Butorphanol Tartrate *(BANM, USAN, rINNM)*

levo-BC-2627 (butorphanol); Butorfanolitartraatti; Butorfanoltartrat; Butorphanol, Tartrate de; Butorphanoli Tartras; Tartrato de butorfanol. (–)-17-(Cyclobutylmethyl)morphinan-3,14-diol hydrogen tartrate.

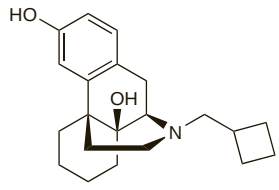
Буторфанола Тартрат

$C_{21}H_{29}NO_2.C_4H_6O_6$ = 477.5.

CAS — 42408-82-2 (butorphanol); 58786-99-5 (butorphanol tartrate).

ATC — N02AF01.

ATC Vet — QN02AF01.



(butorphanol)

Pharmacopoeias. In *US.*

USP 31 (Butorphanol Tartrate). A white powder. Its solutions are slightly acidic. Sparingly soluble in water; insoluble in alcohol, in chloroform, in ether, in ethyl acetate, and in hexane; slightly soluble in methyl alcohol; soluble in dilute acids. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°.

Dependence and Withdrawal

As for Opioid Analgesics, p.101.

Butorphanol may have a lower potential for producing dependence than pure agonists such as morphine. However, it has been subject to abuse (see under Precautions, below). Abruptly stopping chronic butorphanol has produced a less severe withdrawal syndrome than with morphine.

Adverse Effects and Treatment

As for Opioid Analgesics in general, p.102, and for Pentazocine, p.112.

Headache, and feelings of floating may also occur. Hallucinations and other psychotomimetic effects are rare and have been reported less frequently than with pentazocine. In addition insomnia and nasal congestion may occur frequently when butorphanol is given intranasally.

Because butorphanol has opioid agonist and antagonist activity, naloxone is the recommended antagonist for the treatment of overdosage.

Effects on the respiratory system. Butorphanol 2 mg produces a similar degree of respiratory depression to morphine 10 mg, but a ceiling effect is apparent with higher doses of butorphanol.[1] It has been reported to be a less potent respiratory depressant than fentanyl,[2] but more potent than nalbuphine.[3]

1. Nagashima H, *et al.* Respiratory and circulatory effects of intravenous butorphanol and morphine. *Clin Pharmacol Ther* 1976; **19:** 738–45.
2. Dryden GE. Voluntary respiratory effects of butorphanol and fentanyl following barbiturate induction: a double-blind study. *J Clin Pharmacol* 1986; **26:** 203–7.
3. Zucker JR, *et al.* Respiratory effects of nalbuphine and butorphanol in anesthetized patients. *Anesth Analg* 1987; **66:** 879–81.

Precautions

As for Opioid Analgesics in general, p.103.

Although cardiovascular effects may be less than with pentazocine, butorphanol should generally be avoided after myocardial infarction.

Butorphanol may precipitate withdrawal symptoms if given to patients physically dependent on opioids. The dosage regimen of butorphanol may need to be adjusted in the elderly and in patients with hepatic or renal impairment.

Abuse. A WHO expert committee considered in 2006 that the likelihood of butorphanol abuse was low and was not great enough to warrant international control.[1] Abuse had been reported infrequently and only in a few countries. The committee also commented that, pharmacologically, intranasal preparations of butorphanol do not appear to differ in their abuse potential from parenteral preparations; however, other factors such as availability and usage patterns may affect the likelihood of abuse. Indeed, US licensed product information states that there have been more reports of abuse with intranasal preparations than with injectable ones.

Cases of butorphanol abuse have been published[2,3] including a report of fibrous myopathy associated with chronic intramuscular abuse.

1. WHO. WHO expert committee on drug dependence: thirty-fourth report. *WHO Tech Rep Ser 942* 2006. Also available at: http://libdoc.who.int/trs/WHO_TRS_942_eng.pdf (accessed 26/06/08)
2. Wagner JM, Cohen S. Fibrous myopathy from butorphanol injections. *J Rheumatol* 1991; **18:** 1934–5.
3. Loder E. Post-marketing experience with an opioid nasal spray for migraine: lessons for the future. *Cephalalgia* 2006; **26:** 89–97.

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

In a study[2] of 12 women, butorphanol was detected in breast milk after both intramuscular and oral doses. However, the milk-to-plasma ratio after a 2-mg intramuscular dose (0.7) was significantly less than that after an 8-mg oral dose (1.9). Although the mothers were not breast feeding at the time of the study, the authors concluded that the potential for any adverse effects on nursing infants after maternal butorphanol use would be minimal.

