

**Class:** Opioid analgesic.

**Indications:** Intra-operative analgesia; †an alternative in cases of intolerance to other strong opioids, particularly in renal failure,<sup>1</sup> †procedure-related pain,<sup>2,3</sup> †episodic (breakthrough) pain.<sup>4,5</sup>

### **Pharmacology**

Alfentanil is a synthetic derivative of **fentanyl** with distinct properties: a more rapid onset of action, a shorter duration of action, and a potency approximately 1/4 that of **fentanyl**<sup>6</sup> (and about 20 times more than parenteral **morphine**). Alfentanil is less lipophilic than **fentanyl** and is 90% bound to mainly  $\alpha_1$ -acid glycoprotein.<sup>7</sup> However, because most of the unbound alfentanil is unionized, it rapidly enters the CNS. It is metabolized in the liver by CYP3A4 to inactive metabolites that are excreted in the urine. Alfentanil can cumulate with chronic administration, particularly when clearance is reduced, e.g. in the elderly, the obese, patients with burns or with liver impairment. It has been suggested that analgesic tolerance occurs rapidly with alfentanil, but this appears not to be a problem in palliative care practice.<sup>8-10</sup>

Although dose reductions may be necessary in patients with severe liver impairment, this is not necessary in renal failure. Consequently, alfentanil is used at some centers as the parenteral opioid of choice in end-stage renal failure (see Opioid prescribing in renal failure, p.227).<sup>11</sup> Alfentanil is available in a more concentrated form (500microgram/ml) than **fentanyl** (50microgram/ml), reducing the dose volume and facilitating its administration CSCI using a standard syringe driver or SL (see p.383). For similar reasons, **sufentanil**, which is 10 times more potent than **fentanyl**, is also used SL (Table 5.1).<sup>12</sup>

Alfentanil has been used successfully by short-term PCA or CSCI for dressing changes in burns or trauma patients.<sup>2,3</sup> It is used SL (and occasionally nasally) for cancer-related episodic pain.<sup>4</sup> In the UK, a spray bottle containing alfentanil 5mg in 5ml is manufactured from alfentanil powder, delivering 140microgram/0.14ml spray.<sup>5</sup> In an audit of patients already on regular strong opioids, about 3/4 benefited from SL alfentanil in doses of 560–1680microgram (4–12 sprays; titrated as necessary). Pain relief was seen within 10min, with more consistent benefit obtained for the prevention of predictable incident compared with unpredictable episodic pain, possibly reflecting greater natural variation in the latter. This suggests that the p.r.n. dose for unpredictable episodic pain should be a range rather than a fixed dose. As with all fentanils, there is little point in spinal administration because of the rapid clearance into the systemic circulation.<sup>13,14</sup>

**Onset of action** <1min IV; <5min IM.

**Time to peak plasma concentration** 15min IM.

**Plasma half-life** 95min.

**Duration of action** 30min IV; 1h IM.

**Table 5.1** Pharmacokinetics of single IV doses of fentanyl congeners<sup>15-17</sup>

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

**Cautions**

As for **morphine** (see p.229). Alfentanil levels are increased by inhibitors of CYP3A4, e.g. **cimetidine**, **diltiazem**, **erythromycin**, **fluconazole**, **itraconazole**, **ketoconazole**, **ritonavir**, **troleandomycin**, and decreased by inducers of CYP3A4, e.g. **rifampin** (see Cytochrome P450, p.421).

**Undesirable effects**

*For full list, see manufacturer's PI.*

Also see Strong opioids, p.222.

**Dose and use****Alternative to morphine**

Used mostly for patients in renal failure in whom there is evidence of **morphine** neurotoxicity. The following are safe practical conversion ratios:

- PO **morphine** to SC alfentanil, give 1/30–1/40 of the 24h dose, e.g. **morphine** 60mg/24h PO = alfentanil 2mg/24h SC
- SC **morphine** to SC alfentanil, give 1/15–1/20 of the 24h dose, e.g. **morphine** 30mg/24h SC = alfentanil 2mg/24h SC.

Conventionally, SC p.r.n. doses are 1/6–1/10 of the total 24h CSCI dose.

**Procedure-related pain** (see Guidelines, p.243)

- 250–500microgram SL (from ampule for injection) or SC/IV .

**Episodic (breakthrough) pain, SL administration**

There is a poor relationship between the effective p.r.n. dose and regular background opioid dose. Individual dose titration is necessary starting with 250–500microgram. For **fentanyl** and **sufentanil** see Table 5.2. Retaining even 2ml in the mouth (sublingually or buccally) for 5–10 min is difficult. Thus, the smaller the volume, the easier it is for the patient.

