even with an optimally titrated p.r.n. dose frequent dosing may be required; this is one reason why **fentanyl** is recommended first-line in these circumstances (see Pharmacology).

The CSCI dose of alfentanil should be reviewed at least daily and titrated accordingly. For CSCI dilute with WFI, sodium chloride 0.9% or glucose 5%.

CSCI compatibility with other drugs: there are 2-drug compatibility data for alfentanil in WFI with **clonazepam**, **dexamethasone**, **glycopyrronium**, **haloperidol**, **hyoscine *butylbromide***, **levomepromazine**, **metoclopramide**, **midazolam**, **octreotide** and **ondansetron**.

Concentration-dependent *incompatibility* occurs with **cyclizine**.

For more details, charts for mixing drugs in sodium chloride 0.9% and 3-drug compatibility data, see **Compatibility charts**.

Also see *PCF's* Syringe Driver Database on **Drug Compatibility Checker**.

Alternative CSCI dosing schedules

The recommendations above may well be too conservative for some patients. It is important to review sooner rather than later, and increase the dose if necessary. Some centres have used other conversion ratios with apparent success:

- CSCI **morphine** to CSCI alfentanil: give one tenth of the 24h dose, e.g. **morphine** 30mg/24h = alfentanil 3mg/24h [12]
- CSCI **diamorphine** to CSCI alfentanil: give one sixth of the 24h dose, e.g. **diamorphine** 30mg/24h = alfentanil 5mg/24h. [34, 35]

For the latter, p.r.n. SC **diamorphine**/**morphine** is given to supplement CSCI alfentanil, giving the same p.r.n. dose as used before the switch to alfentanil. When the switch has been prompted by opioid neurotoxicity, a recurrence has not been observed with 1–2 p.r.n. doses/24h of **diamorphine**/**morphine**.

†Break-through cancer pain, SL administration

Given the variability in the intensity of break-through pains, p.r.n. recommendations are best expressed as a range of doses rather than a single fixed dose. There is a poor relationship between the effective SL p.r.n. dose and regular CSCI dose. Individual dose titration is necessary, e.g. starting with 1/10–1/6 of the daily alfentanil CSCI dose and titrating upwards if necessary. The alfentanil 500microgram/mL injection formulation can be used SL (Table 2). However, retaining even 2mL in the mouth (sublingually or buccally) for 5–10min is difficult. Generally, authorized **fentanyl transmucosal** products are now used.

Table 2 Equivalent volumes of parenteral formulations of alfentanil, fentanyl and sufentanil for SL use [a]

Alfentanil 500microgram/mL		***Fentanyl 50microgram/mL***		***Sufentanil 50microgram/mL (not UK)***	
Dose (microgram)	***Volume (mL)***	***Dose (microgram)***	***Volume (mL)***	***Dose (microgram)***	***Volume (mL)***
100	0.2	25	0.5	2.5	N/A
200	0.4	50	1	5	0.1
300	0.6	75	1.5	7.5	0.15
400	0.8	100 [b]	2	10	0.2
500	1	125	N/O	12.5	0.25
600	1.2	150	N/O	15	0.3
800	1.6	200 [b]	N/O	20	0.4
1,000	2	250	N/O	25	0.5

Abbreviations: N/A = not applicable; NO = not optimal, because ≥2mL

a. this is *not* a true dose conversion chart. Alfentanil, fentanyl and sufentanil have differing properties (Table 1). As always with analgesics, individual patient dose titration is required

b. fentanyl SL product commercially available (see **Transmucosal fentanyl**); generally use in preference.

Supply

All preparations are Schedule 2 **CD**.

Alfentanil (generic)

Nasal spray (with attachment for buccal/SL use) unauthorised special-order UK product is no longer available.

Injection 500microgram/mL, 2mL amp = £0.75, 10mL amp = £2.75, 50mL vial = £15.

Injection (for dilution and use as a continuous infusion) 5mg/mL, 1mL amp = £2.50.

The high-strength 5mg/mL injection is used at some centres when the CSCI/CIVI dose is >5mg/24h. However, to avoid the risk of the high-strength injection being administered by mistake, in many hospitals its availability is restricted to the ICU.

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