at a concentration of 100 micrograms/mL, in an initial dose of 250 nanograms/kg. Further doses of 250 nanograms/kg may be given at intervals of 2 to 5 minutes until the desired level of opioid reversal is reached; cumulative doses above 1 microgram/kg do not provide additional benefit. In patients with an increased cardiovascular risk a concentration of 50 micrograms/mL and doses and increments of 100 nanograms/kg are recommended.

In the management of known or suspected opioid overdosage, nalmefene is given intravenously at a concentration of 1 mg/mL. An initial dose of 500 micrograms per 70 kg is recommended, followed by a second dose of 1 mg per 70 kg after 2 to 5 minutes if necessary. If a total dose of 1.5 mg per 70 kg is not effective then additional doses are unlikely to have an effect. If the patient is suspected of being physically dependent on opioids an initial test dose of 100 micrograms per 70 kg is recommended; if there is no evidence of withdrawal symptoms within 2 minutes the usual dosage may be used.

Although nalmefene has a longer duration of action than naloxone, all patients should be closely observed and if respiratory depression does recur, the dose of nalmefene should be titrated as above to avoid over-reversal of opioid effects.

Alcohol withdrawal and abstinence. For mention of the use of nalmefene in the adjunctive management of patients with alcohol dependence, see under Naltrexone, p.1456.

Pruritus. It has been suggested that because central opioid receptors modulate itch, an opioid antagonist might be useful in pruritus (p.1582). A systematic review[1] found that opioid antagonists are effective in opioid-induced pruritus, and a number have also been reported to be of benefit in pruritus of other causes.

Rapid improvement of severe pruritus was reported after a single oral dose of *nalmefene* 10 or 20 mg in a double-blind study of 80 patients with either chronic urticaria or atopic dermatitis.[2] Pruritus was almost completely eliminated in up to 60% of patients receiving nalmefene. Adverse effects occurred in 67% of patients and included dizziness or lightheadedness, fatigue, and nausea. In another study,[3] 14 patients with resistant pruritus secondary to cholestatic liver disease were treated with oral nalmefene for 2 to 26 months. The initial dose was 2 mg twice daily and the dose was increased gradually as necessary. Although 13 of the patients reported some amelioration of pruritus, 5 found that increasing doses were required to produce any benefit, and in 3 tolerance appeared to develop.

Continuous infusion of *naloxone* 200 nanograms/kg per minute was reported to reduce perception of pruritus and scratching activity in a double-blind study of 29 patients with pruritus due to cholestasis,[4] although the role of continuous infusion in long-term management may be limited.

Benefit has been reported with oral *naltrexone* 50 mg daily in pruritus of various origins,[5] as well as in patients with cholestatic pruritus.[6,7] In uraemic pruritus, conflicting results have been reported;[8,9] a subsequent study[10] suggested that naltrexone might be of benefit in selected patients.

1. Kjellberg F, Tramèr MR. Pharmacological control of opioid-induced pruritus: a quantitative systematic review of randomized trials. *Eur J Anaesthesiol* 2001; **18:** 346–57.
2. Monroe EW. Efficacy and safety of nalmefene in patients with severe pruritus caused by chronic urticaria and atopic dermatitis. *J Am Acad Dermatol* 1989; **21:** 135–6.
3. Bergasa NV, *et al*. Open-label trial of oral nalmefene therapy for the pruritus of cholestasis. *Hepatology* 1998; **27:** 679–84.
4. Bergasa NV, *et al.* Effects of naloxone infusions in patients with the pruritus of cholestasis. *Ann Intern Med* 1995; **123:** 161–7.
5. Metze D, *et al.* Efficacy and safety of naltrexone, an oral opiate receptor antagonist, in the treatment of pruritus in internal and dermatological diseases. *J Am Acad Dermatol* 1999; **41:** 533–9.
6. Wolfhagen FH, *et al.* Oral naltrexone treatment for cholestatic pruritus: a double-blind, placebo-controlled study. *Gastroenterology* 1997; **113:** 1264–9.
7. Terg R, *et al.* Efficacy and safety of oral naltrexone treatment for pruritus of cholestasis, a crossover, double blind, placebo-controlled study. *J Hepatol* 2002; **37:** 717–22.
8. Peer G, *et al.* Randomised crossover trial of naltrexone in uraemic pruritus. *Lancet* 1996; **348:** 1552–4.
9. Pauli-Magnus C, *et al.* Naltrexone does not relieve uremic pruritus: results of a randomized, double-blind, placebo-controlled crossover study. *J Am Soc Nephrol* 2000; **11:** 514–9.
10. Legroux-Crespel E, *et al.* A comparative study on the effects of naltrexone and loratadine on uremic pruritus. *Dermatology* 2004; **208:** 326–30.

Preparations

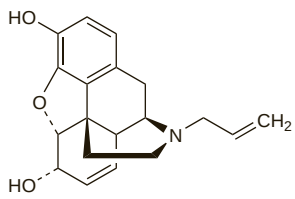
Proprietary Preparations (details are given in Part 3)
Mex.: Nocarex; ***USA:*** Revex.

