Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.
Ph. Eur. 6.2 (Fentanyl Citrate). White or almost white powder. Soluble in water; sparingly soluble in alcohol; freely soluble in methyl alcohol. Protect from light.
USP 31 (Fentanyl Citrate). A white crystalline powder or white glistening crystals. Sparingly soluble in water; slightly soluble in chloroform; soluble in methyl alcohol. Store at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Fentanyl Hydrochloride *(BANM, rINNM)* ⊗

Fentanyl, Chlorhydrate de; Fentanyli Hydrochloridum; Hidrocloruro de fentanilo.

Фентанила Гидрохлорид

$C_{22}H_{28}N_2O,HCl$ = 372.9.

CAS — 1443-54-5.

Incompatibility. Fentanyl citrate is incompatible with thiopental sodium and methohexital sodium.

A thick white precipitate formed in the intravenous tubing when fentanyl citrate with droperidol was given shortly after nafcillin sodium. There was no precipitate when fentanyl citrate alone was mixed with nafcillin sodium.[1]

Fentanyl citrate underwent rapid and extensive loss when admixed with fluorouracil in PVC containers.[2] The loss was due to sorption of fentanyl to the PVC as a result of the alkaline pH of the admixture, and presumably could occur from admixture of fentanyl citrate with any sufficiently alkaline drug.

See also Stability, below.

1. Jeglum EL, *et al.* Nafcillin sodium incompatibility with acidic solutions. *Am J Hosp Pharm* 1981; **38:** 462, 464.
2. Xu QA, *et al.* Rapid loss of fentanyl citrate admixed with fluorouracil in polyvinyl chloride containers. *Ann Pharmacother* 1997; **31:** 297–302.

Stability. In a 48-hour study fentanyl citrate in glucose 5% or sodium chloride 0.9% was stable when stored at room temperature under usual light conditions in glass or PVC containers;[1] the concentration of fentanyl delivered by a patient-controlled system was relatively constant throughout a 30-hour study period. Fentanyl citrate injection diluted to 20 micrograms/mL with sodium chloride 0.9% was stable for 30 days at 3° or 23° in PVC reservoirs for portable infusion pumps.[2] In another study[3] fentanyl citrate diluted to 50 micrograms/mL with sodium chloride 0.9% remained stable for at least 14 days when stored at room temperature in PVC reservoirs for portable patient-controlled systems.

An admixture of fentanyl citrate and bupivacaine in sodium chloride 0.9% appeared[4] compatible and stable when stored for up to 30 days at 3° or 23° in a portable infusion pump. In another study[5] the stability of solutions containing fentanyl, bupivacaine, and adrenaline, alone and in combination was studied over a period of 56 days when stored at various temperatures in the light or in the dark in PVC bags. Both fentanyl and bupivacaine were adsorbed from solution onto the PVC for the first 3 days but thereafter concentrations of these drugs remained relatively stable; freezing appeared to slow the concentration change for bupivacaine but not for fentanyl. Solutions containing adrenaline became more acidic during the study as the adrenaline progressively deteriorated but this was greatly reduced by freezing. Autoclaving produced a further reduction in the concentration of all drugs. There was no sign of precipitation from any of the solutions studied.

An admixture of fentanyl citrate, ketamine hydrochloride, and droperidol in sodium chloride 0.9% was stable[6] for at least 30 days when stored in glass bottles at 25°; the minor decrease in the concentrations of all 3 drugs was attributed to either hydrolytic degradation or adsorption. This admixture also appeared compatible when stored in PVC bags at 4° and 25°; the small increase in drug concentrations over 30 days may be a result of water permeation and evaporation through the bags.

Fentanyl is potentially unstable in PVC containers when admixed with alkaline drugs (see Incompatibility, above).

1. Kowalski SR, Gourlay GK. Stability of fentanyl citrate in glass and plastic containers and in a patient-controlled delivery system. *Am J Hosp Pharm* 1990; **47:** 1584–7.
2. Allen LV, *et al.* Stability of fentanyl citrate in 0.9% sodium chloride solution in portable infusion pumps. *Am J Hosp Pharm* 1990; **47:** 1572–4.
3. Chapalain-Pargade S, *et al.* Microbiological and physicochemical stability of fentanyl and sufentanil solutions for patient-controlled delivery systems. *J Pain Symptom Manage* 2006; **32:** 90–7.
4. Tu Y-H, *et al.* Stability of fentanyl citrate and bupivacaine hydrochloride in portable pump reservoirs. *Am J Hosp Pharm* 1990; **47:** 2037–40.
5. Dawson PJ, *et al.* Stability of fentanyl, bupivacaine and adrenaline solutions for extradural infusion. *Br J Anaesth* 1992; **68:** 414–17.
6. Lee DKT, *et al.* Compatibility of fentanyl citrate, ketamine hydrochloride, and droperidol in 0.9% sodium chloride injection stored in polyvinyl chloride bags. *Am J Health-Syst Pharm* 2005; **62:** 1190–2.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Fentanyl and illicitly manufactured analogues are subject to abuse (see under Precautions, below).

◊ Plasma concentrations required to produce satisfactory sedation have been reported to increase steadily in neonates receiving continuous infusions, suggesting the development of *tolerance* to the sedating effects of fentanyl.[1]

Movement disorders, *extreme irritability*, and symptoms characteristic of *opioid abstinence syndrome* have been reported in children after withdrawal of prolonged fentanyl infusions.[2,3] Similarly, withdrawal symptoms and, in one case, myoclonus have occurred in adults when fentanyl transdermal patches have been stopped.[4,5] Acute opioid withdrawal syndrome has also been seen in cancer patients switched from modified-release oral morphine to transdermal fentanyl despite adequate analgesia being maintained.[6]

1. Arnold JH, *et al.* Changes in the pharmacodynamic response to fentanyl in neonates during continuous infusion. *J Pediatr* 1991; **119:** 639–43.
2. Lane JC, *et al.* Movement disorder after withdrawal of fentanyl infusion. *J Pediatr* 1991; **119:** 649–51.
3. Dominguez KD, *et al.* Opioid withdrawal in critically ill neonates. *Ann Pharmacother* 2003 **37:** 473–7.
4. Han PKJ, *et al.* Myoclonus secondary to withdrawal from transdermal fentanyl: case report and literature review. *J Pain Symptom Manage* 2002; **23:** 66–72.
5. Ishihara C, *et al.* Withdrawal symptom after discontinuation of transdermal fentanyl at a daily dose of 0.6 mg. *Pharm World Sci* 2005; **27:** 13–15.
6. Anonymous. Opiate withdrawal with transdermal fentanyl. *Pharm J* 1995; **255:** 680.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p.102.

Respiratory depression, which occurs especially with high doses of fentanyl, responds to naloxone (see also Effects on the Respiratory System, below). Atropine may be used to block the vagal effects of fentanyl such as bradycardia. Unlike morphine, fentanyl is reported not to cause significant histamine release. Transient hypotension may follow intravenous dosage. Muscle rigidity can occur and may require neuromuscular blockers.

Local reactions such as rash, erythema, and itching have been reported with transdermal use. Gum bleeding and irritation, and taste perversion have been reported with transmucosal use.

Effects on the cardiovascular system. For a reference to the effects of fentanyl on histamine release compared with some other opioids, see under Pethidine, p.114.

Effects on mental function. Fentanyl had some dose-related effects on mental function and motor activity in healthy subjects,[1] but immediate and delayed recall were not affected. See also under Alfentanil (p.16).

Acute toxic delirium has been reported after treatment with transdermal fentanyl.[2]

1. Scamman FL, *et al.* Ventilatory and mental effects of alfentanil and fentanyl. *Acta Anaesthesiol Scand* 1984; **28:** 63–7.
2. Kuzma PJ, *et al.* Acute toxic delirium: a uncommon reaction to transdermal fentanyl. *Anesthesiology* 1995; **83:** 869–71.

Effects on the nervous system. There have been reports of seizures with low and high doses of fentanyl or sufentanil.[1] There was, however, no EEG evidence of cortical seizure activity in a patient who had seizure-like muscle movements during a fentanyl infusion;[2] the muscle movements might have been due to myoclonus produced by depression of higher CNS inhibitory centres or to a pronounced form of opioid-induced muscle rigidity.

For a report of encephalopathy associated with prolonged use of fentanyl and midazolam in infants in intensive care, see Encephalopathy under Adverse Effects of Diazepam, p.988.

