Critical review of BUTORPHANOL

1. Substance Identification

A. International Nonproprietary Name (INN): butorphanol

B. Chemical Abstract Service (CAS) Registry Number
42408-82-2 (base)
58786-99-5 (tartrate)

C. Other names: Butorfanol tartrate

D. Trade names: Alvegesic, APO-Butorphanol, Beforol, Butorject, Butomidor, Butormidor, Butorphanol, Butorphanol Tartrate, Butrum, Dolorex, Equanol, LIN-Butorphanol NS, Moradol, Morphasol, PMS-Butorphanol, Repressor-E, Spofa, Stadol, Stadol FM, Stadol NS, Stadol NS 7, Torate, Torbugesic, Torbutrol, Verstadol FM, Vetus Torphaject.

E. Identification Characteristics: Butorphanol tartrate is a white crystalline substance. Solubility (Tartrate) = Soluble in dilute acid; slightly soluble in water and methanol, practically insoluble in ethanol, chloroform and ether. Melting Point (Tartrate) = 217 – 219oC. The n-octanol/aqueous buffer partition coefficient is 180:1 at pH 7.5 (The Merck Index, 1996).

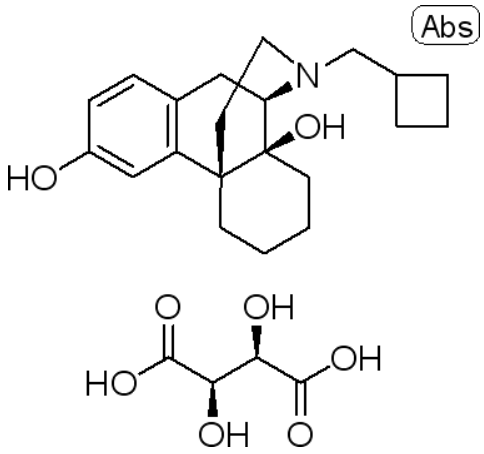
Stadol NS is an aqueous solution of butorphanol tartrate for administration as a metered spray to the nasal mucosa. Stadol NS contains a solution of butorphanol tartrate, sodium chloride, citric acid, benzethonium chloride and sodium hydroxide or hydrochloric acid (to adjust pH to 5.0) in purified water.

F. WHO Review History: Butorphanol was pre-reviewed by the 33rd ECDD in September 2002. This committee recommended a critical review, because at least 4 countries had taken regulatory actions to control butorphanol, indicating that its abuse is considered as a significant problem in more than one country..

2. Chemistry

A. Chemical Name: 17–(Cyclobutylmethyl)morphinan-3,14-diol; L-N-Cyclobutylmethyl-3,14-dihydroxymorphinan tartrate salt

B. Chemical Structure:



Molecular Formula: $C_{21}H_{29}NO_2$
$C_{21}H_{29}NO_2\ C_4H_6O_6$ (tartrate)

Molecular Weight: 327.5
477.6 (tartrate)

3. General pharmacology

Butorphanol tartrate is a synthetic opioid partial agonist analgesic. Although in radioligand binding studies, butorphanol binds to both μ and κ opioid receptors, most of the observed behavioral, pharmacological, and therapeutic effects appear due to its lower efficacy agonist actions at μ opioid receptors. The κ agonist effects may be revealed in an opioid-dependent or opioid-receptor challenged organism. However, therapeutic categories for butorphanol in humans are as an anesthesia or pre-anesthesia adjunct, narcotic analgesic for the relief of moderate to severe migraine, postoperative, or obstetric pain and in veterinary medicine as an analgesic or antitussive agent.

Neuropharmacology

In radioligand binding studies, butorphanol binds to the three principal opioid receptors, μ, κ, and δ with an affinity ratio of 1:4:25, respectively (Chang and Cuatrecasas, 1981; Chang et al., 1981). No studies have revealed any selectivity of butorphanol for any κ receptor subtypes (Commiskey et al., 2005). In rhesus monkey brain, butorphanol revealed a 12-fold selectivity for μ over κ receptors and a 34-fold selectivity of μ over δ receptors (Butelman et al., 1995). In vitro, butorphanol's relative affinity and efficacy is slightly higher for μ than κ (Emmerson et al., 1996; Zhu et al., 1998). Butorphanol bound with intermediate potency and was equally efficacious as morphine to inhibit cAMP production in HEK cells expressing μ receptors (Gharagozlou et al., 2003) yet less efficacious

than morphine (but greater than nalbuphine) to activate [^{35}S]GTPγS binding in C6 glioma cells (Traynor et al., 2002). In vivo studies reveal a rank order of relative efficacy for agonist activity via the μ opioid receptor as etorphine > fentanyl ≥ morphine ≥ buprenorphine> butorphanol > nalbuphine (Zimmerman et al., 1987; Morgan and Picker, 1998; Smith and Picker, 1998; Smith et al., 1999; Walker et al., 2001b; Walker et al., 2004).