Nalorphine *(BAN, rINN)*

Nalorfiini; Nalorfin; Nalorfina; Nalorphinum. (–)-(5*R*,6*S*)-9a-Allyl-4,5-epoxymorphin-7-en-3,6-diol; 17-Allyl-17-normorphine.

Налорфин

$C_{19}H_{21}NO_3$ = 311.4.
CAS — 62-67-9.
ATC — V03AB02.
ATC Vet — QV03AB02.



Nalorphine Hydrobromide *(BANM, rINNM)*

Hidrobromuro de nalorfina; Nalorphine, Bromhydrate de; Nalorphini Hydrobromidum.

Налорфина Гидробромид

$C_{19}H_{21}NO_3$,HBr = 392.3.
ATC — V03AB02.
ATC Vet — QV03AB02.

Pharmacopoeias. In *Chin.*

Nalorphine Hydrochloride *(BANM, rINNM)*

Hidrocloruro de nalorfina; Nalorphine, Chlorhydrate de; Nalorphini Hydrochloridum; Nalorphinium Chloride.

Налорфина Гидрохлорид

$C_{19}H_{21}NO_3$,HCl = 347.8.
CAS — 57-29-4.
ATC — V03AB02.
ATC Vet — QV03AB02.

Pharmacopoeias. In *US.*
USP 31 (Nalorphine Hydrochloride). Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Adverse Effects and Precautions
As for Naloxone (below). Nalorphine also has some opioid agonist properties and adverse effects such as drowsiness, respiratory depression, miosis, dysphoria, and lethargy may occur if it is given to patients who have not received opioids.

Uses and Administration
Nalorphine is an opioid antagonist with properties similar to those of naloxone (below); in addition it also possesses some agonist properties. It has been used as the hydrobromide or hydrochloride in the treatment of opioid-induced respiratory depression; it reverses severe opioid-induced respiratory depression but may exacerbate respiratory depression such as that induced by alcohol or other non-opioid central depressants.

Preparations
USP 31: Nalorphine Hydrochloride Injection.

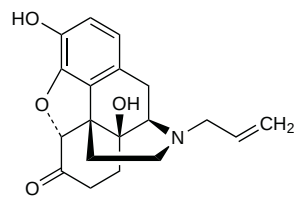
Naloxone Hydrochloride

(BANM, USAN, rINNM)

N-Allylnoroxymorphone Hydrochloride; Cloridrato de Naloxona; EN-15304; Hidrocloruro de naloxona; Nalokson Hidroklorür; Naloksonihydrokloridi; Naloksono hidrochloridas; Naloksonu chlorowodorek dwuwodny; Naloxone, Chlorhydrate de; Naloxone (chlorhydrate de) dihydraté; Naloxon-hidroklorid; Naloxon-hydrochlorid; Naloxonhydroklorid; Naloxoni Hydrochloridum; Naloxoni hydrochloridum dihydricum. 17-Allyl-6-deoxy-7,8-dihydro-14-hydroxy-6-oxo-17-normorphine hydrochloride dihydrate; (–)-(5*R*,14*S*)-9a-Allyl-4,5-epoxy-3,14-dihydroxymorphinan-6-one hydrochloride dihydrate.

Налоксона Гидрохлорид

$C_{19}H_{21}NO_4$,HCl,2H_2O = 399.9.
CAS — 465-65-6 (naloxone); 357-08-4 (anhydrous naloxone hydrochloride); 51481-60-8 (naloxone hydrochloride dihydrate).
ATC — V03AB15.
ATC Vet — QV03AB15.



(naloxone)

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*. Forms specified may be anhydrous, dihydrate, or both.
Ph. Eur. 6.2 (Naloxone Hydrochloride Dihydrate; Naloxone Hydrochloride BP 2008). It contains two molecules of water of hydration. A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; soluble in alcohol; practically insoluble in toluene. Store in airtight containers. Protect from light.
USP 31 (Naloxone Hydrochloride). It is anhydrous or contains two molecules of water of hydration. A white to slightly off-white powder. Soluble in water, in dilute acids, and in strong alkali; slightly soluble in alcohol; practically insoluble in chloroform and in ether. Its aqueous solution is acidic. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Incompatibility. Infusions of naloxone hydrochloride should not be mixed with preparations containing bisulfite, metabisulfite, long-chain or high-molecular-weight anions, or solutions with an alkaline pH.

Adverse Effects
Nausea and vomiting have occurred with naloxone. Some adverse effects may be associated with opioid withdrawal. There have been individual reports of hypotension, hypertension, cardiac arrhythmias, and pulmonary oedema, generally in patients given naloxone postoperatively. Seizures have also been reported infrequently.