1. Zaccara G, *et al.* Clinical features, pathogenesis and management of drug-induced seizures. *Drug Safety* 1990; **5:** 109–51.
2. Scott JC, Sarnquist FH. Seizure-like movements during a fentanyl infusion with absence of seizure activity in a simultaneous EEG recording. *Anesthesiology* 1985; **62:** 812–14.

Effects on the respiratory system. Fentanyl, like other opioid agonists, causes dose-related respiratory depression; it is significant with *intravenous* fentanyl doses of more than 200 micrograms and may be more prolonged than analgesia. Anaesthesia with fentanyl may result in either prolonged or delayed respiratory depression postoperatively.[1] Consequently, patients should continue to be monitored postoperatively until spontaneous breathing has been re-established. Severe respiratory depression in a 14-month-old child after intravenous sedation with fentanyl and midazolam has also highlighted the necessity for careful monitoring when giving with other respiratory depressants.[2] If present at the end of operation respiratory depression may be reversed by an opioid antagonist such as naloxone; alternatively, a respiratory stimulant such as doxapram that does not reverse analgesia has been given.

Rigidity of the respiratory muscles (chest wall rigidity) may occur during fentanyl anaesthesia. The effects can be minimised by using a slow intravenous injection but a neuromuscular blocker may be required to allow artificial ventilation; rigidity has been reversed postoperatively by naloxone. Similar muscle rigidity induced by alfentanil could be attenuated by pretreatment with a benzodiazepine whereas small doses of neuromuscular blockers appeared to be ineffective.[3]

Coughing has been associated[4] with intravenous fentanyl; incidence was decreased with a longer injection time,[5] in light cigarette smokers,[5,6] and in older patients.[6] For the use of beclometasone and lidocaine to prevent cough associated with intravenous fentanyl in anaesthesia, see p.1518 and p.1852, respectively.

The risk of respiratory depression associated with *epidural* doses of fentanyl, a highly lipid-soluble opioid, has been considered relatively small and only slight ventilatory depression was noted[7] after a dose of 50 micrograms. However, profound delayed respiratory depression has been reported in 2 women 100 minutes[8] and 80 minutes,[9] respectively after fentanyl 100 micrograms had been given epidurally for caesarean section. No adverse effects on neonatal respiration or neurobehaviour were detected in a study[10] of neonates of mothers given epidural infusions of bupivacaine and fentanyl during labour. However, a later report[11] described 2 neonates who developed respiratory depression after their mothers were given epidural fentanyl during labour; the effect was reversed by intramuscular naloxone 400 micrograms. The authors noted that the doses of fentanyl used were higher than those in the previous study.

Respiratory depression is also a risk with *topically* applied fentanyl preparations. Severe hypoventilation with some fatalities has occurred in patients given fentanyl as a transdermal patch for minor painful conditions.[12] More recently, Health Canada had received 2 reports of fatal respiratory depression associated with the use of transdermal fentanyl patches in adolescents for relatively minor conditions (chronic headache and throat pain);[13] in both cases the respiratory depression developed within 24 hours of applying the first and only patch. See also Administration, Transdermal Route, under Precautions below.

1. Bennett MRD, Adams AP. Postoperative respiratory complications of opiates. *Clin Anaesthesiol* 1983; **1:** 41–56.
2. Yaster M, *et al.* Midazolam-fentanyl intravenous sedation in children: case report of respiratory arrest. *Pediatrics* 1990; **86:** 463–7.
3. Sanford TJ, *et al.* Pretreatment with sedative-hypnotics, but not with nondepolarizing muscle relaxants, attenuates alfentanil-induced muscle rigidity. *J Clin Anesth* 1994; **6:** 473–80.
4. Tweed WA, Dakin D. Explosive coughing after bolus fentanyl injection. *Anesth Analg* 2001; **92:** 1442–3.
5. Lin J-A, *et al.* Prolonged injection time and light smoking decrease the incidence of fentanyl-induced cough. *Anesth Analg* 2005; **101:** 670–4.
6. Oshima T, *et al.* Identification of independent risk factors for fentanyl-induced cough. *Can J Anesth* 2006; **53:** 753–8.
7. Morisot P, *et al.* Ventilatory response to carbon dioxide during extradural anaesthesia with lignocaine and fentanyl. *Br J Anaesth* 1989; **63:** 97–102.
8. Brockway MS, *et al.* Profound respiratory depression after extradural fentanyl. *Br J Anaesth* 1990; **64:** 243–5.
9. Wang CY. Respiratory depression after extradural fentanyl. *Br J Anaesth* 1992; **69:** 544.
10. Porter J, *et al.* Effect of epidural fentanyl on neonatal respiration. *Anesthesiology* 1998; **89:** 79–85.
11. Kumar M, Paes B. Epidural opioid analgesia and neonatal respiratory depression. *J Perinatol* 2003; **23:** 425–7.
12. *FDC Reports Pink Sheet* 1994; January 24: 12.
13. Health Canada. Transdermal fentanyl (Duragesic): respiratory arrest in adolescents. *Can Adverse React News* 2004; **14** (4): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v14n4-eng.pdf (accessed 26/06/08)

Effects on the skin. A patient developed a macular rash covering the whole body, except for the face and scalp, while using transdermal fentanyl patches.[1]

1. Stoukides CA, Stegman M. Diffuse rash associated with transdermal fentanyl. *Clin Pharm* 1992; **11:** 222.

Effects on the urinary tract. Urinary retention developed in 2 premature infants after sedation with fentanyl infusion at a dose of 3 micrograms/kg per hour.[1] In both cases catheterisation relieved symptoms.

1. Das UG, Sasidharan P. Bladder retention of urine as a result of continuous intravenous infusion of fentanyl: 2 case reports. *Pediatrics* 2001; **108:** 1012–1015.

Precautions

As for Opioid Analgesics in general, p.103.

Caution is advised in patients with myasthenia gravis; the effects of muscular rigidity on respiration may be particularly pronounced in these patients.

US licensed product information contra-indicates the use of standard transdermal fentanyl patches in opioid-naive patients because of the risk of fatal respiratory depression (see Effects on the Respiratory System, above and Administration, Transdermal Route, below). Similar contra-indications apply to fentanyl buccal tablets (see Administration, Transmucosal Route, below).

Absorption of fentanyl from standard transdermal patches may be increased as the temperature rises and patients should therefore avoid exposing the patch to external heat; similarly, patients with fever may require monitoring because of increased absorption. It may take 17 hours or longer for plasma concentrations of fentanyl to decrease by 50% after removal of a transdermal patch; patients who have had adverse effects should be monitored for up to 24 hours and those requiring replacement opioid therapy should initially receive low doses increased gradually thereafter. Similar advice is also given for patients receiving fentanyl via an iontophoretic drug delivery system; the mean half-life of fentanyl in this system is 11 hours.

The bioavailability of different transmucosal fentanyl preparations is not equivalent and consequently they should not be substituted on a dose-per-dose basis.

Abuse. Several synthetic analogues of fentanyl, so-called 'designer drugs', have been manufactured illicitly for recreational use, particularly in the USA. They are highly potent, and respiratory depression and death may occur very rapidly.[1] The 'fentanyls' have been smoked or snorted as well as injected intravenously.

Fentanyl analogues identified by WHO[2,3] as being subject to street abuse or likely to be abused include: alpha-methylfentanyl (also known as 'China white' or 'synthetic heroin'), 3-methylfentanyl, acetyl-alpha-methylfentanyl, alpha-methylthiofentanyl, para-fluorofentanyl, beta-hydroxyfentanyl, beta-hydroxy-3-methylfentanyl, thiofentanyl, and 3-methylthiofentanyl.

Fentanyl itself is also subject to illicit use. It is chemically unrelated to morphine and does not react in screening tests for morphine-related opioids. It has therefore been recommended[4] that fentanyl should be tested for specifically in cases with suspected opioid misuse.

Used fentanyl transdermal systems may contain significant amounts of fentanyl and have been subject to abuse. In some cases the contents of the patches have been injected intravenously; such abuse has resulted in death.[5,6] Licensed product information advises that used patches and iontophoretic transdermal systems should be folded firmly in half, adhesive side inwards to conceal the release membrane, and disposed of safely.