In rhesus monkeys, the behavioral effects of butorphanol such as antinociception, respiratory depression, and self-administration were mediated through μ receptors as indicated by competitive antagonism by opioid antagonists (Butelman et al., 1995). Whereas most of the preclinical laboratory animal data in rhesus monkeys and pigeons indicate butorphanol produces pharmacological effects through the μ opioid receptor (Picker, 1994; Butelman et al., 1995; Walker et al., 2001b), the preclinical laboratory rodent literature indicates butorphanol can produce pharmacological effects through both μ (Smith and Picker, 1998; Smith et al., 1999) and κ opioid receptors (Jaw et al., 1993a; Jaw et al., 1993b; Jaw et al., 1993c). Therefore, whereas butorphanol can serve as potent κ agonist, these effects are often overwhelmed by butorphanol's pharmacological effects at μ opioid receptors (Commiskey et al., 2005).

There are indications that certain conditions or states of the μ opioid receptor will unmask the κ agonist effects of butorphanol. For example, high doses of opioid antagonist quadazocine decreased the maximal reinforcing effects (Butelman et al., 1995) and insurmountable antagonist clocinnamox 24h prior to butorphanol revealed ethylketocyclazocine-like discriminative stimulus effects and diuretic effects (Vivian et al., 1999). These data suggest that when the μ opioid receptor is substantially reduced or dysfunctional (as might be seen in opioid dependence), κ opioid agonist effects may be observed.

Respiratory effects

Early studies suggested that butorphanol did not produce compete respiratory depressant effects and a 'plateau or ceiling effect' was observed. For example, a dose of approximately 0.03 mg/kg butorphanol, i.v., decreased respiration similar to 10 mg of morphine or 70 mg of meperidine with a 'plateau or ceiling effect' observed at higher doses such as 15 mg/70 kg (Kallos and Caruso, 1979; Talbert et al., 1988). This observation is consistent with the earlier characterization that butorphanol is a κ agonist or a μ antagonist.

However, more recent data in rhesus monkeys and humans contest these earlier observations. In rhesus monkeys, butorphanol, i.m., dose-dependently decreased ventilation so that the highest dose tested (0.32 mg/kg) decreased minute volume in the presence of CO_2 to 10-30% of session control values and decreased minute volume in air to 30-40% of session control values (Butelman et al., 1995; Liguori et al., 1996; Paronis and Woods, 1997). Daily treatment with 3.2 mg/kg morphine failed to produce tolerance to the ventilatory effects of fentanyl, butorphanol, morphine, or nalbuphine (Paronis and Woods, 1997). The δ antagonist naltrindole did not antagonize butorphanol's respiratory depressant effect (Negus et al., 1994).

In humans with drug abuse histories, butorphanol (3-12 mg/70 kg) significantly decreased oxygen saturation similar to other μ opioid agonists such as hydromorphone with no observed ceiling effect (Zucker et al., 1987; Walsh et al., 2001a; Walsh et al., 2001b). In healthy volunteers, butorphanol (0.5-2 mg/70 kg) decreased O_2 saturation and respiration rate (Walker et al., 2001a).

As a nasal preparation, respiratory depression did not occur with any appreciable frequency at therapeutic doses (Gillis et al., 1995). Butorphanol administration to 12 mothers just prior to or after delivery did not cause respiratory depression in newborn infants

Gastrointestinal effects

Animal studies indicate butorphanol, like other opioid agonists, inhibits GI motility. However, these effects were slight and little increase in duodenal smooth muscle activity or bile duct flow was observed (AHFS, 2005).

Cardiac effects

Heart rate and blood pressure were not significantly altered after butorphanol i.v. in normal volunteers (AHFS, 2005) although some studies do indicate some indices of cardiovascular function can be altered (Popio et al., 1978). A dose of 0.025 mg/kg butorphanol, i.v., increased pulmonary artery pressure, pulmonary wedge pressure, left ventricular end-diastolic pressure, systemic arterial pressure, pulmonary vascular resistance, and cardiac index (AHFS, 2005). As a nasal preparation, hypotension did not occur with any appreciable frequency (Gillis et al., 1995). No change in cardiac or vital signs were observed in volunteers receiving multiple doses of 1-4 mg for 16 days (Shyu et al., 1993). Interestingly, butorphanol (1.5-6 mg/70 kg, i.m.) dampened the tachycardic response to cocaine administration (Walsh et al., 2001a).

Adjunct pre-anesthesia and anesthesia

Butorphanol, 20-40 mcg/kg i.v. was comparable or preferable to fentanyl 1-2 mcg/kg i.v. as a supplement to balanced anesthesia in most studies (Day et al., 1986; Philip et al., 1991). Groups receiving butorphanol as part of balanced anesthesia were reported to be satisfied with their anesthetic experience, require less post-operative analgesic (compared to not receiving butorphanol), and also reported postoperative drowsiness and sedation (Pandit et al., 1987; Sklar et al., 1989; Philip et al., 1991; Lawhorn and Schmitz, 1995). In one study, neither butorphanol nor fentanyl was considered to be an ideal narcotic agent for balanced anesthesia (Pandit et al., 1987).