◊ Hypertension,[1,2] pulmonary oedema,[3] and cardiac arrhythmias including ventricular tachycardia and fibrillation[4] have been reported after the postoperative use of naloxone, generally in patients with pre-existing heart disease undergoing cardiac surgery. However, there have also been reports in healthy patients,[5,6] including some fatalities.[5]

Hypotension, bradycardia, and precipitation of focal seizures have been reported in patients given high-dose naloxone for acute ischaemic stroke.[7]

Ventricular fibrillation has been observed in an opioid addict given naloxone to reverse the effects of diamorphine.[8] However, this patient was later shown to have hepatic cirrhosis and alcoholic cardiomyopathy and the National Poisons Information Service in London noted that it had never been informed of such a suspected adverse reaction despite being contacted in about 800 cases of opioid poisoning each year.[9] In a later report severe adverse effects were noted in 6 of 453 subjects given naloxone to reverse diamorphine intoxication.[10] The effects were: asystole (1 case), generalised convulsions (3), pulmonary oedema (1), and violent behaviour (1).

1. Tanaka GY. Hypertensive reaction to naloxone. *JAMA* 1974; **228:** 25–6.
2. Azar I, Turndorf H. Severe hypertension and multiple atrial premature contractions following naloxone administration. *Anesth Analg* 1979; **58:** 524–5.
3. Flacke JW, *et al.* Acute pulmonary edema following naloxone reversal of high-dose morphine anesthesia. *Anesthesiology* 1977; **47:** 376–8.
4. Michaelis LL, *et al.* Ventricular irritability associated with the use of naloxone hydrochloride: two case reports and laboratory assessment of the effects of the drug on cardiac excitability. *Ann Thorac Surg* 1974; **18:** 608–14.
5. Wride SRN, *et al.* A fatal case of pulmonary oedema in a healthy young male following naloxone administration. *Anaesth Intensive Care* 1989; **17:** 374–7.
6. Taff RH. Pulmonary edema following naloxone administration in a patient without heart disease. *Anesthesiology* 1983; **59:** 576–7.
7. Barsan WG, *et al.* Use of high dose naloxone in acute stroke: possible side effects. *Crit Care Med* 1989; **17:** 762–7.
8. Cuss FM, *et al.* Cardiac arrest after reversal of effects of opiates with naloxone. *BMJ* 1984; **288:** 363–4.
9. Barret L, *et al.* Cardiac arrest following naloxone. *BMJ* 1984; **288:** 936.
10. Osterwalder JJ. Naloxone—for intoxications with intravenous heroin and heroin mixtures—harmless or hazardous? A prospective clinical study. *Clin Toxicol* 1996; **34:** 409–16.

Precautions
Naloxone should be used with caution in patients physically dependent on opioids, or who have received large doses of opioids, as an acute withdrawal syndrome may be precipitated (see Dependence and With-

drawal under Opioid Analgesics, p.101). Naloxone crosses the placenta and a withdrawal syndrome may be precipitated in neonates of opioid-dependent mothers.

Caution is required in patients with cardiac disease or those receiving cardiotoxic drugs.

The duration of action of some opioids exceeds that of naloxone; patients should therefore be carefully observed after administration in case of relapse.

Pharmacokinetics

Naloxone is absorbed from the gastrointestinal tract but it is subject to considerable first-pass metabolism. It is metabolised in the liver, mainly by glucuronide conjugation, and excreted in the urine. It has a plasma half-life of about 1 hour after parenteral administration. Naloxone crosses the placenta.

Pregnancy and the neonate. A study in 30 mothers given a single intravenous dose of naloxone during the second stage of labour, indicated that naloxone rapidly crossed the placental barrier so that some therapeutic effect might be anticipated in most neonates.[1] Placental transfer in 7 further mothers given naloxone intramuscularly was considered to be too variable for therapeutic purposes.

In 12 neonates given naloxone hydrochloride 35 or 70 micrograms intravenously via the umbilical vein, the mean plasma half-life was 3.53 or 2.65 hours respectively.[2] These half-lives were 2 to 3 times longer than those reported for adults, possibly due to a diminished ability of the newborn to metabolise drugs by conjugation with glucuronic acid. Mean peak plasma concentrations of 8.2 nanograms/mL or 13.7 nanograms/mL in those given 35 or 70 micrograms respectively, were reached within 40 minutes but this time was very variable, and in 5 neonates peak concentrations were reached within 5 minutes. Naloxone hydrochloride 200 micrograms intramuscularly in 17 further neonates produced peak concentrations of 7.4 to 34.6 nanograms/mL at 0.5 to 2 hours.

1. Hibbard BM, *et al*. Placental transfer of naloxone. *Br J Anaesth* 1986; **58:** 45–8.
2. Moreland TA, *et al*. Naloxone pharmacokinetics in the newborn. *Br J Clin Pharmacol* 1980; **9:** 609–12.

