Dependence and Withdrawal

As for Opioid Analgesics, p.101.

◊ A WHO expert committee considered in 1989 that the likelihood of nalbuphine abuse was low to moderate and was not great enough to warrant international control.[1] Abuse had been reported infrequently and the withdrawal syndrome produced when naloxone was given after continuous nalbuphine dosage was less severe than that in morphine dependence. Subsequently, there have been occasional reports of abuse[2,3] including misuse among athletes.[4,5]

1. WHO. WHO expert committee on drug dependence: twenty-fifth report. *WHO Tech Rep Ser 775* 1989. Also available at: http://libdoc.who.int/trs/WHO_TRS_775.pdf (accessed 26/06/08)
2. Spadari M, *et al.* Pharmacodépendance à la nalbuphine (Nubain): à propos de 2 cas. *Therapie* 2002; **57:** 504–5.
3. Klinzig F, *et al.* Hair analysis by LC-MS as evidence of nalbuphine abuse by a nurse. *J Anal Toxicol* 2007; **31:** 62–5.
4. McBride AJ, *et al.* Three cases of nalbuphine hydrochloride dependence associated with anabolic steroid use. *Br J Sports Med* 1996; **30:** 69–70.
5. Wines JD, *et al.*. Nalbuphine hydrochloride dependence in anabolic steroid users. *Am J Addict* 1999; **8:** 161–4.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p.102.

Headache may occur. Nausea and vomiting occur less than with other opioids. Hallucinations and other psychotomimetic effects are rare and have been reported less frequently than with pentazocine. As nalbuphine has both antagonist and agonist activity its effects may be only partially reversed by naloxone, but use of the latter is still recommended in nalbuphine overdose.

Effects on the respiratory system. Nalbuphine produces similar respiratory depression to morphine at equianalgesic doses, but there is a ceiling effect with nalbuphine and, unlike morphine, respiratory depression does not increase appreciably with higher doses.[1] In a cumulative-dose study[2] a plateau effect was seen with nalbuphine above a total dose of 30 mg per 70 kg intravenously. Similar ventilatory depression has been noted[3] with single intravenous doses of nalbuphine of 15, 30, or 60 mg per 70 kg; naloxone failed to reverse the depression at the highest dose.

1. Klepper ID, *et al.* Respiratory function following nalbuphine and morphine in anaesthetized man. *Br J Anaesth* 1986; **58:** 625–9.
2. Romagnoli A, Keats AS. Ceiling effect for respiratory depression by nalbuphine. *Clin Pharmacol Ther* 1980; **27:** 478–85.
3. Pugh GC, *et al.* Effect of nalbuphine hydrochloride on the ventilatory and occlusion pressure responses to carbon dioxide in volunteers. *Br J Anaesth* 1989; **62:** 601–9.

Precautions

As for Opioid Analgesics in general, p.103.

Nalbuphine may precipitate withdrawal symptoms if given to patients physically dependent on opioids.

The dose of nalbuphine should be reduced in patients with hepatic or renal impairment.

Abuse. See under Dependence and Withdrawal, above.

Pregnancy. When nalbuphine is used for analgesia during labour there is more placental transfer and sedation in mothers and their infants than with pethidine.[1] There have also been reports of bradycardia and respiratory depression in neonates whose mothers received nalbuphine during labour.[2,3] It was considered that nalbuphine should be given with caution during labour, especially by the intravenous route. Some[2] have recommended subcutaneous dosage and advised that nalbuphine should not be given around the expected time of delivery.

Further references on the transplacental transfer of nalbuphine are given under Pharmacokinetics, below.

1. Wilson CM, *et al.* Transplacental gradient of pethidine and nalbuphine in labour. *Br J Clin Pharmacol* 1986; **21:** 571P–572P.
2. Guillonneau M, *et al.* Perinatal adverse effects of nalbuphine given during parturition. *Lancet* 1990; **335:** 1588.
3. Sgro C, *et al.* Perinatal adverse effects of nalbuphine given during labour. *Lancet* 1990; **336:** 1070.

Interactions

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

Pharmacokinetics

There appears to be considerable first-pass metabolism of nalbuphine after oral doses. On intramuscular injection nalbuphine has been reported to produce peak plasma concentrations after 30 minutes. It is metabolised in the liver and is excreted in the urine and faeces as unchanged drug and conjugates. Nalbuphine crosses the placenta and small amounts are distributed into breast milk.

◊ References.