Preclinical studies on analgesic effects

In preclinical laboratory animal studies, butorphanol produces antinociception in a variety of models in rhesus monkeys (Butelman et al., 1995; Negus and Mello, 1999) and rodents (Garner et al., 1997; Smith et al., 1999). In higher demand thermal antinociception assays, however, butorphanol fails to produce antinociception and will block the effects of higher efficacy μ agonists such as etonitazene, morphine (Butelman et al., 1995; Smith et al., 1999; Smith and French, 2002). Interestingly, butorphanol and morphine blocked U50,488 antinociception in these high temperature thermal assays. Similarly, in the squirrel monkey shock-titration model of analgesia, butorphanol produced modest increases in median shock levels (i.e., titrated the shock to a higher level) than methadone and U50,488 yet also dose-dependently antagonized the antinociception produced by methadone and U50,488 (Dykstra, 1990). These studies support the notion that butorphanol is a lower efficacy agonist at μ and κ opioid receptors than morphine, methadone and U50,488, respectively, but the expression of the κ agonist effects may depend on species examined.

In preclinical research studies using non-drug-abusing human volunteers, experimental pain induced by cold stressors modulated the subjective effects of butorphanol, i.v., in females but not males (Zacny and Beckman, 2004). However, in rhesus monkeys, butorphanol produced greater

antinociceptive effects in males than ovariectomized females although no difference was observed after treatment with estradiol (Negus and Mello, 1999).

Clinical studies on the use for acute and post-operative pain

The parenteral injection of butorphanol is used in the treatment of moderate to severe pain associated with acute pain such as orthopedic issues, burns, renal colic, and surgical. Injection formulation is also used for obstetric analgesia. In humans, after IM injection, the analgesic activity of butorphanol is 4-7 time that of morphine, 15-30 times that of pentazocine, and 30-50 times that of meperidine (AHFS, 2005). Postoperative use of butorphanol in patient controlled analgesia, provided excellent analgesia in 21/25 (89%) of patients for two days although four patients withdrew from the study due to lack of analgesia (Wermeling et al., 1988). In three groups of healthy pregnant women requesting analgesia during labor, 1 mg butorphanol i.v., 50 mg meperidine i.v., or the 0.5 mg butorphanol plus 25 mg meperidine i.v. reduced pain intensity by an average of 25-35% and increased sedation to a similar degree (Nelson and Eisenach, 2005). Epidural, intravenous, or intramuscular butorphanol can prolong analgesia of other agents and reduce opioid-induced nausea and pruritus (Rodriguez et al., 1990; Lawhorn et al., 1991) although not all studies find these effects (Gambling et al., 1994; Sakai et al., 2001). A dose of 2 mg butorphanol i.m. was equivalent to 80 mg meperidine i.m. in reducing the pain of ureteric colic (Elliott et al., 1979; Henry, 1986).

The nasal spray formulation is an effective analgesic for the relief of moderate to severe pain such as migraine attacks, dental, maxillofacial, or other surgical pain. For the marketed therapeutic doses of 1 and 2 mg, clinical studies have indicated that the transnasal preparation is safe and effective with an analgesic efficacy similar injected butorphanol (Abboud et al., 1991; Diamond et al., 1991; Schwesinger et al., 1992). In a retrospective case study of 83 patients, Stadol NS was effective in 51% of the patients in treating migraine (Robbins, 2002). For postoperative pain from cholecystectomies, abdominal hysterectomies, laporotomies, and general surgical procedures, nasal butorphanol at doses of 1 or 2 mg had an onset time of 15 min, peak effects 30-60 min, and a duration of action of 3-5 h (Schwesinger et al., 1992; Wermeling et al., 2005a). Relief from moderate to severe pain was comparable to pethidine (Schwesinger et al., 1992). For women with postcesarean pain, nasal butorphanol was better than placebo with a faster onset in the intravenous group (5 min) compared to transnasal administration (15 min) although the transnasal group displayed a longer duration of action (4.5 vs. 3 h). Higher rates of withdrawal from study were observed in the intravenous group due to adverse effects such as somnolence, dizziness, and sweating (Abboud et al., 1991). In other studies, the 2 mg dose was reliably better than lower doses or placebo for moderate to severe postepisiotomy pain (Schwesinger et al., 1992; Striebel et al., 1995).

In ambulatory surgery and outpatients followed for three days, mean doses of 2.7, 1.8, and 1.4 mg transnasal butorphanol were required on the first, second, and third day, respectively and satisfactory pain relief was reported by greater than 80% of the patients. Mild adverse effects such as dizziness, drowsiness or nausea were reported on the first day by 70% of the patients. Despite the high rate of adverse effects, 90% of the patients would request the medication for future pain relief (Wetchler et al., 1989; Wetchler et al., 1992). In an uncontrolled, open study emergency room treatment of acute musculoskeletal pain in 28 patients, nasal butorphanol reduced pain by 50% in 70-80% with adverse effects of nausea, nasal irritation, and drowsiness in 11-80% of the patients (Scott et al., 1994). Transnasal butorphanol 1 mg (every hour for the first 2 h and then every 3-4 h as needed) provided adequate or complete post-operative pain relief in most head and neck surgery patients (70-75%)

although by 4 h only 10% of the patients had complete relief of pain (Cannon, 1997). In an open, randomized and prospective study enrolling 51 patients with musculoskeletal pain, 1 mg butorphanol every 60 min if required produced comparable similar pain relief to standard oral treatment with codeine (30 mg) and paracetamol (300 mg) although more adverse effects were reported with butorphanol (Wolford et al., 1997). In 50 patients undergoing surgical removal of impacted wisdom teeth, 1 mg Stadol transnasally every 4 h reduced pain by 50% within 15 min in combination with oral ibuprofen. The majority of patients (81%) rated the effectiveness of butorphanol as good to excellent (Ladov et al., 2000).