Uses and Administration

Naloxone is a specific opioid antagonist that acts competitively at opioid receptors. It is an effective antagonist of opioids that possess agonist or mixed agonist-antagonist activity although larger doses may be needed for compounds with the latter activity. It is used to reverse opioid central depression, including respiratory depression, induced by natural or synthetic opioids in the treatment of known or suspected opioid overdosage, postoperatively after the use of opioids during surgery, and in neonates when opioid analgesics have been given to the mother during labour.

Naloxone hydrochloride is usually given intravenously for a rapid onset of action, which occurs within 2 minutes. The onset of action is only slightly less rapid when it is given intramuscularly or subcutaneously. Other routes, including the endotracheal, have also been used. The duration of action of naloxone is dependent on the dose and route; it is usually reported to be several hours, but may be much shorter, in the region of 1 hour or less.

In the treatment of known or suspected **opioid overdosage**, the initial dose of naloxone hydrochloride is 0.4 to 2 mg given intravenously and repeated if necessary at intervals of 2 to 3 minutes. If no response has been seen after a total dose of 10 mg then the diagnosis of overdosage with drugs other than opioids should be considered. If the patient is suspected of being physically dependent on opioids the dose may be reduced to 100 to 200 micrograms to avoid precipitating withdrawal symptoms. If the intravenous route is not feasible the intramuscular or subcutaneous route can be used.

Naloxone hydrochloride may also be used **postoperatively** to reverse central depression resulting from the use of opioids during surgery. For adults, a dose of 100 to 200 micrograms may be given intravenously at intervals of 2 to 3 minutes, titrated for each patient in order to obtain an optimum respiratory response while maintaining adequate analgesia.

All patients receiving naloxone should be closely observed as the duration of action of many opioids exceeds that of naloxone and repeated doses may be required. Alternatively, to sustain opioid antagonism, an intravenous infusion may be used. Dosage regimens have not been well established, and the rate of infusion must be titrated according to the patient's response. Some have recommended an infusion of 60% of the initial dose per hour, diluted to a concentration of 200 micrograms/mL in glucose. Others have suggested an initial intravenous loading dose of 400 micrograms, followed by a continuous infusion at an initial rate of 400 micrograms/hour. Alternatively, an intravenous loading dose of 5 micrograms/kg has been suggested, followed by a continuous infusion of 2.5 micrograms/kg per hour.

For doses in children, see Administration in Children, below.

Some opioid analgesics have been formulated with naloxone hydrochloride to reduce their potential for parenteral abuse, or as a substitution treatment for opioid dependence. Naloxone hydrochloride has also been used cautiously in small doses to diagnose opioid dependence by precipitating the withdrawal syndrome (see below and under Naltrexone, p.1455).

Administration in children. In the treatment of known or suspected **opioid overdosage** in children, licensed product information recommends an initial dose of naloxone hydrochloride of 10 micrograms/kg intravenously, followed, if necessary, by a larger dose of 100 micrograms/kg. If the intravenous route is not feasible the intramuscular or subcutaneous route can be used.

For **acute respiratory depression induced by opioids** the Committee on Drugs of the American Academy of Pediatrics has recommended a dose for naloxone of 100 micrograms/kg by the intramuscular, intravenous, or intratracheal routes for neonates, including premature infants, to the age of 5 years or 20 kg bodyweight; absorption may be erratic after intramuscular use. They advocated that children over 5 years or 20 kg should be given a *minimum* of 2 mg. These doses may be repeated as necessary to maintain opioid reversal.[1,2] The Committee noted that these higher dose recommendations were based partly on the concern that 10 micrograms/kg might not provide optimal opiate reversal in some infants, and that it was felt that the higher doses posed no increased risk.[3] The American Heart Association guidelines for paediatric advanced life support gave the same doses as the Committee for children to the age of 5 years or 20 kg bodyweight, but stated that those aged over 5 years or 20 kg be given a dose of 2 mg, without specifying this as a minimum.[4] The use of injections containing 20 micrograms/mL of naloxone hydrochloride is no longer recommended because of the fluid load involved at these doses, especially in small neonates.[1] It has been noted that specialists differ in their dosage of naloxone;[5] a study in the USA found that paediatric intensive care and emergency medicine physicians tended to use 100 micrograms/kg up to a *maximum* initial dose of 2 mg.

In contrast, anaesthesiologists have tended to use initial doses of 10 to 20 micrograms naloxone, regardless of body-weight;[5] the American Academy of Pediatrics states that lower initial doses of 10 micrograms/kg may be considered for other clinical situations such as **respiratory depression during pain management**.[2] Licensed product information states that for **postoperative use**, initial doses of 5 to 10 micrograms may be given intravenously at 2 to 3 minute intervals until the desired response is obtained.

Opioid-induced depression in **neonates** resulting from the use of opioid analgesics in the mother during labour may be reversed by giving naloxone hydrochloride 10 micrograms/kg to the infant by intravenous, intramuscular, or subcutaneous injection, repeated at intervals of 2 to 3 minutes if necessary. Alternatively, a single intramuscular dose of about 60 micrograms/kg may be given at birth for a more prolonged action. Naloxone should be given with caution to the infants of opioid dependent mothers since withdrawal symptoms can result.