When given by CSCI, alfentanil is compatible with **clonazepam**, **dexamethasone**, **glycopyrrolate**, **haloperidol**, **scopolamine butylbromide**, **levomepromazine**, **metoclopramide**, **midazolam** and **ondansetron**; precipitation may occur with **cyclizine** (not USA; see Continuous subcutaneous infusions, p.383).

**Table 5.2** Equivalent volumes of parenteral formulations of alfentanil, sufentanil and fentanyl for SL use<sup>a,b</sup>

Alfentanil (500microgram/ml)		Sufentanil (50microgram/ml)		Fentanyl (50microgram/ml)	
<i>Dose (microgram)</i>	<i>Volume (ml)</i>	<i>Dose (microgram)</i>	<i>Volume (ml)</i>	<i>Dose (microgram)</i>	<i>Volume (ml)</i>
100	0.2	2.5	N/A	25	0.5
200	0.4	5	0.1	50	1
300	0.6	7.5	0.15	75	1.5
400	0.8	10	0.2	100	2
500	1	12.5	0.25	125	N/O
600	1.2	15	0.3	150	N/O
800	1.6	20	0.4	200	N/O
1000	2	25	0.5	250	N/O
2000	N/O	50	1	500	N/O
3000	N/O	75	1.5	750	N/O
4000	N/O	100	2	1000	N/O

- a. this is not a true dose conversion chart. Alfentanil, sufentanil and fentanyl have differing properties and, although bio-availability and onset of effect are broadly similar, duration of effect differs (fentanyl>sufentanil>alfentanil). As always with analgesics, individual patient dose titration is required
- b. N/O = not optimal, because >2ml.

## Supply

Unless indicated otherwise, all preparations are Schedule II controlled substances.

Alfentanil (generic)

**Injection** 500microgram/ml, 2ml amp = \$8, 5ml amp = \$12, 10ml amp = \$14 (AWP).

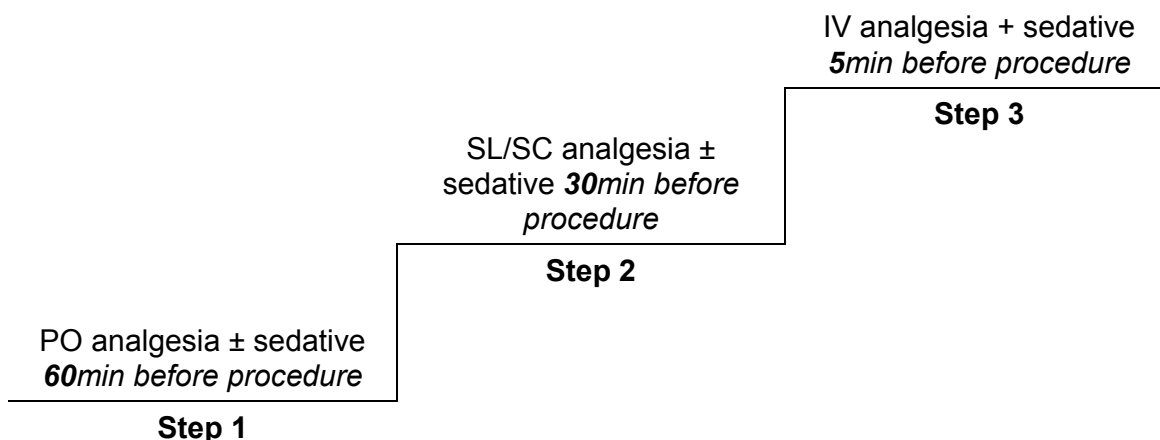
Alfenta® (Akorn)

**Injection** 500microgram/ml, 2ml amp = \$11, 5ml amp = \$15, 10ml amp = \$25 (AWP).

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- 1 Kirkham SR and Pugh R (1995) Opioid analgesia in uraemic patients. *Lancet*. **345**: 1185.
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  - 3 Gallagher G *et al.* (2001) Target-controlled alfentanil analgesia for dressing change following extensive reconstructive surgery for trauma. *Journal of Pain and Symptom Management*. **21**: 1–2.
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  - 5 Anonymous (2003) *August Newsletter. Hot Topics: alternatives to sublingual fentanyl*. Available at [www.palliativedrugs.com](http://www.palliativedrugs.com)
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  - 8 Hill HF *et al.* (1992) Patient-controlled analgesia infusions: alfentanil versus morphine. *Pain*. **49**: 301–310.
  - 9 Kissin I *et al.* (2000) Acute tolerance to continuously infused alfentanil: the role of cholecystinin and N-methyl-D-aspartate-nitric oxide systems. *Anesthesia and Analgesia*. **91**: 110–116.
  - 10 Urch CE *et al.* (2004) A retrospective review of the use of alfentanil in a hospital palliative care setting. *Palliative Medicine*. **18**: 516–519.
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  - 15 Willens JS and Myslinski NR (1993) Pharmacodynamics, pharmacokinetics, and clinical uses of fentanyl, sufentanil, and alfentanil. *Heart and Lung*. **22**: 239–251.
  - 16 Scholz J *et al.* (1996) Clinical pharmacokinetics of alfentanil, fentanyl and sufentanil. An update. *Clinical Pharmacokinetics*. **31**: 275–292.
  - 17 Hall T and Hardy J (2005) The lipophilic opioids: fentanyl, alfentanil, sufentanil and remifentanil. In: M Davis *et al.* (eds) *Opioids in Cancer Pain*. Oxford University Press, Oxford.