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. Pittman KA, *et al.* Human perinatal distribution of butorphanol. *Am J Obstet Gynecol* 1980; **138:** 797–800.

Pregnancy. Two instances of sinusoidal fetal heart rate pattern were noted out of 188 consecutive cases of butorphanol use in active-phase labour.[1] Visual hallucinations and paranoid delusions developed in a woman on receiving a 1-mg intravenous injection of butorphanol early in labour; the psychosis had resolved 40 hours after the injection and was not noted on follow-up 2 weeks later.[2]

1. Welt SI. Sinusoidal fetal heart rate and butorphanol administration. *Am J Obstet Gynecol* 1985; **152:** 362–3.
2. Davis A, *et al.* Acute psychosis associated with butorphanol. *J Neuropsychiatr Clin Neurosci* 1998; **10:** 236–7.

Interactions

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

Antimigraine drugs. No pharmacokinetic interactions were reported when butorphanol nasal spray and subcutaneous *sumatriptan* were used together within a minute of each other in healthy subjects.[1] However, another study[2] in healthy subjects found that the AUC and maximum plasma concentration of intranasal butorphanol were reduced by about 29% and 38%, respectively when given 1 minute after intranasal sumatriptan. No such effect was noted when administration was separated by 30 minutes. It was suggested that sumatriptan may reduce butorphanol absorption by inducing transient nasal vasoconstriction.

1. Srinivas NR, *et al.* Lack of pharmacokinetic interaction between butorphanol tartrate nasal spray and sumatriptan succinate. *J Clin Pharmacol* 1995; **35:** 432–7.
2. Vachharajani NN, *et al.* A pharmacokinetic interaction study between butorphanol and sumatriptan nasal sprays in healthy subjects: importance of the timing of butorphanol administration. *Cephalalgia* 2002; **22:** 282–7.

Pharmacokinetics

Butorphanol is absorbed from the gastrointestinal tract but it undergoes extensive first-pass metabolism. Peak plasma concentrations occur 0.5 to 1 hour after intramuscular and intranasal doses and 1 to 1.5 hours after oral doses. Butorphanol has a plasma elimination half-life of about 4.5 hours. About 80% is bound to plasma proteins.

Butorphanol is extensively metabolised in the liver through hydroxylation, *N*-dealkylation, and conjugation, only 5% being excreted unchanged. Excretion is mainly in the urine; about 15% of a parenteral dose is excreted in the bile. It crosses the placenta and is distributed into breast milk.

Administration. *INTRANASAL ROUTE.* References.

1. Davis GA, *et al.* Pharmacokinetics of butorphanol tartrate administered from single-dose intranasal sprayer. *Am J Health-Syst Pharm* 2004; **61:** 261–6.
2. Davis GA, *et al.* Bioavailability of intranasal butorphanol administered from a single-dose sprayer. *Am J Health-Syst Pharm* 2005; **62:** 48–53.
3. Wermeling DP, *et al.* Pharmacokinetics, bioequivalence, and spray weight reproducibility of intranasal butorphanol after administration with 2 different nasal spray pumps. *J Clin Pharmacol* 2005; **45:** 969–73.

Uses and Administration

Butorphanol tartrate, a phenanthrene derivative, is an opioid analgesic (p.104) with opioid agonist and antagonist properties; it is pharmacologically similar to pentazocine (p.113). Butorphanol is used for the relief of moderate to severe pain, including the pain of labour, and as an adjunct to anaesthesia. Onset of analgesia occurs within 15 minutes of intramuscular injection or an intranasal dose and may last for 3 to 4 hours after parenteral doses or for 4 to 5 hours after intranasal doses.

For the relief of moderate to severe **pain**, butorphanol tartrate is given in doses of 1 to 4 mg (usually 2 mg) by intramuscular injection or in doses of 0.5 to 2 mg (usually 1 mg) by intravenous injection every 3 to 4 hours. It may also be given as a nasal spray, in usual doses of 1 mg (1 spray in 1 nostril), repeated after 60 to 90 minutes, if necessary. This sequence may be repeated after 3 to 4 hours as needed. An initial dose of 2 mg (1 spray in each nostril) may be given for severe pain, but should not be repeated until 3 to 4 hours later.

In *obstetric analgesia* 1 to 2 mg may be given by intramuscular or intravenous injection during early labour in women at term. This dose may be repeated after 4 hours if necessary but an alternative analgesic should be used if delivery is expected within 4 hours.

