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.

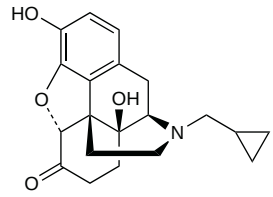
Налтрексон

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