1. Buchanan JF, Brown CR. 'Designer drugs': a problem in clinical toxicology. *Med Toxicol* 1988; **3:** 1–17.
2. WHO. WHO expert committee on drug dependence: twenty-fourth report. *WHO Tech Rep Ser 761* 1988.
3. WHO. WHO expert committee on drug dependence: twenty-sixth report. *WHO Tech Rep Ser 787* 1989.
4. Berens AIL, *et al.* Illicit fentanyl in Europe. *Lancet* 1996; **347:** 1334–5.
5. Reeves MD, Ginifer CJ. Fatal intravenous misuse of transdermal fentanyl. *Med J Aust* 2002; **177:** 552–3.
6. Tharp AM, *et al.* Fatal intravenous fentanyl abuse: four cases involving extraction of fentanyl from transdermal patches. *Am J Forensic Med Pathol* 2004; **25:** 178–81.

Administration. ***INTRAVENOUS ROUTE.*** Fentanyl is much more lipid-soluble than morphine and after standard single intravenous doses has a rapid onset and short duration of action. However, fentanyl is rapidly redistributed in the body and has a longer elimination half-life than morphine (see under Pharmacokinetics, below). Hence, with high or repeated doses, fentanyl becomes a relatively long-acting drug; to avoid accumulation patients should be monitored and doses adjusted accordingly.

Repeated intra-operative doses of fentanyl should be given with care, since not only may the respiratory depression persist into the postoperative period but it may become apparent for the first time postoperatively when the patient is away from immediate nursing attention.

TRANSDERMAL ROUTE. Fatalities have been associated with the use of standard fentanyl transdermal patches (see Effects on the Respiratory System, above). Incorrect or inappropriate use resulting in serious adverse effects and fatalities had prompted regulatory authorities to issue warnings and recommendations for changes to product labelling; in particular transdermal fentanyl patches are not appropriate for the treatment of acute or postoperative pain. Nonetheless, reports of fatalities and life-threatening adverse reactions have continued to be received[1,2] and, in December 2007, the FDA[1] reiterated that:

- fentanyl patches are indicated for the management of persistent, moderate to severe chronic pain in opioid-tolerant patients
- licensed product information must be consulted when determining the initial dose as overestimating when converting patients from another opioid analgesic can result in fatal overdose with the first dose
- use with any inhibitors of the cytochrome P450 isoenzyme CYP3A4 may result in an increase in plasma-fentanyl concentrations, which may cause potentially fatal respiratory depression; patients who are taking CYP3A4 inhibitors and using fentanyl patches for an extended period of time should be monitored and the dose of fentanyl adjusted if necessary

1. FDA. Information for healthcare professionals: fentanyl transdermal system (marketed as Duragesic and generics) (issued 21st December, 2007). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/fentanyl_2007HCP.htm (accessed 23/07/08)
2. Health Canada. Fentanyl transdermal patch and fatal adverse reactions. *Can Adverse React News* 2008; **18** (3): 1–2. Also available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/carn-bcei_v18n3-eng.pdf (accessed 23/07/08)

TRANSMUCOSAL ROUTE. The FDA[1] has received reports of serious adverse effects, including fatalities, in patients who have taken the fentanyl buccal tablets, *Fentora* (*Cephalon, USA*), resulting from inappropriate use in patients who were not opioid tolerant, misunderstanding of dosing instructions, or inappropriate substitution for other fentanyl-containing formulations. The FDA reiterated that *Fentora*:

- should only be used for breakthrough pain in opioid-tolerant cancer patients
- should not be used in those who only need an opioid on an intermittent, or as required, basis and who are not on around-the-clock opioids
- should not be used for the management of acute or postoperative pain including headaches, migraines, and pain due to injury
- should not be directly substituted for other fentanyl-containing formulations

1. FDA. Information for healthcare professionals: fentanyl buccal tablets (marketed as Fentora) (issued 26th September, 2007). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/fentanyl_buccal.htm (accessed 24/07/08)

Breast feeding. The American Academy of Pediatrics[1] states that there have been no reports of any clinical effect in infants of breast-feeding mothers given fentanyl, and that therefore it may be considered to be usually compatible with breast feeding. The *BNF* also considers that the amount of fentanyl distributed into breast milk is too small to be harmful to a breast-fed infant. However, licensed product information states that, since fentanyl is distributed into breast milk, it should be avoided in nursing mothers because of the possibility of sedation or respiratory depression in breast-fed infants.

A study[2] using fentanyl 100 micrograms intravenously for induction of anaesthesia in 5 mothers concluded that the amount of fentanyl excreted into breast milk within 24 hours of induction was less than 0.1% of the maternal dose, and hence unlikely to affect a healthy full-term breast-feeding infant.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 26/06/08)
2. Nitsun M, *et al.* Pharmacokinetics of midazolam, propofol, and fentanyl transfer to human breast milk. *Clin Pharmacol Ther* 2006; **79:** 549–57.

Children. The *BNFC* states that the half-life of fentanyl is prolonged in neonates and accumulation is likely with prolonged use; muscle rigidity may occur and the use of muscle relaxants may be required. See also under Pharmacokinetics, below.

Exercise. Opioid toxicity requiring naloxone treatment occurred in a patient who wore a fentanyl patch while engaging in vigorous outdoor exercise.[1] Physicians should be aware that along with fever and external heat sources, physical activity may cause increased absorption of transdermal fentanyl.

1. Carter KA. Heat-associated increase in transdermal fentanyl absorption. *Am J Health-Syst Pharm* 2003; **60:** 191–2.

Handling. Avoid contact with skin and the inhalation of fentanyl citrate particles.

Interactions

For interactions associated with opioid analgesics, see p.103. Use of fentanyl with non-vagolytic neuromuscular blockers may produce bradycardia and possibly asystole.

Fentanyl is metabolised via the cytochrome P450 isoenzyme CYP3A4; use with potent inhibitors of this isoenzyme, such as ritonavir and other HIV-protease inhibitors, may increase fentanyl plasma concentrations.

Antidepressants. For reference to a possible case of serotonin syndrome associated with use of fentanyl and *SSRIs*, see Opioid Analgesics under Interactions of Fluoxetine, p.397.

Antivirals. *Ritonavir*, an inhibitor of the cytochrome P450 isoenzyme CYP3A4, might prolong fentanyl-induced respiratory depression. The plasma clearance of fentanyl was decreased, and the elimination half-life and area under the plasma concentration-time curve increased, when given with ritonavir in a study in healthy subjects.[1]

1. Olkkola KT, *et al.* Ritonavir's role in reducing fentanyl clearance and prolonging its half-life. *Anesthesiology* 1999; **91:** 681–5.

Benzodiazepines. For the effects of opioids such as fentanyl with benzodiazepines, see Analgesics under Interactions of Diazepam, p.989.

Propofol. For reference to the effect that fentanyl has on blood concentrations of propofol, see p.1792.

Pharmacokinetics

After parenteral doses fentanyl citrate has a rapid onset and short duration of action. After transmucosal delivery, up to 50% of the dose is rapidly absorbed from the buccal mucosa; the remainder is swallowed and slowly absorbed from the gastrointestinal tract. Some first-pass metabolism occurs via this route. The absolute bioavailability of transmucosal delivery is about half that for intravenous fentanyl but varies between formulations. Absorption is slow after transdermal application. Fentanyl is metabolised in the liver by *N*-dealkylation and hydroxylation via the cytochrome P450 isoenzyme CYP3A4. Metabolites and some unchanged drug are excreted mainly in the urine. The short duration of action is probably due to rapid redistribution into the tissues rather than metabolism and excretion. The relatively longer elimination half-life reflects slower release from tissue depots. About 80% has been reported to be bound to plasma proteins. Fentanyl appears in the CSF. It crosses the placenta and has been detected in breast milk.

◊ Marked differences in results of pharmacokinetic studies of fentanyl have been attributed[1] to differences in assay methods. The need for sensitive assay methods has been emphasised because the potency of fentanyl means that small doses are used. However, there are differences in pharmacokinetics between bolus doses and prolonged infusion with highly lipophilic drugs such as fentanyl.[2] Terminal half-lives ranging from 2 to 7 hours have been reported in healthy subjects and surgical patients. However, the duration of action of fentanyl after a single intravenous dose of up to 100 micrograms may be only 30 to 60 minutes as a result of rapid redistribution into the tissues. US licensed product information has given values for a three-compartment pharmacokinetic model with a distribution time of 1.7 minutes, a redistribution time of 13 minutes, and a terminal elimination half-life of 219 minutes. Giving repeated or large doses, or continuous infusions, may result in accumulation and a more prolonged action.