## HPCFusa Guidelines: Management of procedure-related pain

- 1 Palliative care patients may experience pain while undergoing procedures, e.g.:
  - position change
  - investigation, e.g. MRI
  - wound dressing change
  - venous cannulation
  - urethral catheterization
  - insertion of nasogastric tube
  - insertion/removal of central line
  - insertion/removal of spinal line
  - drainage of chest/abdomen
  - treatment, e.g. radiation therapy.
- 2 The goal is adequate pain relief without undesirable effects. What is appropriate depends on the anticipated pain severity, procedure duration, current opioid use, and the patient's past personal experience. Thus, severe procedure-related pain may necessitate parenteral analgesia and sedation as first-line therapy.
- 3 Always include non-drug approaches:
  - discuss past experiences of procedure-related pain, identify what was helpful or unhelpful, and clarify present concerns
  - explain the procedure thoroughly before starting
  - assure that you will stop immediately if requested
  - as far as possible, choose the most comfortable position for the patient
  - distract and relax, e.g. through talking, music, hypnosis and other relaxation techniques.
- 4 Use a local anesthetic when a cannula, urinary catheter or tube is inserted transdermally, e.g.:
  - EMLA cream for venous cannulation, if needle phobic or if requested (wait 60min)
  - always use lidocaine gel for urethral catheterization (wait 5min)
  - always use lidocaine tissue infiltration for chest aspiration (wait 5min).
- 5 Consider nitrous oxide-oxygen (Entonox®) inhalation if the procedure is short and the patient is able to use the mask or mouthpiece effectively.
- 6 Give analgesia from the appropriate step of the ladder. (General anesthetic approaches are beyond the scope of these guidelines.)



*Continued*

## Examples of analgesia for procedure-related pain

### Step 1: If anticipating mild–moderate pain

*Give 60min before the procedure:*

PO morphine, give the patient's usual rescue dose for episodic (breakthrough) pain. If necessary, combine with:

- PO diazepam 5mg *or*
- SL lorazepam 500–1000microgram *or*
- an alternative sedative.

### Step 2: If anticipating moderate–severe pain

*Give 30min before procedure:*

SC morphine, give 50% of the patient's usual PO morphine rescue dose.

If necessary, combine with:

- SL/SC midazolam 2.5–5mg *or*
- SL lorazepam 500–1000microgram *or*
- an alternative sedative.

### Step 3: If anticipating severe–excruciating pain

*Give 5min before procedure:*

IV morphine, give 50% of the patient's usual PO morphine rescue dose *or*

IV ketamine 0.5–1mg/kg (typically 25–50mg). Combine with:

- IV midazolam 2.5–5mg *or*
- an alternative sedative.

### Alternatives to SC/IV morphine

- fentanyl citrate (OTFC) 200microgram or more transmucosally
- alfentanil 250–500microgram SL (*from ampule for injection*) or SC/IV
- fentanyl 50–100microgram SL (*from ampule for injection*) or SC/IV
- sufentanil 12.5–25microgram SL (*from ampule for injection*) or SC/IV.

- 7 If pain relief inadequate, give a repeat dose and wait again; if still inadequate, move to the next step.
- 8 If a sedative or sedative analgesic is used, monitor the patient to ensure that the airway remains patent, and consider intervention if the patient becomes cyanosed because of severely depressed respiration, e.g. rate  $\leq 8$  breaths/min.
- 9 An opioid antagonist (naloxone) and a benzodiazepine antagonist (flumazenil) should be available in case of need. To prevent the complete reversal of any background regular opioid analgesic therapy, use naloxone 20–100microgram IV, repeated every 2min until the respiratory rate and cyanosis have improved.
- 10 If the procedure is to be repeated, give analgesia based on previous experience, e.g. drugs used and the patient's comments.