In **anaesthesia**, 2 mg may be given intramuscularly for premedication 60 to 90 minutes before surgery. For use in balanced anaesthesia, a usual dose is 2 mg given intravenously shortly before induction and/or 0.5 to 1 mg given intravenously in increments during anaesthesia. The total dose needed varies but most patients require 4 to 12.5 mg.

Dosage adjustment may be needed in the elderly. When given by injection the initial dose of butorphanol for pain should be half the usual initial adult dose. Subsequent doses should be determined by the patient's response; a dosage interval of at least 6 hours has been recommended. For nasal use the initial dose should be limited to 1 mg followed by 1 mg after 90 to 120 minutes if necessary; subsequent doses if required should generally be given at intervals of not less than 6 hours. Similar recommendations have also been made for patients with hepatic or renal impairment, see below.

◊ References.

1. Atkinson BD, *et al.* Double-blind comparison of intravenous butorphanol (Stadol) and fentanyl (Sublimaze) for analgesia during labor. *Am J Obstet Gynecol* 1994; **171:** 993–8.
2. Gillis JC, *et al.* Transnasal butorphanol: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute pain management. *Drugs* 1995; **50:** 157–75.
3. Commiskey S, *et al.* Butorphanol: effects of a prototypical agonist-antagonist analgesic on κ-opioid receptors. *J Pharmacol Sci* 2005; **98:** 109–16.

Administration in hepatic or renal impairment. The dosage of butorphanol may need to be adjusted in patients with hepatic or renal impairment. When given by injection the initial dose for pain should be half the usual initial adult dose (see above). Subsequent doses should be determined by the patient's response; a dosage interval of at least 6 hours has been recommended. For nasal use the initial dose should be limited to 1 mg followed by 1 mg after 90 to 120 minutes if necessary; subsequent doses if required should generally be given at intervals of not less than 6 hours.

Headache. Butorphanol has been advocated for use as a nasal spray in the treatment of migraine, but there have been problems with abuse and dependence (see above) and its place in therapy, if any, still remains to be established. See also Antimigraine Drugs, under Interactions, above.

References.

1. Freitag FG. The acute treatment of migraine with transnasal butorphanol (TNB). *Headache Q* 1993; **4** (suppl 3): 22–8.
2. Hoffert MJ, *et al.* Transnasal butorphanol in the treatment of acute migraine. *Headache* 1995; **35:** 65–9.
3. Melanson SW, *et al.* Transnasal butorphanol in the emergency department management of migraine headache. *Am J Emerg Med* 1997; **15:** 57–61.

Pruritus. Results from a small study[1] of 6 patients with severe opioid-induced pruritus unresponsive to diphenhydramine, and from a case series of 5 patients with intractable pruritus from other causes,[2] suggest that intranasal butorphanol may be an effective treatment. Doses have ranged from 1 mg every other day to 2 mg every 4 to 6 hours.

1. Dunteman E, *et al.* Transnasal butorphanol for the treatment of opioid-induced pruritus unresponsive to antihistamines. *J Pain Symptom Manage* 1996; **12:** 255–60.
2. Dawn AG, Yosipovitch G. Butorphanol for treatment of intractable pruritus. *J Am Acad Dermatol* 2006; **54:** 527–31.

Preparations

USP 31: Butorphanol Tartrate Injection; Butorphanol Tartrate Nasal Solution.

Proprietary Preparations (details are given in Part 3)
Canad.: Stadol†; ***Chile:*** Stadol†; ***Cz.:*** Beforal†; Moradol†; ***India:*** Butrum; ***Mex.:*** Stadol; ***Philipp.:*** Stadol; ***Rus.:*** Stadol (Стадол); ***USA:*** Stadol.

Capsaicin

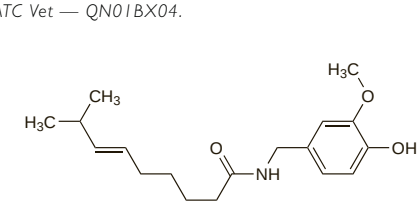
Capsaicina; Capsaicinum; Kapsaicin; Kapsaicyna; Kapsaisiini. (*E*)-8-Methyl-*N*-vanillylnon-6-enamide.

$C_{18}H_{27}NO_3$ = 305.4.

CAS — 404-86-4.

ATC — N01BX04.

ATC Vet — QN01BX04.



NOTE. Do not confuse capsaicin with capsicin, which is capsicum oleoresin (see Capsicum, p.2276).

Pharmacopoeias. In *US.*

USP 31 (Capsaicin). An off-white powder. M.p. 57° to 66°. Practically insoluble in cold water; soluble in alcohol, in chloro-