1. American Academy of Pediatrics. Emergency drug doses for infants and children and naloxone use in newborns: clarification. *Pediatrics* 1989; **83:** 803.
2. Committee on Drugs. Drugs for pediatric emergencies. Abstract: *Pediatrics* 1998; **101:** e13. Full version: http://pediatrics.aappublications.org/cgi/reprint/101/1/e13.pdf (accessed 30/06/06)
3. American Academy of Pediatrics. Naloxone dosage and route of administration for infants and children: addendum to emergency drug doses for infants and children. *Pediatrics* 1990; **86:** 484–5.
4. American Heart Association. 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 12: Pediatric Advanced Life Support. *Circulation* 2005; **112** (suppl): IV-167–IV-187. Also available at: http://circ.ahajournals.org/cgi/reprint/112/24_suppl/IV-1.pdf (accessed 05/02/08)
5. Hasan RA, *et al.* Cardiorespiratory effects of naloxone in children. *Ann Pharmacother* 2003; **37:** 1587–92.

Eating disorders. Endogenous opioids may have a role in the pathophysiology of eating disorders,[1] thus opioid antagonists such as naloxone and naltrexone have been tried in their management. However, their role appears to be limited and they do not form part of the usual management of these conditions.

1. de Zwaan M, Mitchell JE. Opiate antagonists and eating behavior in humans: a review. *J Clin Pharmacol* 1992; **32**; 1060–72.

Non-opioid overdosage. Naloxone antagonises the action of exogenous and endogenous opioids. This may explain the varying responses reported to naloxone used in the treatment of overdosage with non-opioids, some of which may modulate endogenous opioids.

Benefit has been reported[1] with naloxone in valproate overdosage, although the evidence is based on case reports. There have also been case reports suggesting benefit in overdosage with camylofin,[2] chlorpromazine,[3] and ibuprofen.[4] A study[5] with midazolam in healthy subjects found that naloxone did not reverse respiratory depression, although there had been earlier reports of benefit in coma due to benzodiazepines.

Naloxone has been used for clonidine intoxication, but retrospective reviews[6,7] have concluded that responses are inconsistent, and there have been reports of hypertension. A lack of response has also been reported[8] in brimonidine overdosage. There has been a report[9] of the successful use of naloxone after captopril overdosage.

Naloxone may also be of benefit in overdosage with drugs that are structurally related to opioids, including apomorphine,[10] dextromethorphan,[11] and loperamide.[12]

1. Roberge RJ, Francis EH. Use of naloxone in valproic acid overdose: case report and review. *J Emerg Med* 2002; **22:** 67–70.
2. Schvartsman S, *et al.* Camylofin intoxication reversed by naloxone. *Lancet* 1988; **ii:** 1246.
3. Chandavasu O, Chatkupt S. Central nervous system depression from chlorpromazine poisoning: successful treatment with naloxone. *J Pediatr* 1985; **106:** 515–6.
4. Easley RB, Altemeier WA. Central nervous system manifestations of an ibuprofen overdose reversed by naloxone. *Pediatr Emerg Care* 2000; **16:** 39–41.
5. Forster A, *et al.* Respiratory depressant effects of different doses of midazolam and lack of reversal with naloxone—a double-blind randomized study. *Anesth Analg* 1983; **62:** 920–4.
6. Fiser DH, *et al.* Critical care for clonidine poisoning in toddlers. *Crit Care Med* 1990; **18:** 1124–8.
7. Wiley JF, *et al.* Clonidine poisoning in young children. *J Pediatr* 1990; **116:** 654–8.
8. Sztajnbok J. Failure of naloxone to reverse brimonidine-induced coma in an infant. *J Pediatr* 2002; **140:** 485–6.
9. Varon J, Duncan SR. Naloxone reversal of hypotension due to captopril overdose. *Ann Emerg Med* 1991; **20:** 1125–7.
10. Bonuccelli U, *et al.* Naloxone partly counteracts apomorphine side effects. *Clin Neuropharmacol* 1991; **14:** 442–9.
11. Schneider SM, *et al.* Dextromethorphan poisoning reversed by naloxone. *Am J Emerg Med* 1991; **9:** 237–8.
12. Friedli G, Haenggeli C-A. Loperamide overdose managed by naloxone. *Lancet* 1980; **i:** 1413.

Pruritus. For reference to the use of opioid antagonists, including naloxone, in the management of pruritus, see under Nalmefene, p.1453

Reversal of opioid effects. Naloxone is used postoperatively to reverse central depression resulting from the use of opioids during surgery. However, the beneficial analgesic effects of the opioids may also be reversed, and the increasing use of short-acting intravenous opioid analgesics should reduce the need for its use.