The clinical significance of secondary peak plasma-fentanyl concentrations and the possible role of entero-systemic recirculation[3] has been controversial, but some[4] considered that irregular decay curves were not unlikely for lipophilic compounds such as fentanyl, especially in patients undergoing operations and subject to large changes in blood flow. Unexpectedly high plasma-fentanyl concentrations in a patient following epidural use were thought to be a result of aortic clamping and might reflect the effect of changes in blood flow.[5]

The main metabolites of fentanyl, which are excreted in the urine, have been identified as 4-*N*-(*N*-propionylanilino) piperidine and 4-*N*-(*N*-hydroxypropionylanilino) piperidine; 1-(2-phenethyl)-4-*N*-(*N*-hydroxypropionylanilino) piperidine is a minor metabolite.[6] Fentanyl has no active or toxic metabolites.[4]

1. Mather LE. Clinical pharmacokinetics of fentanyl and its newer derivatives. *Clin Pharmacokinet* 1983; **8:** 422–46.
2. Scholz J, *et al.* Clinical pharmacokinetics of alfentanil, fentanyl and sufentanil: an update. *Clin Pharmacokinet* 1996; **31:** 275–92.
3. Bennett MRD, Adams AP. Postoperative respiratory complications of opiates. *Clin Anaesthesiol* 1983; **1:** 41–56.
4. Moore RA, *et al.* Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; **1:** 829–58.
5. Bullingham RES, *et al.* Unexpectedly high plasma fentanyl levels after epidural use. *Lancet* 1980; **i:** 1361–2.
6. Goromaru T, *et al.* Identification and quantitative determination of fentanyl metabolites in patients by gas chromatography-mass spectrometry. *Anesthesiology* 1984; **61:** 73–7.

Administration. Some references to the pharmacokinetics of fentanyl after constant rate intravenous infusion,[1] transdermal application,[2-5] use of the oral sublingual[6] and transmucosal[7-11] routes, intranasal dosage,[12] subcutaneous infusion,[13] and epidural use.[14-16]

1. Duthie DJR, *et al.* Pharmacokinetics of fentanyl during constant rate iv infusion for the relief of pain after surgery. *Br J Anaesth* 1986; **58:** 950–6.
2. Grond S, *et al.* Clinical pharmacokinetics of transdermal opioids: focus on transdermal fentanyl. *Clin Pharmacokinet* 2000; **38:** 59–89.
3. Solassol I, *et al.* Inter- and intraindividual variabilities in pharmacokinetics of fentanyl after repeated 72-hour transdermal applications in cancer pain patients. *Ther Drug Monit* 2005; **27:** 491–8.

4. Marier J-F, *et al.* Pharmacokinetics, tolerability, and performance of a novel matrix transdermal delivery system of fentanyl relative to the commercially available reservoir formulation in healthy subjects. *J Clin Pharmacol* 2006; **46:** 642–53.
5. Marier J-F, *et al.* Comparative bioequivalence study between a novel matrix transdermal delivery system of fentanyl and a commercially available reservoir formulation. *Br J Clin Pharmacol* 2007; **63:** 121–4.
6. Lennernäs B, *et al.* Pharmacokinetics and tolerability of different doses of fentanyl following sublingual administration of a rapidly dissolving tablet to cancer patients: a new approach to treatment of incident pain. *Br J Clin Pharmacol* 2005; **59:** 249–53.
7. Streisand JB, *et al.* Absorption and bioavailability of oral transmucosal fentanyl citrate. *Anesthesiology* 1991; **75:** 223–9.
8. Darwish M, *et al.* Pharmacokinetics and dose proportionality of fentanyl effervescent buccal tablets in healthy volunteers. *Clin Pharmacokinet* 2005; **44:** 1279–86.
9. Darwish M, *et al.* Comparison of equivalent doses of fentanyl buccal tablets and arteriovenous differences in fentanyl pharmacokinetics. *Clin Pharmacokinet* 2006; **45:** 843–50.
10. Darwish M, *et al.* Single-dose and steady-state pharmacokinetics of fentanyl buccal tablet in healthy volunteers. *J Clin Pharmacol* 2007; **47:** 56–63.
11. Darwish M, *et al.* Absolute and relative bioavailability of fentanyl buccal tablet and oral transmucosal fentanyl citrate. *J Clin Pharmacol* 2007; **47:** 343–50.
12. Walter SH, *et al.* Pharmacokinetics of intranasal fentanyl. *Br J Anaesth* 1993; **70** (suppl 1): 108.
13. Miller RS, *et al.* Plasma concentrations of fentanyl with subcutaneous infusion in palliative care patients. *Br J Clin Pharmacol* 1995; **40:** 553–6.
14. Gourlay GK, *et al.* Pharmacokinetics of fentanyl in lumbar and cervical CSF following lumbar epidural and intravenous administration. *Pain* 1989; **38:** 253–9.
15. Bader AM, *et al.* Maternal and neonatal fentanyl and bupivacaine concentrations after epidural infusion during labor. *Anesth Analg* 1995; **81:** 829–32.
16. Moises EC, *et al.* Pharmacokinetics and transplacental distribution of fentanyl in epidural anesthesia for normal pregnant women. *Eur J Clin Pharmacol* 2005; **61:** 517–22.

Cardiopulmonary bypass. In general, studies[1,2] indicate that serum concentrations of fentanyl during cardiopulmonary bypass decrease initially and then remain stable. The fall in concentrations has been attributed to haemodilution although adsorption to the bypass apparatus has also been found.

1. Buylaert WA, *et al.* Cardiopulmonary bypass and the pharmacokinetics of drugs: an update. *Clin Pharmacokinet* 1989; **17:** 10–26.
2. Gedney JA, Ghosh S. Pharmacokinetics of analgesics, sedatives and anaesthetic agents during cardiopulmonary bypass. *Br J Anaesth* 1995; **75:** 344–51.

Children. The disposition of intravenous fentanyl 10 to 50 micrograms/kg in 14 neonates undergoing various major surgical procedures was highly variable.[1] The mean elimination half-life of 317 minutes and other pharmacokinetic parameters including volume of distribution and total body clearance were greater than reported in adults, but both pharmacodynamic and pharmacokinetic mechanisms appeared responsible for the very prolonged respiratory depression that can occur in neonates after fentanyl anaesthesia. In 9 premature neonates given fentanyl 30 micrograms/kg intravenously for induction of anaesthesia[2] the elimination half-life ranged from 6 to 32 hours, but cautious interpretation was advised because of the method of calculation.

1. Koehntop DE, *et al.* Pharmacokinetics of fentanyl in neonates. *Anesth Analg* 1986; **65:** 227–32.
2. Collins C, *et al.* Fentanyl pharmacokinetics and hemodynamic effects in preterm infants during ligation of patent ductus arteriosus. *Anesth Analg* 1985; **64:** 1078–80.

The elderly. In one study the elimination half-life of intravenous fentanyl increased from 265 minutes in patients with a mean age of 36 years to 945 minutes in those with a mean age of 67 years.[1] The authors of another study were critical of the relatively short sampling time used and in contrast found that major fentanyl pharmacokinetic parameters did not correlate with age.[2] However, elderly patients had increased brain sensitivity to intravenous fentanyl, as shown by EEG changes[2] and lower doses might be indicated in older patients for pharmacodynamic rather than pharmacokinetic reasons.

1. Bentley JB, *et al.* Age and fentanyl pharmacokinetics. *Anesth Analg* 1982; **61:** 968–71.
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.

Hepatic impairment. The pharmacokinetics of fentanyl were not affected significantly in surgical patients with cirrhosis of the liver.[1] A 1987 review[2] considered that fentanyl had not been associated with clinical problems when given to patients with liver dysfunction.

1. Haberer JP, *et al.* Fentanyl pharmacokinetics in anaesthetized patients with cirrhosis. *Br J Anaesth* 1982; **54:** 1267–70.
2. Moore RA, *et al.* Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; **1:** 829–58.

Renal impairment. Clearance of fentanyl from plasma was reported to be enhanced in surgical patients with end-stage renal disease,[1] although clearance was reduced and elimination half-life increased in patients with renal failure undergoing transplantation,[2] possibly because of the influence of uraemia on metabolism in the liver. Nevertheless, a 1987 review[2] noted that fentanyl had no active or toxic metabolites and had not been associated with clinical problems when given to patients with renal dysfunction.

1. Corall IM, *et al.* Plasma concentrations of fentanyl in normal surgical patients and those with severe renal and hepatic disease. *Br J Anaesth* 1980; **52:** 101P.
2. Moore RA, *et al.* Opiate metabolism and excretion. *Baillieres Clin Anaesthesiol* 1987; **1:** 829–58.

Uses and Administration

Fentanyl, a phenylpiperidine derivative, is a potent opioid analgesic (p.104) chemically related to pethidine (p.113) and is primarily a μ-opioid agonist.