Use for chronic pain

The parenteral injection of butorphanol can be used in the treatment of moderate to severe pain associated with chronic pain such as cancer, spastic and neuropathic conditions. However, most clinical studies evaluating butorphanol efficacy for chronic pain are not recent. For example, the efficacy of 1-8 mg butorphanol i.m. every 3-4 h for 2-34 wk was evaluated in 63 patients with chronic pain syndrome due to malignant disease, neuropathy, orthopedic associated pain) and found to be excellent in 51%, good to fair in 30%, and poor to ineffective in the remaining patients (Kliman et al., 1977). It appears butorphanol was evaluated for chronic pain conditions such as cancer surgery and advanced cancer pain in adults and children during the 1980s in Russia and Japan (De la Garza, 1981; Rangel-Guerra, 1981; Konno et al., 1983; Stambaugh and McAdams, 1987; Voznyi et al., 1988; Nakadate et al., 1989). In a review, mixed agonist-antagonists including pentazocine, nalbuphine, and butorphanol were reported of very limited usefulness as analgesics for chronic pain due to weaker efficacy, some psychotomimetic effects and required parenteral administration (Hanks, 1987). In a case study of a patient with neuropathic pain of central origin that showed newly developed severe lightning pain after therapeutic subarachnoid block, the authors found intravenous but not intramuscular butorphanol to be effective in relieving this specific type of pain (Wajima et al., 2000).

The nasal spray formulation has not been evaluated for breakthrough pain in cancer patients (Dale et al., 2002).

Diuresis

A characteristic of κ agonists are their ability to produce relatively dramatic diuresis in preclinical laboratory animals. Butorphanol produces a moderate degree of diuresis in rats and mice but much less than ethylketocyclazocine or U50,488 which are full κ agonists (Leander et al., 1987; Horan and Ho, 1989b). Butorphanol blocked the diuresis produced by full κ agonist bremazocine (Leander, 1983) suggesting κ partial agonist activity for butorphanol. However, butorphanol failed to produce diuresis in rhesus monkeys (Butelman et al., 1995). This observation is consistent with the notion that butorphanol may be a partial agonist at κ opioid receptors and expresses greater κ activity in rodents than primates.

Other effects

Epidural butorphanol can be used to reduce the pruritus or nausea associated with epidural morphine in pediatric and adult populations (Lawhorn et al., 1991; Wittels et al., 1993; Lawhorn and Brown, 1994). Not all studies report a decrease in pruritus or nausea however (Gambling et al., 1994). Furthermore, reduced pruritus and nausea are not necessarily observed when butorphanol is given i.v. Indeed, butorphanol, i.v., may even reduce the analgesia produced by intrathecal morphine and produce increased somnolence (Sakai et al., 2001). Butorphanol (i.v., i.m., t.n.), decreases pupil

diameter and increases skin temperature like typical opioid agonists (Preston et al., 1994; Walsh et al., 2001b).

Interactions of butorphanol with other compounds
Administration of butorphanol may precipitate withdrawal signs if administered to individuals maintained on higher efficacy opioids such as heroin, methadone, or morphine. Eight day treatment with tranylcypromine decreased the LD_{50} of butorphanol and produced hypotension and tachycardia after a dose of 2 mg/kg butorphanol in rabbits (Gomaa et al., 1991). Acute doses of butorphanol were administered safely in combination with cocaine. No evidence of synergistic effects that may pose safety risks was observed (Walsh et al., 2001a).

4. Toxicology, including adverse reactions in humans

Toxicity in Animals
Butorphanol, like morphine and buprenorphine produced dose-related stupor and muscle relaxation that was reversed by naloxone in rhesus monkeys (Woods and Gmerek, 1985); however more recent studies found that only mild sedation or muscle relaxation was observed for butorphanol and morphine (Butelman et al., 1995). In both of the studies, κ agonists MR 2033, U50,488 and ethylketocyclazocine produced much greater stupor, muscle relaxation, and sedation than morphine, buprenorphine, or butorphanol. A dose of 25.6 mg/kg butorphanol produced convulsions in 14 h morphine-deprived, morphine-dependent rhesus monkeys (Woods and Gmerek, 1985). Toxicity studies indicated LD_{50} values as follows in mice and rats: 40-57, 17-20 i.v.; 395-527, 570-756 orally (Heel et al., 1978).