In patients receiving longer-term opioids, naloxone has been reported to alleviate some of their adverse effects without loss of therapeutic efficacy. Naloxone reversed respiratory depression in a patient given intrathecal morphine,[1] and urinary retention in 3 patients after epidural morphine,[2] without reversing analgesia. However, a study[3] in patients receiving extradural fentanyl found that naloxone failed to relieve urinary retention whereas pain scores rapidly increased. Naloxone given intravenously has been shown to reverse the delay in gastric emptying induced by opioid analgesics in healthy subjects[4] and in women during labour.[5] Continuous intravenous infusion of naloxone reduced the incidence of adverse effects in patients receiving morphine by patient-controlled analgesia for postoperative pain.[6] Pain control was not compromised and the lower dose of naloxone used (250 nanograms/kg hourly as opposed to 1 microgram/kg hourly) appeared to have an opioid-sparing effect. In patients receiving long-term opioids, oral naloxone in a daily dose equivalent to 20 to 40% of the daily opioid dose relieved opioid-induced constipation without compromising analgesic control.[7,8] Doses equivalent to 10% or less of the opioid dose were ineffective.[9] However, other studies[10] have found adverse effects even at low doses of naloxone, and the optimum dose remains unclear. Methylnaltrexone, a related opioid antagonist is also used for the reversal of opioid-induced constipation (see p.1747).

1. Jones RDM, Jones JG. Intrathecal morphine: naloxone reverses respiratory depression but not analgesia. *BMJ* 1980; **281:** 645–6.
2. Rawal N, *et al.* Naloxone reversal of urinary retention after epidural morphine. *Lancet* 1981; **ii:** 1411.

3. Wang J, *et al.* Low-dose naloxone in the treatment of urinary retention during extradural fentanyl causes excessive reversal of analgesia. *Br J Anaesth* 1998; **80:** 565–6.
4. Nimmo WS, *et al.* Reversal of narcotic-induced delay in gastric emptying and paracetamol absorption by naloxone. *BMJ* 1979; **2:** 1189.
5. Frame WT, *et al.* Effect of naloxone on gastric emptying during labour. *Br J Anaesth* 1984; **56:** 263–5.
6. Gan TJ, *et al.* Opioid-sparing effects of a low-dose infusion of naloxone in patient-administered morphine sulfate. *Anesthesiology* 1997; **87:** 1075–81.
7. Sykes NP. Oral naloxone in opioid-associated constipation. *Lancet* 1991; **337:** 1475.
8. Sykes NP. Oral naloxone in opioid-associated constipation. *Lancet* 1991; **338:** 582.
9. Robinson BA, *et al.* Oral naloxone in opioid-associated constipation. *Lancet* 1991; **338:** 581–2.
10. Thomas MC, Erstad BL. Safety of enteral naloxone and i.v. neostigmine when used to relieve constipation. *Am J Health-Syst Pharm* 2003; **60:** 1264–7.

DIAGNOSTIC USE. Naloxone is used to reverse opioid effects in the diagnosis of opioid overdose, although some workers have recommended that it should only be used in patients with clinical signs of opioid overdose.[1]

Naloxone has also been used in the diagnosis of opioid dependence. It has been given intravenously to precipitate withdrawal symptoms, but methods that do not induce acute withdrawal have also been investigated. Pupillary dilatation in response to topical naloxone solution (naloxone eye drops) has been suggested as a useful method, but varying results have been reported depending on the strength of the solution used. A study[2] using naloxone hydrochloride solution 1 mg/mL distinguished patients with a physical dependence from non-dependent patients who had received opioids on a single occasion as pre-operative medication, but this response was not confirmed in another study[3] using naloxone 400 micrograms/mL solution. Another study[4] reported that a 2 mg/mL solution of naloxone hydrochloride gave useful results in an outpatient setting. However, there has been a report[5] of withdrawal syndrome and pupillary dilatation in 4 opioid dependent subjects after instillation of naloxone solution 40 mg/mL.

1. Hoffman JR, *et al.* The empiric use of naloxone in patients with altered mental status: a reappraisal. *Ann Emerg Med* 1991; **20:** 246–52.
2. Creighton FJ, Ghodse AH. Naloxone applied to conjunctiva as a test for physical opiate dependence. *Lancet* 1989; **i:** 748–50.
3. Loimer N, *et al.* Conjunctival naloxone is no decision aid in opioid addiction. *Lancet* 1990; **335:** 1107–8.
4. Ghodse AH, *et al.* Evaluation of the opioid addiction test in an out-patient drug dependency unit. *Br J Psychiatry* 1999; **175:** 158–62.
5. Sanchez-Ramos JR, Senay EC. Ophthalmic naloxone elicits abstinence in opioid-dependent subjects. *Br J Addict* 1987; **82:** 313–15.

OPIOID OVERDOSAGE. Naloxone is usually given intravenously in opioid overdosage but may also be given intramuscularly if intravenous access is not available. Alternative routes have also been tried; a study[1] using intranasal naloxone found that it was effective for prehospital management of suspected opioid overdosage, although response was slower than with intramuscular injection.