1. Sear JW, *et al.* Disposition of nalbuphine in patients undergoing general anaesthesia. *Br J Anaesth* 1987; **59:** 572–5.
2. Kay B, *et al.* Pharmacokinetics of oral nalbuphine in postoperative patients. *Br J Anaesth* 1987; **59:** 1327P.
3. Aitkenhead AR, *et al.* The pharmacokinetics of oral and intravenous nalbuphine in healthy volunteers. *Br J Clin Pharmacol* 1988; **25:** 264–8.
4. Jaillon P, *et al.* Pharmacokinetics of nalbuphine in infants, young healthy volunteers, and elderly patients. *Clin Pharmacol Ther* 1989; **46:** 226–33.

Pregnancy. References.

1. Wilson CM, *et al.* Transplacental gradient of pethidine and nalbuphine in labour. *Br J Clin Pharmacol* 1986; **21:** 571P–572P.
2. Dadabhoy ZP, *et al.* Transplacental transfer of nalbuphine in patients undergoing cesarean section: a pilot study. *Acta Anaesthesiol Ital* 1988; **39:** 227–32.
3. Nicolle E, *et al.* Therapeutic monitoring of nalbuphine: transplacental transfer and estimated pharmacokinetics in the neonate. *Eur J Clin Pharmacol* 1996; **49:** 485–9.

Uses and Administration

Nalbuphine hydrochloride, a phenanthrene derivative, is an opioid analgesic (p.104). It has mixed opioid agonist and antagonist activity. It is used for the relief of moderate to severe pain and as an adjunct to anaesthesia. Nalbuphine hydrochloride is reported to act within 15 minutes of subcutaneous or intramuscular injection or within 2 to 3 minutes of intravenous injection and generally to produce analgesia for 3 to 6 hours. It is given subcutaneously, intramuscularly, or intravenously. Intravenous infusion as part of a patient-controlled analgesia system has also been used.

The usual adult dose of nalbuphine hydrochloride for **pain** relief is 10 to 20 mg every 3 to 6 hours as required.

As an adjunct in balanced **anaesthesia** a usual dose is 0.3 to 3 mg/kg given intravenously over 10 to 15 minutes at induction. Maintenance doses of 250 to 500 micrograms/kg may be given as intravenous boluses if required.

Action. Nalbuphine is generally described as a mixed agonist and antagonist acting mainly as an agonist at κ opioid receptors and as an antagonist or partial agonist at μ receptors. It has shown antagonist activity similar to that seen with naloxone in opioid-dependent subjects.[1] Nalbuphine is structurally related to naloxone and oxymorphone. Pharmacologically nalbuphine is qualitatively similar to pentazocine, but nalbuphine is a more potent antagonist at μ opioid receptors, is less likely to produce psychotomimetic effects such as hallucinations, and is reported to produce no significant cardiovascular effects in patients with ischaemic heart disease. It differs from pure μ agonists such as morphine in that its analgesic, sedative, and respiratory depressant actions are subject to a 'ceiling' effect and may not increase proportionately with dose.

1. Preston KL, *et al.* Antagonist effects of nalbuphine in opioid-dependent human volunteers. *J Pharmacol Exp Ther* 1989; **248:** 929–37.

Administration. References to alternative routes or dosage schedules.

1. Krenn H, *et al.* Nalbuphine by PCA-pump for analgesia following hysterectomy: bolus application versus continuous infusion with bolus application. *Eur J Pain* 2001; **5:** 219–26.
2. Woollard M, *et al.* Hitting them where it hurts? Low dose nalbuphine therapy. *Emerg Med J* 2002; **19:** 565–70.
3. Sung KC, *et al.* Transdermal delivery of nalbuphine and its prodrugs by electroporation. *Eur J Pharm Sci* 2003; **18:** 63–70.
4. Gear RW, *et al.* Dose ratio is important in maximizing naloxone enhancement of nalbuphine analgesia in humans. *Neurosci Lett* 2003; **351:** 5–8.
5. Liu KS, *et al.* Antinociceptive effect of a novel long-acting nalbuphine preparation. *Br J Anaesth* 2004; **92:** 712–15.
6. Woollard M, *et al.* Less IS less: a randomised controlled trial comparing cautious and rapid nalbuphine dosing regimens. *Emerg Med J* 2004; **21:** 362–4.
7. Gordon AT, *et al.* Open-label exploration of an intravenous nalbuphine and naloxone mixture as an analgesic agent following gynecologic surgery. *Pain Med* 2007; **8:** 525–30.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Gobbinal; Naltrox; Nubaina; Nubak†; Onfor; ***Austria:*** Nubain; ***Braz.:*** Nubain; ***Canad.:*** Nubain†; ***Cz.:*** Nubain; ***Fr.:*** Nubain†; ***Ger.:*** Nubain†; ***Gr.:*** Nubain; ***Hong Kong:*** Intapan; Nubain†; ***Hung.:*** Nubain; ***Israel:*** Nubain†; ***Malaysia:*** Nubain†; ***Mex.:*** Bufigen; Bufilem; Nalcryn; Nubain†; ***NZ:*** Nubain†; ***Philipp.:*** Nubain; ***S.Afr.:*** Nubain†; ***Singapore:*** Nubain†; ***Switz.:*** Nubain; ***Thai.:*** Nubain; ***UK:*** Nubain†; ***USA:*** Nubain; ***Venez.:*** Bufidol; Nubain†.