Toxicity in Humans
Sedation is the most frequent adverse effect reported 43%; dizziness 19%; nausea/vomiting 13%; clamminess, sweatiness, headache, vertigo, floating feeling, asthenia, anxiety, euphoria, nervousness, paresthesia, lethargy, confusion, and lightheadedness (1-10%).(AHFS, 2005)

Within the period of 1979 to 1992, the Food and Drug Administration received approximately 60 adverse drug reactions, six reports of dependence-addiction, and one death per year from intramuscular butorphanol. These reports included such psychological disturbances as paranoid reactions, confusion, and hallucinations (Fisher and Glass, 1997) (Drug Abuse Advisory Committee, FDA, February 4, 1991). However, these reports of use of intramuscular butorphanol were relatively limited.

Three years after the release of the nasal spray formulation (1991-1994), the number of adverse drug reactions reported to the FDA increased from 60 to 400 per year including major psychological disturbances such as depersonalization, hallucinations, depression, psychosis, paranoid reaction or dependence/addiction. The percentage of dependence/addiction as a total of reported adverse reactions increased from approximately 6.5 to 24% (Fisher and Glass, 1997). Other more common adverse effects of nasal butorphanol include dose-dependent somnolence, dizziness, and sweating. In a retrospective case study, 22% of patients had overused (as defined as the use of 15 or more bottles per month) or become addicted to Stadol NS (as defined by patient interview self-report). These users had a history of anxiety and depression. At least one adverse event was reported by

49% of the patients including the following: bad reaction, felt strange, weird, stoned or numb (25%); nausea or gastrointestinal upset (11%); anxious, panicked, or wired (8%); fatigue (6%); dizzy or lightheaded (5%); agitated or mean (4%); pruritus or allergic (4%); insomnia (2%); tremulousness (2%); hallucinations (1%); constipation (1%); and nasal irritation (1%) (Robbins, 2002).

In moderate and severe post-operative pain, 1 or 2 mg nasal butorphanol had adverse effects in 57% of patients although mild (Schwesinger et al., 1992). For the nasal formulation, nasal congestion was observed in 13%, dyspnea, epistaxis, nasal irritation, pharyngitis, rhinitis, sinus congestion, or upper respiratory infection in 3-9% (AHFS, 2005).

Non-fatal Reports of Butorphanol Intoxication in Humans:
On the Erowid webpage (http://www.erowid.org), three voluntary reports were described of butorphanol intoxication from 2001- December 2005 as opposed to the 45, 25 and 16 voluntary reports of oxycodone, morphine, and buprenorphine, respectively. From these three case reports on butorphanol use, the following comments were notable:

> "What this [butorphanol as a partial opiate agonist] tends to mean for the user is (1) they are going to be infinitely easier to get than any other heavy duty pharmaceutical meant for injection and (2) while they may not be as fully opiate-like in their feel, and could be somewhat unpleasant at first, if used properly they can be very pleasant and fun. [Stadol] can be somewhat addictive, but withdrawals seem to be slight if at all noticeable. I never found myself increasing my dose or building much of a noticeable tolerance even with 2-3 weeks of pretty regular use. Partials also seem to reach a dose-response peak unlike normal opiates." Exp Year: 2002; ID: 20957. "I have taken many painkillers over the years but yet have I found one to help with my headaches like Stadol. Also, as you might guess, Stadol is very addictive and very hard not to do when I have nothing else better to do that day." Exp Year: 2001; ID: 9577. "I obtained a bottle of Torbutrol from a veterinarian for administration to my cat...The room was spinning, and I had an awesome warm, jello sensation throughout my entire body. It was pretty incredible, for a veterinary medicine. I highly recommend keeping the dosage low, and resisting the temptation to redose." Exp Year: 2004; ID: 31534**.**

Fatal cases
A 24 yr old law student was prescribed Stadol NS for migraines and became increasingly dependent on the medication until his physician stopped the prescription. The patient then committed suicide prompting his father a neurologist (Morris Fisher, M.D.) and his cousin a journalist (Stephanie Glass) to write a review critical of the handling of butorphanol's scheduling by the U.S. Food and Drug Administration and Bristol-Meyers Squibb (Fisher and Glass, 1997).
The WHO Uppsala Monitoring Centre (UMC) reported of world wide PMS-data 57 cases of death (0.7 %) and no cases of sudden death out of 8114 reported adverse effects (unpublished, communication to WHO, 2005).

5. Pharmacokinetics

Overall, the pharmacokinetic profile of transnasal butorphanol is qualitatively and quantitatively similar to that observed with parenteral butorphanol. Butorphanol is rapidly absorbed, widely

distributed, undergoes extensive hepatic first-pass metabolism, and is excreted primarily via the kidneys.

Due to the extensive hepatic metabolism of butorphanol, oral bioavailability is approximately 5 to 17%. Sublingual tablet and buccal disk formulations only increased mean absolute bioavailability to 19 and 29% (Shyu et al., 1993). Peak plasma concentrations of 2.2 ng/mL butorphanol occur between 30-60 min after a single 2-mg i.m. administration. Peak plasma concentrations of 1.5 ng/mL butorphanol occur almost immediately after a single 1-mg i.v. administration. Apparent plasma half-lives of butorphanol were between 6 and 10 h (Boulton et al., 2002). After intramuscular or intravenous administration, butorphanol is widely distributed to tissues with an estimated volume of distribution ranging from 300-900 mL. The extent of plasma protein binding is approximately 80% (Gaver et al., 1980). Butorphanol rapidly crosses the placenta and neonatal serum concentrations are 0.4-1.4 times maternal concentrations. Butorphanol is distributed into breast milk although breastfed infants would receive a negligible amount. Doses of 8 mg intramuscular to 12 healthy nursing mothers resulted in neonatal exposure of only 4 mcg (Pittman et al., 1980a; Pittman et al., 1980b).