Fentanyl is used as an analgesic, as an adjunct to general anaesthetics, and as an anaesthetic for induction and maintenance. It is also used as a respiratory depressant in the management of mechanically ventilated patients under intensive care. When used with an antipsychotic such as droperidol it can induce a state of neuroleptanalgesia in which the patient is calm and indifferent to his surroundings and is able to cooperate with the surgeon.

Fentanyl is usually given parenterally or by the transmucosal route as the citrate, in transdermal patches as the base, or by iontophoretic transdermal delivery as the hydrochloride. Fentanyl citrate 157 micrograms and fentanyl hydrochloride 111 micrograms are each equivalent to about 100 micrograms of fentanyl. Doses are expressed in terms of the base.

It is more lipid soluble than morphine and after an intravenous injection of 100 micrograms the effects of fentanyl begin almost immediately, although maximum analgesia and respiratory depression may not occur for several minutes; the duration of action of fentanyl depends on the dose and the intensity of the pain involved, and may vary from 10 minutes to several hours.

For **premedication** the equivalent of 50 to 100 micrograms of fentanyl may be given *intramuscularly* 30 to 60 minutes before the induction of anaesthesia.

As an **adjunct** to general anaesthesia, fentanyl is usually given by *intravenous* injection. Dosage recommendations show a wide range depending on the technique.

- *Patients with spontaneous respiration* may be given 50 to 200 micrograms as an initial dose with supplements of 50 micrograms. In the USA it is recommended that doses above 2 micrograms/kg be accompanied by assisted ventilation. Significant respiratory depression follows doses of more than 200 micrograms
- *Patients whose ventilation is assisted* may be given 300 micrograms to 3.5 mg (up to 50 micrograms/kg) as an initial dose, with supplements of 100 to 200 micrograms depending on the patient's response. High doses have been reported to moderate or attenuate the response to surgical stress (see Anaesthesia, below)

Fentanyl may also be given by intravenous infusion. In ventilated patients a loading dose of about 1 microgram/kg per minute is given for the first 10 minutes followed by an infusion of about 100 nanograms/kg per minute; alternatively, the loading dose may be given as a bolus. The infusion rate should be titrated according to response and rates of up to 3 micrograms/kg per minute have been used in cardiac surgery. Infusions should be stopped about 40 minutes before the end of surgery unless artificial ventilation is to be continued postoperatively. In patients with spontaneous respiration, lower infusion rates of 50 to 80 nanograms/kg per minute are used.

Reduced doses are used in *the elderly* or debilitated patients

Similar doses to those used for premedication may also be given by *intramuscular* injection **postoperatively**, and by *intramuscular* or *slow intravenous injection* as an adjunct to **regional anaesthesia**.

For the treatment of **intractable chronic pain** in adults when opioid analgesia is indicated *transdermal* patches delivering amounts of fentanyl ranging from 12 to 100 micrograms/hour are available. In the UK, fentanyl patches may be used in strong opioid-naive patients; however, in the USA, use is restricted to patients who are already tolerant to opioid therapy of comparable potency.

- Doses should be individually titrated for each patient according to previous opioid usage. Initial dosages should not exceed 25 micrograms/hour in *opioid-naive* patients; in addition, it is recommended that these patients are initially titrated with low doses of short-acting opioids before transferring to fentanyl patches
- For *patients who have been receiving a strong opioid analgesic* the initial dose of the fentanyl patch should be based on the previous 24-hour opioid requirement. Use of a patch providing 25 micrograms of fentanyl per hour is equivalent to about 60 to 90 mg daily of oral morphine sulfate. During transfer to treatment with fentanyl patches previous opioid analgesic therapy should be phased out gradually in order to allow for the gradual increase in plasma-fentanyl concentrations
- More than one patch may be applied if doses greater than 100 micrograms/hour are required (applied at the same time to avoid confusion); additional or alternative analgesic therapy should be considered if doses greater than 300 micrograms/hour are required. Patches should be replaced every 72 hours with the new patch being applied to a different site; use of the same area of the skin should be avoided for several days
- *Elderly* or debilitated patients should be observed carefully for signs of toxicity and the dose reduced if necessary

Fentanyl patches are not appropriate for acute or postoperative pain.

A patient-activated *iontophoretic transdermal* fentanyl delivery system, *IONSYS* (*Janssen-Cilag, UK*; *Ortho-McNeil, USA*), is available for the management of acute moderate to severe **postoperative pain** in hospitalised patients. Patients should be titrated to an acceptable level of analgesia before starting therapy. *IONSYS* contains fentanyl hydrochloride and each system delivers an equivalent of 40 micrograms of fentanyl per dose over 10 minutes, to a maximum of 6 doses per hour, for 24 hours after the first dose or for 80 doses (maximum of 3.2 mg), whichever is reached first. The maximum duration of treatment is 72 hours, or 3 consecutive systems applied sequentially, with the new system being applied to a different site; only one system should be worn at a time. It should be applied to intact, non-irritated, and non-irradiated skin on the chest or upper outer arm.

A lozenge-on-a-stick dosage form of fentanyl citrate for *transmucosal* delivery is used as an analgesic in the management of **breakthrough cancer pain** in those already receiving and tolerant to opioid treatment. Lozenges containing the equivalent of 200 micrograms to up to 1.6 mg of fentanyl are available. An initial unit dose of 200 micrograms may be taken over 15 minutes for an episode of breakthrough pain and repeated once if necessary after a further 15 minutes. Doses are subsequently titrated according to response, up to a unit dose of 1.6 mg if necessary. Once the patient has been stabilised on an effective dose, no more than 4 unit doses should be taken daily.

In the USA, a buccal tablet containing fentanyl citrate for transmucosal delivery is also available and licensed for the same indication as the lozenge. Tablets containing the equivalent of 100 micrograms to up to 800 micrograms of fentanyl are available. An initial dose of 100 micrograms may be taken for an episode of breakthrough pain and repeated once if necessary after 30 minutes; thereafter, patients must wait at least 4

hours before treating another episode. Doses are subsequently titrated according to response. The dose of the maintenance opioid used for persistent pain should be re-evaluated if the patient has more than 4 episodes of breakthrough pain a day.

Caution must be exercised when switching between the lozenge and buccal tablet as the extent of absorption may be substantially different.

For details of doses in *children*, see below.

Administration. ***INHALATION ROUTE.*** In a study[1] inhaled fentanyl provided plasma concentrations similar to those after intravenous doses; use as patient-controlled analgesia was suggested. Inhaled formulations of fentanyl are under investigation for the treatment of breakthrough cancer pain and acute pain.

1. Mather LE, *et al.* Pulmonary administration of aerosolised fentanyl: pharmacokinetic analysis of systemic delivery. *Br J Clin Pharmacol* 1998; **46:** 37–43.

INTRANASAL ROUTE. Studies[1-3] have shown that intranasal fentanyl is as effective as the intravenous route for postoperative pain management and that it can be used in a patient-controlled analgesia system. Intranasal fentanyl has also been studied[4-6] for the management of acute pain in children. Intranasal spray formulations of fentanyl are under investigation for the treatment of breakthrough cancer pain.

1. Striebel HW, *et al.* Intranasal fentanyl titration for postoperative pain management in an unselected population. *Anaesthesia* 1993; **48:** 753–7.
2. Striebel HW, *et al.* Patient-controlled intranasal analgesia: a method for noninvasive postoperative pain management. *Anesth Analg* 1996; **83:** 548–51.
3. Toussaint S, *et al.* Patient-controlled intranasal analgesia: effective alternative to intravenous PCA for postoperative pain relief. *Can J Anesth* 2000; **47:** 299–302.
4. Manjushree R, *et al.* Intranasal fentanyl provides adequate postoperative analgesia in pediatric patients. *Can J Anesth* 2002; **49:** 190–3.
5. Borland ML, *et al.* Intranasal fentanyl is an equivalent analgesic to oral morphine in paediatric burns patients for dressing changes: a randomised double blind crossover study. *Burns* 2005; **31:** 831–7.
6. Borland M, *et al.* A randomized controlled trial comparing intranasal fentanyl to intravenous morphine for managing acute pain in children in the emergency department. *Ann Emerg Med* 2007; **49:** 335–40.

INTRASPINAL ROUTE. For a discussion on the intraspinal use of fentanyl, see Postoperative Pain, below.