Naproxen *(BAN, USAN, rINN)*

Naprokseeni; Naproksen; Naproksenas; Naproxén; Naproxène; Naproxeno; Naproxenum; RS-3540. (+)-2-(6-Methoxy-2-naphthyl)propionic acid.

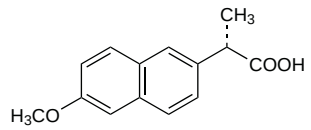
Напроксен

$C_{14}H_{14}O_3$ = 230.3.

CAS — 22204-53-1.

ATC — G02CC02; M01AE02; M02AA12.

ATC Vet — QG02CC02; QM01AE02; QM02AA12.



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

Ph. Eur. 6.2 (Naproxen). A white or almost white, crystalline powder. Practically insoluble in water; soluble in alcohol and in methyl alcohol. Protect from light.

USP 31 (Naproxen). A white to off-white, practically odourless, crystalline powder. Practically insoluble in water; soluble in alcohol, in dehydrated alcohol, and in chloroform; sparingly soluble in ether. Store in airtight containers.

Naproxen Sodium *(BANM, USAN, rINNM)*

Naproksen Sodyum; Naproxène sodique; Naproxeno sódico; Naproxenum natricum; Natrii Naproxenum; RS-3650.

Натрий Напроксен

$C_{14}H_{13}NaO_3$ = 252.2.

CAS — 26159-34-2.

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

Ph. Eur. 6.2 (Naproxen Sodium). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; sparingly soluble in alcohol; freely soluble or soluble in methyl alcohol. A 2% solution in water has a pH of 7.0 to 9.8. Store in airtight containers. Protect from light.

USP 31 (Naproxen Sodium). A white to creamy crystalline powder. Soluble in water and in methyl alcohol; sparingly soluble in alcohol; very slightly soluble in acetone; practically insoluble in chloroform and in toluene. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

As for NSAIDs in general, p.96.

Suppositories containing naproxen may cause rectal irritation and occasional bleeding.

Naproxen should be used with caution in renal impairment, and use is not recommended in patients whose creatinine clearance is less than 20 mL/min.

◊ Reviews.

1. Bansal V, *et al.* A look at the safety profile of over-the-counter naproxen sodium: a meta-analysis. *J Clin Pharmacol* 2001; **41:** 127–38.

Breast feeding. The American Academy of Pediatrics[1] states that there have been no reports of any clinical effect on the infant associated with the use of naproxen by breast-feeding mothers, and that therefore it may be considered to be usually compatible with breast feeding. The *BNF* also considers that the amount of naproxen distributed into breast milk is too small to be harmful to a breast-fed infant; however, some licensed product information recommends that breast feeding should be avoided during naproxen therapy.

In a study[2] of a breast-fed infant only 0.26% of the mother's dose was recovered from the 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 08/11/07)
2. Jamali F, Stevens DRS. Naproxen excretion in milk and its uptake by the infant. *Drug Intell Clin Pharm* 1983; **17:** 910–11.

Effects on the blood. Haematological adverse effects reported in patients given naproxen include haemolytic anaemia,[1,2] aplastic anaemia,[3] agranulocytosis,[4] and immune thrombocytopenia.[5]

1. Hughes JA, Sudell W. Hemolytic anemia associated with naproxen. *Arthritis Rheum* 1983; **26:** 1054.
2. Lo TCN, Martin MA. Autoimmune haemolytic anaemia associated with naproxen suppositories. *BMJ* 1986; **292:** 1430.
3. McNeil P, *et al.* Naproxen-associated aplastic anaemia. *Med J Aust* 1986; **145:** 53–4.
4. Nygard N, Starkebaum G. Naproxen and agranulocytosis. *JAMA* 1987; **257:** 1732.
5. Bougie D, Aster R. Immune thrombocytopenia resulting from sensitivity to metabolites of naproxen and acetaminophen. *Blood* 2001; **97:** 3846–50.

Effects on the cardiovascular system. For a discussion of the possible cardiovascular effects of naproxen, see p.96.