1. Kelly A-M, *et al.* Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. *Med J Aust* 2005; **182:** 24–7.

Shock. Endogenous opioids may have a role in the pathophysiology of shock but studies investigating naloxone for the treatment of shock have produced contradictory results. A systematic review[1] concluded that naloxone does increase blood pressure in various forms of shock, but no significant effect on mortality was shown. US licensed product information has noted that the optimal dose and duration of therapy with naloxone have not been established, and that caution should be exercised before its use, particularly in patients with underlying pain or who have previously received opioids and may have developed opioid tolerance.

1. Boeuf B, *et al.* Naloxone for shock. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 04/10/05).

Preparations

BP 2008: Naloxone Injection; Neonatal Naloxone Injection;
USP 31: Naloxone Hydrochloride Injection; Pentazocine and Naloxone Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Antiopiaz; Grayxona; Narcanti; Narxona; ***Austral.:*** Narcan; ***Austria:*** Narcanti; ***Belg.:*** Narcan†; ***Braz.:*** Narcan; ***Canad.:*** Narcan†; ***Cz.:*** Intrenon; Narcanti†; ***Denm.:*** Narcanti; ***Fin.:*** Narcanti; ***Fr.:*** Nalone†; Narcan†; ***Ger.:*** Naloselect†; Narcanti; ***Gr.:*** Narcan; ***Hong Kong:*** Mapin; Narcan†; ***Hung.:*** Narcanti†; ***India:*** Narcotan; ***Indon.:*** Nokoba; ***Irl.:*** Narcan; ***Israel:*** Narcan†; ***Ital.:*** Narcan; ***Malaysia:*** Mapin; Narcan†; ***Mex.:*** Narcanti†; ***Norw.:*** Narcanti; ***NZ:*** Narcan; ***Port.:*** Narcan†; Naxan; Naxolan; ***Rus.:*** Naloxon (Налоксон); ***S.Afr.:*** Narcan†; Zynox; ***Singapore:*** Narcan†; ***Swed.:*** Narcanti; ***Switz.:*** Narcan; ***Thai.:*** Narcan; ***UK:*** Narcan†; ***USA:*** Narcan†; ***Venez.:*** Narcan; Oxogina.

Used as an adjunct in: ***Belg.:*** Tinalox; Valtran; ***Cz.:*** Suboxone; ***Fr.:*** Suboxone; ***Ger.:*** Andolor; Celldolor; Findol N†; Gruntin Tropfen†; Nalidin; Tili Comp; Tili-Puren; Tili†; Tilicomp; Tilidalor†; Tilidin comp; Tilidin N; Tilidin plus; Tilidin-saar; Tilidura; Tiligetic†; Tilimerck†; Tilnalox; Valoron N; ***Israel:*** Talwin NX†; ***Malaysia:*** Suboxone; ***NZ:*** Suboxone; ***Port.:*** Suboxone; ***UK:*** Suboxone; ***USA:*** Suboxone; Talwin NX.

Naltrexone *(BAN, USAN, rINN)*

Naltrexona; Naltrexonum. (5*R*)-9a-Cyclopropylmethyl-3,14-dihydroxy-4,5-epoxymorphinan-6-one; 17-(Cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6-one.

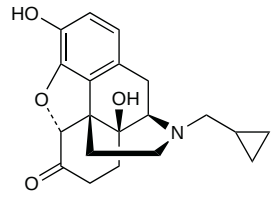
Налтрексон

$C_{20}H_{23}NO_4$ = 341.4.

CAS — 16590-41-3.

ATC — N07BB04.

ATC Vet — QN07BB04; QV03AB30.



Naltrexone Hydrochloride *(BANM, rINNM)*

EN-1639A; Hidrocloruro de naltrexona; Naltreksonihydroklorid; Naltreksono hidrochloridas; Naltrexone, chlorhydrate de; Naltrexon-hydrochlorid; Naltrexonhydroklorid; Naltrexoni hydrochloridum.

Налтрексона Гидрохлорид

$C_{20}H_{23}NO_4$,HCl = 377.9.

CAS — 16676-29-2.

ATC — N07BB04.

ATC Vet — QN07BB04.

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

Ph. Eur. 6.2 (Naltrexone Hydrochloride). A white or almost white, very hygroscopic, powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in dichloromethane. Store in airtight containers. Protect from light.

USP 31 (Naltrexone Hydrochloride). Store in airtight containers.

Adverse Effects

Difficulty in sleeping, loss of energy, anxiety, dysphoria, abdominal pain, nausea, vomiting, reduction in appetite, joint and muscle pain, and headache may occur with naltrexone. Dizziness, constipation, diarrhoea, skin rashes, and reduced potency and ejaculatory difficulties have also been reported. Some adverse effects may be associated with opioid withdrawal. Thrombocytopenic purpura has occurred rarely. High doses may cause hepatocellular injury. Injection site reactions, including abscesses and tissue necrosis, have been reported with use of the intramuscular preparation.