Intranasal butorphanol formulations of butorphanol were developed as an alternative to intravenous administration. With transnasal administration, butorphanol bioavailability increases to 48-70% (Shyu et al., 1993; Gillis et al., 1995). Transnasal butorphanol was well-tolerated by all subjects and plasma concentrations and AUCs increased in a dose-dependent manner indicating linear kinetics. Single dose or steady-state following repeated regular dosing of transnasally administered butorphanol gives relatively low plasma concentrations of less than 5 ng/ml at normal doses. Peak plasma concentrations of 0.9-1.04 ng/mL butorphanol occur 30-60 min after a single 1-mg i.m. administration (Shyu et al., 1993; Vachharajani et al., 1997a; Vachharajani et al., 1997b). The mean elimination half-life of transnasal butorphanol is 47 min -5.8 h in healthy volunteers; 6.6 h in the elderly; and 8.6-10.5 h in patients with renal impairment (Gillis et al., 1995). Although there is no clinical experience with the use of butorphanol nasal spray in nursing mothers, based on the similar pharmacokinetics and metabolism of butorphanol, one would expect similar levels of amounts distributed into breast milk as after intramuscular butorphanol.

Butorphanol is metabolized by hydroxylation and N-dealkylation to form the major metabolite hydroxybutorphanol (45-50% of parenterally administered dose) and norbutorphanol (5-10% of parenterally administered dose). Neither metabolite appears to have any pharmacological effects (Gaver et al., 1980). Hydroxybutorphanol accumulates with a long terminal half-life of 15 h but adverse effects reported on Day 1 did not differ from those reported on Day 6 supporting the previous findings that this metabolite is not pharmacologically active (Vachharajani et al., 1997a; Vachharajani et al., 1997b).

Recently, single unit dose, intranasal spray pumps are being examined as an alternative to the multidose, intranasal spray pumps. Single dose units for butorphanol would have the following advantages: 1) a sterile product; 2) elimination of product contamination after use; 3) lack of potentially irritating antimicrobial preservatives; 4) reduced risk of diversion for remaining unused portion in multidose sprayer; and 5) prescribing and dispensing based on individual patient requirements (Wermeling et al., 2005b). Initial studies have indicated that the single unit dose intranasal pumps delivered a more accurate spray weight delivery, resulted in less pharmacokinetic

variability (Wermeling et al., 2005b), and provided a similar degree of postsurgical analgesia as the multiple dose intransnasal pump (Wermeling et al., 2005a). This packaging for transnasal butorphanol has the potential to decrease misuse, diversion, and abuse.

6. Dependence and abuse potential

Tolerance and physical dependence to butorphanol or the precipitation of withdrawal from μ agonists by butorphanol is influenced both by the maintenance dose of butorphanol or μ agonist as well as the relative efficacy of the test compound. Most findings indicate tolerance and dependence to butorphanol represents combinations of μ and κ receptors.

A. Studies in animals

1. Drug discrimination - In rats, pigeons, and rhesus monkeys, butorphanol, like morphine and buprenorphine substitutes, fully for the stimulus effects of μ full agonists etorphine (Young et al., 1984), morphine (Holtzman, 1982), fentanyl (Picker et al., 1993; Picker et al., 1994), intermediate efficacy μ agonists buprenorphine (Holtzman, 1997; Galici et al., 2002) and dezocine (Picker, 1997) and lower efficacy agonist nalbuphine (Walker and Young, 1993; Gerak and France, 1996; Walker et al., 2001a). Butorphanol also produces discriminative stimulus effects similar to δ agonist BW373U86 in pigeons (Picker and Cook, 1998), and mixed action agonists cyclazocine in squirrel monkeys (Schaefer and Holtzman, 1978) but not rats (White and Holtzman, 1983), pentazocine in squirrel monkeys (White and Holtzman, 1982), and N-allynormetazocine in pigeons (Picker, 1991). Butorphanol also partially substitutes for κ agonist bremazocine (Picker, 1994; Smith and Picker, 1995) but failed to produce ethylketazocine-like discriminative stimulus effects (Young et al., 1984) or spiradoline-like discriminative stimulus effects (Holtzman et al., 1991). In pigeons trained to discriminate various training doses of butorphanol, μ opioid agonists substituted whereas κ and δ agonists only substituted for butorphanol at low doses and these effects were not naloxone-reversible (Picker et al., 1996). Nonopioids, as well as sigma/phencyclidine compounds (+)-cyclazocine and N-allynormetazocine failed to substitute for any training dose of butorphanol.