TRANSDERMAL ROUTE. Transdermal fentanyl is used for chronic intractable cancer pain in adults and children.[1-5]

Transdermal fentanyl is also used in the treatment of chronic non-cancer pain;[4-6] however transdermal use is contra-indicated in the management of acute or postoperative pain because the problems of dose titration in the short term increase the possibility of development of significant respiratory depression[4] (see also under Adverse Effects and under Precautions, above).

Although the licensed dosage interval for transdermal patches of fentanyl is 72 hours studies have suggested that up to about 25% of cancer patients may require more frequent application with some patients requiring fresh patches every 48 hours.[7,8] Equally, in an attempt to supply lower doses than are allowed for by existing transdermal dosage forms, patches have sometimes been cut, folded, or partially masked with non-porous dressings; the manufacturers do not recommend such practices as they consider the dose supplied will be unreliable, and there is potential for overdosage.

An iontophoretic drug delivery system containing fentanyl hydrochloride is also available for the management of acute moderate to severe postoperative pain in a hospital setting (see Postoperative Pain, below for some references).

1. Jeal W, Benfield P. Transdermal fentanyl: a review of its pharmacological properties and therapeutic efficacy in pain control. *Drugs* 1997; **53:** 109–38.
2. Muijsers RBR, Wagstaff AJ. Transdermal fentanyl: an updated review of its pharmacological properties and therapeutic efficacy in chronic cancer pain control. *Drugs* 2001; **61:** 2289–2307.
3. Gourlay GK. Treatment of cancer pain with transdermal fentanyl. *Lancet Oncol* 2001; **2:** 165–72.
4. Kornick CA, *et al.* Benefit-risk assessment of transdermal fentanyl for the treatment of chronic pain. *Drug Safety* 2003; **26:** 951–73.
5. Zernikow B, *et al.* Transdermal fentanyl in childhood and adolescence: a comprehensive literature review. *J Pain* 2007; **8:** 187–207.
6. Allan L, *et al.* Randomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. *BMJ* 2001; **322:** 1154–8.
7. Radbruch L, *et al.* Transdermal fentanyl for the management of cancer pain: a survey of 1005 patients. *Palliat Med* 2001; **15:** 309–21.
8. Donner B, *et al.* Long-term treatment of cancer pain with transdermal fentanyl. *J Pain Symptom Manage* 1998; **15:** 168–75.

TRANSMUCOSAL ROUTE. Transmucosal fentanyl has been tried for sedation and analgesia before anaesthesia or painful procedures in adults[1] and children[2,3] and is used for breakthrough cancer pain in opioid-tolerant patients.[4,5] It has been noted[6] that this dosage method can cause all the adverse effects of parenteral opioids; nausea and vomiting are common and potentially lethal respiratory depression can occur (see also under Precautions, above). Dosage guidelines have been suggested.[7]

1. Macaluso AD, *et al.* Oral transmucosal fentanyl citrate for premedication in adults. *Anesth Analg* 1996; **82:** 158–61.
2. Nelson PS, *et al.* Comparison of oral transmucosal fentanyl citrate and an oral solution of meperidine, diazepam, and atropine for premedication in children. *Anesthesiology* 1989; **70:** 616–21.
3. Schechter NL, *et al.* The use of oral transmucosal fentanyl citrate for painful procedures in children. *Pediatrics* 1995; **95:** 335–9.
4. Blick SKA, Wagstaff AJ. Fentanyl buccal tablet: in breakthrough pain in opioid-tolerant patients with cancer. *Drugs* 2006; **66:** 2387–93.
5. Zeppetella G, Ribeiro MDC. Opioids for the management of breakthrough (episodic) pain in cancer patients. Available in the Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 26/06/08).
6. Anonymous. Oral transmucosal fentanyl citrate. *Med Lett Drugs Ther* 1994; **36:** 24–5.
7. Aronoff GM, *et al.* Evidence-based oral transmucosal fentanyl citrate (OTFC) dosing guidelines. *Pain Med* 2005; **6:** 305–14.

Administration in children. Indications for fentanyl therapy in children are similar to those in adults (see above).

Fentanyl is usually given by *intravenous* injection as an **adjunct** to general anaesthesia. In the UK recommended initial doses range from 2 to 3 micrograms/kg in children aged 2 to 12 years with *spontaneous respiration*; supplements of 1 microgram/kg may be given. (The *BNFC* suggests initial doses of 1 to 5 micrograms/kg for neonates and children up to 12 years of age.) When *ventilation* is *assisted*, the initial recommended dose is also 2 to 3 micrograms/kg, with supplements of 1 microgram/kg. (The *BNFC* suggests an initial dose of 5 to 10 micrograms/kg for neonates and children up to 12 years of age, with supplements of 1 to 3 micrograms/kg.) In the USA doses are similar to those licensed in the UK.

Children may also be given fentanyl by intravenous infusion: licensed product information implies that doses are similar to those used in adults (see above) although the *BNFC* recommends that the infusion rate in ventilated patients is 1.5 micrograms/kg per hour in neonates and is 1 to 6 micrograms/kg per hour in older children.

Transdermal patches delivering amounts of fentanyl ranging from 12 to 100 micrograms/hour may be used for the treatment of **intractable chronic pain** in children aged 2 years and older who are already tolerant to opioid therapy of comparable potency. The initial dose should be based on the previous 24-hour opioid requirement. Use of a patch providing 12 micrograms of fentanyl per hour is equivalent to about 30 to 44 mg daily of oral morphine sulfate. See Uses and Administration, above for further details. Patches should be applied to the upper backs of young children to minimise the potential for removal.

Although the *transmucosal* lozenge-on-a-stick formulation is not licensed for use in children, the *BNFC* suggests a single dose of 15 to 20 micrograms/kg (maximum of 400 micrograms) for the management of **breakthrough pain** and as **premedication** in those aged 2 years and older, and who weigh more than 10 kg.

Anaesthesia. Fentanyl and its congeners alfentanil and sufentanil are shorter-acting than morphine and appear to produce fewer circulatory changes; they are preferred for use as supplements during anaesthesia with inhalational or intravenous drugs. Fentanyl is widely used as the analgesic component of balanced anaesthesia. It has been used to attenuate cardiovascular stress responses to intubation (see Anaesthesia, p.1900), and may be used in higher doses in an attempt to reduce the cardiovascular, endocrine, and metabolic changes that may accompany surgery. When attenuation of surgical stress is especially important, for example in cardiac surgery, intravenous fentanyl 50 to 100 micrograms/kg in conjunction with oxygen and a neuromuscular blocker, and sometimes up to 150 micrograms/kg, may be used for general anaesthesia. Total intravenous anaesthesia with fentanyl and propofol has been successful.[1]

Satisfactory anaesthesia has been reported[2] with high-dose fentanyl citrate (30 to 50 micrograms/kg) in *premature infants* when used as sole anaesthetic, in conjunction with pancuronium, for ligation of patent ductus arteriosus; cardiovascular stability was maintained throughout the procedure. However, others[3] found significant hypotension in preterm infants given either fentanyl 20 micrograms/kg, isoflurane, halothane, or ketamine; systolic arterial pressure was best maintained with the ketamine technique. The surgical stress response in preterm babies was abolished by the addition of fentanyl 10 micrograms/kg intravenously to an anaesthetic regimen of nitrous oxide and tubocurarine.[4] Dose responses of fentanyl in *neonatal* anaesthesia have been discussed.[5]

For details of doses in neonates and children, see above.

Neuroleptanalgesia. An injection of short-acting fentanyl 50 micrograms/mL with the longer-acting antipsychotic droperidol 2.5 mg/mL has been used for neuroleptanalgesia, premedication, and as an adjunct to anaesthesia. However, the use of such a fixed-ratio combination cannot be recommended.

1. Jenstrup M, *et al.* Total iv anaesthesia with propofol-alfentanil or propofol-fentanyl. *Br J Anaesth* 1990; **64:** 717–22.
2. Robinson S, Gregory GA. Fentanyl-air-oxygen anesthesia for ligation of patent ductus arteriosus in preterm infants. *Anesth Analg* 1981; **60:** 331–4.
3. Friesen RH, Henry DB. Cardiovascular changes in preterm neonates receiving isoflurane, halothane, fentanyl, and ketamine. *Anesthesiology* 1986; **64:** 238–42.
4. Anand KJS, *et al.* Randomised trial of fentanyl anaesthesia in preterm babies undergoing surgery: effects on the stress response. *Lancet* 1987; **i:** 243–8.
5. Yaster M. The dose response of fentanyl in neonatal anesthesia. *Anesthesiology* 1987; **66:** 433–5.