Effects on the liver. Increased liver enzyme values were reported in 6 of 40 obese patients given naltrexone 50 or 100 mg daily for 8 weeks.[1] Five of the 6 patients had minimally abnormal liver function before naltrexone was given and liver function tests returned to baseline values or better on stopping naltrexone.

Raised transaminase levels were noted in 5 of 26 obese patients after 3 weeks of treatment with naltrexone 300 mg daily; transaminase activity returned to normal when treatment was stopped.[2]

1. Atkinson RL, *et al.* Effects of long-term therapy with naltrexone on body weight in obesity. *Clin Pharmacol Ther* 1985; **38:** 419–22.
2. Mitchell JE. Naltrexone and hepatotoxicity. *Lancet* 1986; **i:** 1215.

Effects on the muscles. Asymptomatic rhabdomyolysis has been reported[1] in a patient receiving naltrexone; the condition resolved when naltrexone was withdrawn.

1. Zaim S, *et al.* Rhabdomyolysis associated with naltrexone. *Ann Pharmacother* 1999; **33:** 312–3.

Precautions

Naltrexone should be avoided in patients receiving opioids therapeutically, or in those misusing them, as an acute withdrawal syndrome may be precipitated (see Dependence and Withdrawal under Opioid Analgesics, p.101). Withdrawal symptoms may develop within 5 minutes and last up to 48 hours. Naltrexone should be discontinued at least 48 hours before elective surgery involving opioid analgesia. For further precautions when using naltrexone as an adjunct in the treatment of opioid dependence, see Uses and Administration, below.

When analgesia is required, larger doses than usual of opioids will be needed and there is an increased risk of respiratory depression and other adverse effects.

Naltrexone should be used with caution in patients with hepatic impairment and is contra-indicated in patients with acute hepatitis or hepatic failure. Regular monitoring of hepatic function has been recommended. Naltrexone should be given with caution to patients with renal impairment.

Pharmacokinetics

Naltrexone is well absorbed from the gastrointestinal tract but is subject to considerable first-pass metabolism and may undergo enterohepatic recycling. It is extensively metabolised in the liver and the major metabolite, 6-β-naltrexol, may also possess weak opioid antagonist activity. Maximum plasma concentrations of naltrexone and 6-β-naltrexol are achieved in about 1 hour and naltrexone is about 20% bound to plasma proteins at therapeutic doses. The elimination half-life of naltrexone is approximately 4 hours and that of 6-β-naltrexol about 13 hours. Naltrexone and its metabolites are excreted mainly in the urine. Less than 1% of an oral dose of naltrexone is excreted unchanged.

Hepatic impairment. A study[1] in 11 patients with hepatic cirrhosis found that the systemic availability of naltrexone was significantly increased, particularly in those with decompensated disease.

1. Bertolotti M, *et al.* Effect of liver cirrhosis on the systemic availability of naltrexone in humans. *J Hepatol* 1997; **27:** 505–511.

Uses and Administration

Naltrexone is a specific opioid antagonist with actions similar to those of naloxone (p.1454); however, it is more potent than naloxone and has a longer duration of action. It is used in the management of opioid dependence and alcohol dependence, and has also been investigated in other addictive disorders.

Naltrexone is used as the hydrochloride as an aid to maintaining abstinence after opioid withdrawal in detoxified, formerly **opioid-dependent** patients. Naltrexone treatment should not be started until the patient has been detoxified and abstinent from opioids for at least 7 to 10 days because of the risk of acute withdrawal; abstinence should be verified by analysis of the patient's urine. A *naloxone challenge test* should then be performed to confirm the absence of opioid dependence, as follows: naloxone hydrochloride 200 micrograms is given intravenously and the patient observed for 30 seconds for evidence of withdrawal symptoms; if none occur, a further dose of 600 micrograms is given and the patient observed for 30 minutes. A confirmatory rechallenge with naloxone hydrochloride 1.6 mg intravenously may be considered if results are ambiguous. Sources in the USA suggest a naloxone challenge test with a single dose of 800 micrograms given subcutaneously as an alternative to the intravenous route.

Once a negative naloxone challenge test has been obtained, naltrexone hydrochloride is given orally to maintain abstinence. Treatment may be initiated with a dose of 25 mg. If no signs of opioid withdrawal occur subsequent doses may be increased to 50 mg daily. The usual maintenance dose of naltrexone hydrochloride is 350 mg weekly given as 50 mg daily, but the dosing interval may be lengthened to improve compliance; for example, doses of 100 mg on Monday and Wednesday and 150 mg on Friday may be effective, and various other intermittent dosage regimens have been used. Patients should be carefully counselled and warned that attempts to overcome the opioid blockade with large doses of opioids could result in fatal opioid intoxication.

Naltrexone hydrochloride is also used as an adjunct in the management of **alcohol dependence** at a recommended oral dose of 50 mg daily. Alternatively, naltrexone (as the base) may be given as a modified-release intramuscular injection in a dose of 380 mg once every 4 weeks.