2. Self-administration – Butorphanol is readily self-administered in rhesus monkeys (Young et al., 1984; Butelman et al., 1995), baboons (Lukas et al., 1982), and squirrel monkeys (C.A. Paronis, personal communication); however generally at rates lower than codeine, morphine, buprenorphine, or heroin. In mice, butorphanol dose-dependently inhibited initiation of cocaine self-administration and reduced the potency of the optimal unit dose cocaine although this effect was not reversed by naloxone (Kuzmin et al., 2000). Butorphanol decreased cocaine self-administration and produced partial substitution and augmentation of cocaine's discriminative stimulus effects in rhesus monkeys (Negus and Mello, 2002).

3. Dependence – Early preclinical laboratory animal studies suggested that butorphanol has lower abuse potential than full μ agonists such as morphine (Jacob et al., 1979). In rhesus monkeys dependent on 12 mg/kg morphine per day (3 mg/kg, s.c. every 6 h), butorphanol (unlike buprenorphine) produced no signs of withdrawal suggesting enough efficacy of butorphanol at the μ opioid receptor to prevent reversal or blockade of morphine.

However, in 14 h morphine-abstinent monkeys, low doses of butorphanol and buprenorphine failed to alter morphine withdrawal but higher doses of these lower efficacy agonists exacerbated rather than reduced the signs of withdrawal. This observation futher support the notion that buprenorphine and butorphanol are lower efficacy agonists than morphine. Chronic administration of 0.8-6.4 mg/kg per day butorphanol for 38 days produced physical dependence as indicated by mild withdrawal after 2 mg/kg nalorphine and severe withdrawal after 2 mg/kg naloxone. Interestingly, naloxone-precipitated withdrawal in butorphanol-dependent monkeys was indistinguishable from morphine withdrawal (miosis, increased respiration rate, piloerection, muscle rigidity, calling out, extreme irritability). However, unlike the morphine-dependent monkeys, the butorphanol-dependent monkeys failed to exhibit much abdominal defense reactions during withdrawal (Woods and Gmerek, 1985). The less severe withdrawal after nalorphine was probably due to the weak μ and κ agonist effects of nalorphine (Zimmerman et al., 1987; Walker and Young, 1993).

Signs of opioid withdrawal (wet-dog shakes, teeth-chattering, scratching, rearing, vocalization, ptosis, penis-licking) from chronic butorphanol in rodents can be precipitated by μ, κ, and δ opioid antagonists such as naloxone (but not β-funaltrexamine), nor-binaltorphimine, and naltrindole, respectively (Horan and Ho, 1989a; Jaw et al., 1993a; Jaw et al., 1993b; Jaw et al., 1993c; Jaw et al., 1994; Fan et al., 2003a). In these butorphanol-withdrawn rats, κ-opioid receptors levels and κ opioid receptor gene expression were significantly increased as compared to morphine-withdrawn rats suggesting an important role for κ opioid receptors in physical dependence to butorphanol in rats (Fan et al., 2003a; Tanaka et al., 2005). Furthermore, in butorphanol-dependent and butorphanol-withdrawn rats, κ1 and κ2 receptor subtypes developed a supersensitivity to nor-binaltorphimine in an autoradiographic binding study (Fan et al., 2003b). In rats physically dependent on butorphanol, natural withdrawal typically begins to appear 6-8 h after the termination of chronic butorphanol treatment which was also associated with changes in κ opioid receptor binding (Fan et al., 2002a; Fan et al., 2002b).

4. Tolerance – Chronic treatment with 0.8-6.4 mg/kg per day over 38 days produced rapid tolerance to stupor and muscle relaxation in rhesus monkeys (Woods and Gmerek, 1985). In rhesus monkeys treated once a day with a low to intermediate dose of morphine, butorphanol does not substitute for naltrexone indicating that in less dependent or tolerant monkeys, butorphanol does not precipitate a withdrawal-like cue (France and Woods, 1989). Tolerance and cross-tolerance to the antinociceptive and hyperthermic effects of μ opioid agonists morphine, fentanyl, butorphanol and buprenorphine, and κ agonist U50,488 was observed after high but not low treatment doses of butorphanol in rats (Bhargava, 1994; Feng et al., 1994a; Feng et al., 1994b; Smith and Picker, 1998). Also, chronic treatment with butorphanol conferred greater tolerance to lower efficacy μ agonists buprenorphine and butorphanol than higher efficacy μ agonists morphine and fentanyl (Smith and Picker, 1998).

Taken together, the preclinical laboratory animal data on dependence indicate that butorphanol can produce tolerance and dependence like most opioid agonists. The patterns of substitution in drug discrimination assays and self-administration, and the results of the dependence studies confirm that butorphanol possesses low to intermediate efficacy relative to morphine.

Furthermore, the studies in rodents indicate that butorphanol possesses κ agonist-like effects especially after repeated treatment with butorphanol.