PHAEOCHROMOCYTOMA. Unlike morphine and some other opioids, fentanyl and alfentanil do not release histamine and may be used safely in the anaesthetic management of patients with phaeochromocytoma.[1]

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

POSTOPERATIVE SHIVERING. As pethidine appears to be effective in the treatment of postoperative shivering a number of other opioids including fentanyl have also been tried. Not all opioids are necessarily effective but fentanyl has been reported to be so,[1] although information is scanty.[2]

1. Alfonsi P, *et al.* Fentanyl, as pethidine, inhibits post anaesthesia shivering. *Br J Anaesth* 1993; **70** (suppl 1): 38.
2. Kranke P, *et al.* Pharmacological treatment of postoperative shivering: a quantitative systematic review of randomized controlled trials. *Anesth Analg* 2002; **94:** 453–60.

Intensive care. Despite the short duration of action of fentanyl after single doses, rapid redistribution in the body results in an elimination half-life longer than that of morphine. Consequently fentanyl is not a short-acting drug when used for analgesia in intensive care, and may offer little advantage over morphine.[1]

1. Aitkenhead AR. Analgesia and sedation in intensive care. *Br J Anaesth* 1989; **63:** 196–206.

Pain. ***CANCER PAIN.*** Transdermal fentanyl is used in the management of chronic intractable cancer pain; for references see Administration, Transdermal Route, above. For references to the use of transmucosal fentanyl in the management of breakthrough cancer pain, see Administration, Transmucosal Route, above.

LABOUR PAIN. Fentanyl has been reported to be an effective intravenous analgesic during active labour. Epidural fentanyl is unreliable when used alone,[1,2] although it does enhance the epidural analgesia achieved with the local anaesthetic bupivacaine. The reduction in the minimum local analgesic concentration of epidural bupivacaine for labour pain increased with increasing dose of fentanyl added to bupivacaine.[3] However, the incidence of pruritus increased significantly with fentanyl in a dose of 4 micrograms/mL and therefore the optimum dose of fentanyl may be 3 micrograms/mL for bupivacaine-sparing epidural analgesia during labour. Respiratory depression has also been reported with the combination.[4]

1. Reynolds F. Extradural opioids in labour. *Br J Anaesth* 1989; **63:** 251–3.
2. Lindow SW, *et al.* A randomised double-blind comparison of epidural fentanyl versus fentanyl and bupivicaine [sic] for pain relief in the second stage of labour. *Br J Obstet Gynaecol* 2004; **111:** 1075–80.
3. Lyons G, *et al.* Extradural pain relief in labour: bupivacaine sparing by extradural fentanyl is dose dependent. *Br J Anaesth* 1997; **78:** 493–7.
4. McClure JH, Jones G. Comparison of bupivacaine and bupivacaine with fentanyl in continuous extradural analgesia during labour. *Br J Anaesth* 1989; **63:** 637–40.

POSTOPERATIVE PAIN. Small intravenous bolus doses of an opioid analgesic may be injected immediately after surgery for postoperative analgesia and faster acting opioids such as fentanyl may be preferable to morphine.[1] Fentanyl has also been given by epidural injection in doses of 100 or 200 micrograms or by continuous epidural infusion in doses of 20 to 80 micrograms/hour; patient-controlled systems have been used.[2]

Epidural fentanyl or sufentanil provided effective postoperative analgesia after caesarean section with comparable adverse effect profiles.[3] The suggested optimal dose of fentanyl was 100 micrograms. For references comparing epidural fentanyl with alfentanil, see Postoperative Analgesia under Uses and Administration of Alfentanil, p.18. In a review[4] of perioperative pain management epidural opioids were considered to provide effective analgesia at lower doses than systemic opioids. Fentanyl may be given through a lumbar epidural catheter that is often inserted immediately postoperatively. After an initial loading dose of 1 to 1.5 micrograms/kg of fentanyl, infusion at the rate of 0.7 to 2 micrograms/kg per hour is begun and continued for about 48 hours on average. Some prefer to use intermittent injection. A small study[5] comparing 2 patient-controlled routes of administration found that cervical epidural fentanyl provided better postoperative pain relief at rest than intravenous fentanyl; however, there was no decrease in the total dose required and the authors considered that the benefits of epidural fentanyl did not outweigh its potential complications.

Combined opioid and local anaesthetic epidural infusions have also proved effective, for example fentanyl 1 microgram/mL with bupivacaine 0.1%; both could be infused at lower rates than either drug alone. Although a study[6] comparing bupivacaine-fentanyl combinations with each drug alone for epidural analge-

sia after caesarean section confirmed an additive analgesic effect for the combination, there was no demonstrable clinical benefit compared with fentanyl alone in this patient group who expect early mobilisation. However, the combination may be of greater benefit in patients for whom early ambulation is not routine.

Fentanyl has also been given by epidural injection to children for postoperative analgesia.[7]

Fentanyl has been tried by intrathecal injection for postoperative pain.[8]

As mentioned in Administration, Transdermal Route, above, an iontophoretic transdermal system for postoperative pain is also available.[9-11]

1. Mitchell RWD, Smith G. The control of acute postoperative pain. *Br J Anaesth* 1989; **63:** 147–58.
2. Morgan M. The rational use of intrathecal and extradural opioids. *Br J Anaesth* 1989; **63:** 165–88.
3. Grass JA, *et al*. A randomized, double-blind, dose-response comparison of epidural fentanyl versus sufentanil analgesia after cesarean section. *Anesth Analg* 1997; **85:** 365–71.
4. Swarm RA, *et al*. Pain treatment in the perioperative period. *Curr Probl Surg* 2001; **38:** 835–920.
5. Roussier M, *et al*. Patient-controlled cervical epidural fentanyl compared with patient-controlled i.v. fentanyl for pain after pharyngolaryngeal surgery. *Br J Anaesth* 2006; **96:** 492–6.
6. Cooper DW, *et al*. Patient-controlled extradural analgesia with bupivacaine, fentanyl, or a mixture of both, after caesarean section. *Br J Anaesth* 1996; **76:** 611–15.
7. Lejus C, *et al*. Postoperative extradural analgesia in children: comparison of morphine with fentanyl. *Br J Anaesth* 1994; **72:** 156–9.
8. Sudarshan G, *et al*. Intrathecal fentanyl for post-thoracotomy pain. *Br J Anaesth* 1995; **75:** 19–22.
9. Chelly JE. An iontophoretic, fentanyl HCl patient-controlled transdermal system for acute postoperative pain management. *Expert Opin Pharmacother* 2005; **6:** 1205–14.
10. Koo PJ. Postoperative pain management with a patient-controlled transdermal delivery system for fentanyl. *Am J Health-Syst Pharm* 2005; **62:** 1171–6.
11. Mayes S, Ferrone M. Fentanyl HCl patient-controlled iontophoretic transdermal system for the management of acute postoperative pain. *Ann Pharmacother* 2006; **40:** 2178–86.

Preparations

BP 2008: Fentanyl Injection;
USP 31: Fentanyl Citrate Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Durogesic; Fentax; Gray-F; Nafluvent; Sublimaze; Talnur; ***Austral.:*** Actiq; Durogesic; Sublimaze; ***Austria:*** Durogesic; ***Belg.:*** Durogesic; ***Braz.:*** Durogesic; Fentabbott; Fentanest; Fentatil; ***Canad.:*** Duragesic; ***Chile:*** Durogesic; ***Cz.:*** Durogesic; Fentagesic; Fentahexal; Fentalis; Ionsys; Matrifen; Wintanyl; ***Denm.:*** Actiq; Durogesic; Haldid; ***Fin.:*** Actiq; Durogesic; ***Fr.:*** Actiq; Durogesic; Ionsys; ***Ger.:*** Actiq; Durogesic; Fenta-Hameln†; ***Gr.:*** Actiq; Durogesic; Fentadur; Matrifen; ***Hong Kong:*** Durogesic; ***Hung.:*** Durogesic; Matrifen; Sedaton; ***India:*** Durogesic; Trofentyl; ***Indon.:*** Durogesic; ***Irl.:*** Actiq; Durogesic; Fental; Sublimaze; ***Israel:*** Durogesic; Tanyl; ***Ital.:*** Actiq; Durogesic; Fentanest; ***Jpn:*** Durotep; ***Malaysia:*** Durogesic; Talgesil; ***Mex.:*** Durogesic; Fenodid; Fentanest; ***Neth.:*** Actiq; Durogesic; ***Norw.:*** Actiq; Durogesic; Leptanal; ***NZ:*** Durogesic; Sublimaze; ***Philipp.:*** Durogesic; Sublimaze; ***Pol.:*** Durogesic; Fentahexal; ***Port.:*** Durogesic; Fentanest; Ionsys; Nilfene; ***Rus.:*** Durogesic (Дюрогезик); ***S.Afr.:*** Durogesic; Sublimaze; Tanyl; ***Singapore:*** Durogesic; ***Spain:*** Actiq; Durogesic; Fentanest; ***Swed.:*** Actiq; Durogesic; Leptanal; Matrifen; ***Switz.:*** Actiq; Durogesic; Sintenyl; ***Thai.:*** Durogesic; ***Turk.:*** Durogesic; ***UK:*** Actiq; Durogesic; Fentalis; Ionsys; Matrifen; Osmach; Sublimaze; Tilofyl; ***USA:*** Actiq; Duragesic; Fentora; Ionsys; Sublimaze; ***Venez.:*** Durogesic.

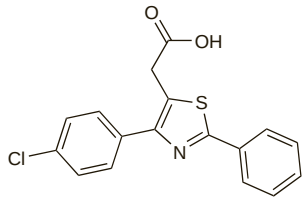
Multi-ingredient: *Arg.:* Disifelit; ***Austral.:*** Marcain with Fentanyl; Naropin with Fentanyl; ***Braz.:*** Nilperidol; ***Ital.:*** Leptofen; ***NZ:*** Bupafen; Marcain with Fentanyl; Naropin with Fentanyl.

Fentiazac *(BAN, USAN, rINN)*

BR-700; Fentiazaco; Fentiazacum; Wy-21894. [4-(4-Chlorophenyl)-2-phenylthiazol-5-yl]acetic acid.

Фентиазак

$C_{17}H_{12}ClNO_2S$ = 329.8.
CAS — 18046-21-4.
ATC — M01AB10; M02AA14.
ATC Vet — QM01AB10; QM02AA14.



Profile

Fentiazac is an NSAID (p.96) that has been used for the relief of pain and inflammation associated with musculoskeletal, joint, peri-articular, and soft-tissue disorders. It has also been used in the treatment of fever. Fentiazac has been given in usual oral doses of 200 mg once or twice daily. Fentiazac has also been applied topically and has been given rectally as the calcium salt.

Preparations

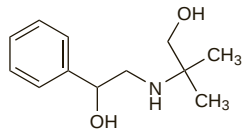
Proprietary Preparations (details are given in Part 3)
Ital.: O-Flam; ***Port.:*** Donorest†; IDR†; Norvedan†.

Fepradinol *(rINN)*

Fépradinol; Fepradinolum. (±)-α-{[(2-Hydroxy-1,1-dimethylethyl)amino]methyl}benzyl alcohol.

Фепрадинол

$C_{12}H_{19}NO_2$ = 209.3.
CAS — 63075-47-8.



Profile

Fepradinol is an NSAID (p.96) that has been used topically in a concentration of 6% for the relief of pain and inflammation. The hydrochloride has been used similarly.

Preparations

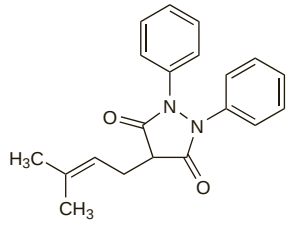
Proprietary Preparations (details are given in Part 3)
Chile: Sinalgia†; ***Mex.:*** Sinalgia; ***Spain:*** Dalgen; Flexidol†.

Feprazone *(BAN, rINN)*

DA-2370; Feprazona; Féprazone; Feprazonum; Phenylprenazone; Prenazone. 4-(3-Methylbut-2-enyl)-1,2-diphenylpyrazolidine-3,5-dione.

Фепразон

$C_{20}H_{20}N_2O_2$ = 320.4.
CAS — 30748-29-9 (feprazone); 57148-60-4 (feprazone piperazine salt 1:1).
ATC — M01AX18; M02AA16.
ATC Vet — QM01AX18; QM02AA16.



Profile

Feprazone, a phenylbutazone (p.117) derivative, is an NSAID (p.96). It has been given orally in the treatment of mild to moderate pain, fever, and inflammation associated with musculoskeletal and joint disorders. Feprazone has also been given rectally and used topically as a 5% cream.

Pinazone, the piperazine salt of feprazone, has been used similarly.

Preparations

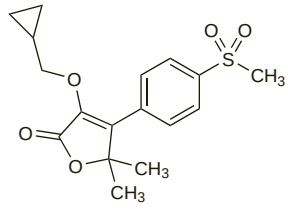
Proprietary Preparations (details are given in Part 3)
Ital.: Zepelin; ***Spain:*** Brotazona; ***Venez.:*** Vapesin.

Firocoxib *(USAN, rINN)*

Firocoxibum; ML-1785713. 3-(Cyclopropylmethoxy)-5,5-dimethyl-4-[4-(methylsulfonyl)phenyl]furan-2(5*H*)-one.

Фирококсиб

$C_{17}H_{20}O_5S$ = 336.4.
CAS — 189954-96-9.
ATC Vet — QM01AH90.



Profile

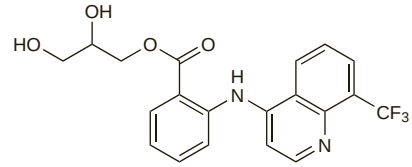
Firocoxib, a selective cyclo-oxygenase-2 (COX-2) inhibitor, is an NSAID used in veterinary medicine for the treatment of inflammation and pain associated with osteoarthritis in dogs.

Floctafenine *(BAN, USAN, rINN)*

Floctafenina; Floctafénine; Floctafeninum; R-4318; RU-15750. 2,3-Dihydroxypropyl *N*-(8-trifluoromethyl-4-quinolyl)anthranilate.

Флоктафенин

$C_{20}H_{17}F_3N_2O_4$ = 406.4.
CAS — 23779-99-9.
ATC — N02BG04.
ATC Vet — QN02BG04.



Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Anaphylactic shock has been reported, and may be preceded by minor allergic manifestations; floctafenine should be stopped in any patient who develops signs suggestive of allergy (such as pruritus or urticaria). Reactions may also involve the liver. Floctafenine may cross-react with glafenine (p.62) and should not be given to patients who have had glafenine-associated reactions.

Porphyria. Floctafenine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Interactions

For interactions associated with NSAIDs, see p.99.

Pharmacokinetics

Floctafenine is absorbed from the gastrointestinal tract; peak plasma concentrations are obtained 1 to 2 hours after ingestion. Its plasma half-life is about 8 hours. It is metabolised in the liver to floctafenic acid. It is excreted mainly as glucuronide conjugates in the urine and bile.

Uses and Administration

Floctafenine, an anthranilic acid derivative related to glafenine (p.62), is an NSAID (p.99) used in oral doses of up to 1.2 g daily, in divided doses, for the short-term relief of pain.

Preparations

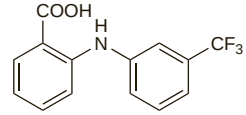
Proprietary Preparations (details are given in Part 3)
Canad.: Idarac†; ***Fr.:*** Idarac; ***Irl.:*** Idarac†; ***Thai.:*** Idarac.

Flufenamic Acid *(BAN, USAN, rINN)*

Acide Flufénamique; Ácido flufenámico; Acidum Flufenamicum; CI-440; CN-27554; Flufenaamihappo; Flufenamsyra; INF-1837; Kwas flufenamowy; NSC-82699. *N*-(ααα-Trifluoro-*m*-tolyl)anthranilic acid.

Флуфенамовая Кислота

$C_{14}H_{10}F_3NO_2$ = 281.2.
CAS — 530-78-9 (flufenamic acid); 61891-34-7 (flufenamate aluminium); 16449-54-0 (flufenamate aluminium).
ATC — M01AG03.
ATC Vet — QM01AG03.



Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Breast feeding. No adverse effects have been seen in breast-fed infants whose mothers were receiving flufenamic acid, and the American Academy of Pediatrics considers[1] that it is therefore usually compatible with breast feeding.

An early study[2] found that only very small amounts of flufenamic acid were excreted into breast milk after oral doses.

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 01/11/07)
2. Buchanan RA, *et al*. The breast milk excretion of flufenamic acid. *Curr Ther Res* 1969; **11:** 533–8.

Effects on the gastrointestinal tract. Acute proctocolitis associated with oral flufenamic acid in a patient.[1]

1. Ravi S, *et al*. Colitis caused by non-steroidal anti-inflammatory drugs. *Postgrad Med J* 1986; **62:** 773–6.

Porphyria. Flufenamic acid has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.