B. Human studies

1. Drug discrimination - In opioid-abusing volunteers trained to discriminate 3 mg hydromorphone from saline, butorphanol, nalbuphine, pentazocine and buprenorphine fully substitute for hydromorphone (Preston et al., 1992). Butorphanol can be discriminated from hydromorphone, however, with different training procedures such as three-choice discriminations or in more opioid-dependent individuals. For example, opioid-abusing, non-dependent volunteers can be trained to discriminate hydromorphone, from butorphanol, from saline. In these subjects discriminating hydromorphone, butorphanol, and saline, butorphanol and nalbuphine fully substitutes for butorphanol and not hydromorphone, buprenorphine fully substitutes for hydromorphone, and pentazocine partially substitutes for both butorphanol and hydromorphone (Preston and Bigelow, 1994). These individuals may be discriminating an intensity difference at the μ opioid receptor between hydromorphone (higher efficacy agonist) and butorphanol (lower efficacy agonist) as opposed to μ vs. κ receptor selectivity differences. In support of this notion, when subjects were trained to discriminate a high dose of hydromorphone, low dose of hydromorphone, and saline, butorphanol, like buprenorphine, substituted fully for the low and partially for the high dose of hydromorphone (Jones et al., 1999).

   Similarly, in opioid-abusing, non-dependent volunteers trained to discriminate among hydromorphone, pentazocine, and saline, both pentazocine and butorphanol fully substitute for butorphanol and not hydromorphone while nalbuphine and buprenorphine partially substitute for hydromorphone and pentazocine (Preston et al., 1989). Similar to the preclinical animal drug discrimination experiments, these studies suggest that butorphanol, nalbuphine, and pentazocine share discriminative stimulus effects as predominantly lower efficacy μ and, possibly some κ, agonist effects. In an interesting modification of the drug discrimination training procedure, human volunteers with histories of opioid abuse were trained to discriminate hydromorphone from saline using the specific instructional set to choose 'Drug A' (hydromorphone only if the test drug was identical to hydromorphone and choose 'Not Drug A' (saline) for all other drugs. Under these conditions, butorphanol, nalbuphine, and buprenorphine only produced 30-60% hydromorphone responding (Preston and Bigelow, 2000) as opposed to the full substitution observed when the subjects chose either Drug A (hydromorphone) or Drug B (saline) (Preston et al., 1992). In physically dependent subjects trained to discriminate hydromorphone, naloxone, and saline, butorphanol and nalbuphine produced naloxone responding (Preston et al., 1988). However, when opioid-dependent subjects were trained in a three-choice discriminate to discriminate Drug A (naloxone), placebo (Drug B), and 'neither A or B' (novel), butorphanol and nalbuphine produced approximately 40-70% naloxone responding and 29-33% novel responding. Therefore, butorphanol and nalbuphine share some characteristics with naloxone in opioid-dependent subjects but they are not identical (Oliveto et al., 2002).

   Taken together, the drug discrimination findings support the notion that butorphanol is a lower efficacy agonist at μ opioid receptors and can be differentiated from hydromorphone under certain training conditions. Butorphanol can mimic, or partially mimic, withdrawal-like discriminative stimulus effects if an organism is opioid-dependent.

2. Subjective effects – Subjective effects are generally studied using the Addiction Research Center Inventory (ARCI), Visual Analog Scale (VAS), pharmacological class questionnaires, and adjective rating scales. Initial studies of the subjective effects of butorphanol were performed in nondependent subjects with a history of drug use and most often was identified as more similar to pentazocine than hydromorphone (Jasinski, 1977; Preston et al., 1989; Preston et al., 1992; Preston and Bigelow, 1994). For example, butorphanol produced higher ratings of feeling sleepy, drunken, shaky, tired, restless, confused, and lightheaded and lower ratings of itchy, talkative, drive, and energetic than hydromorphone (Preston and Bigelow, 2000). Although butorphanol did not share many subjective effects with hydromorphone and was often more likely to be identified as like pentazocine, the subjective effects of butorphanol differed significantly enough from pentazocine and cyclazocine to suggest reasonable differences among these agonists (Jasinski et al., 1975).

   In postaddicts, butorphanol produces dose-dependent ratings of "Any Drug Effect," "High," drunken, floating/spaced out, nodding and skin itchy" (Walsh et al., 2001b). In healthy volunteers, butorphanol produced significant ratings of high, sedated, lightheaded, dizzy, feel bad, unpleasant bodily sensations, difficulty concentrating, confused, drunk, and hungry on the VAS. Drug-effect strength was also rated high and at some time points, higher than morphine (Walker et al., 2001a). When transnasal butorphanol was compared to intramuscular butorphanol in opioid abusers not currently physically dependent, both routes of administration produced significant increases in mean AUC scores for 'feel the drug', 'high', and 'dislike the effect'. For the 'feel the drug' and 'high' scales, 4 mg intramuscular butorphanol were greater than those for transnasal butorphanol although these routes of administration were similar for 'dislike the effect'(Preston et al., 1994). Administration of butorphanol 3 or 6 mg/70 kg produced subjective effects of "bad drug effects" and changes in regional cerebral blood flow in areas of both temporal lobes in nondependent opioid-abusing volunteers. These effects were distinguished from hydromorphone (Schlaepfer et al., 1998).

   On Subject's Drug Identification Questionnaire, intramuscular butorphanol produced small but significant identifications as opiate, opiate antagonist, and phenothiazine and transnasal butorphanol produced small by significant identifications as opiate and barbiturate (Jasinski, 1977; Preston et al., 1989). On the ARCI, intramuscular butorphanol was identified on the PCAG scale (a measure of sedation) and the LSD scale (a measure of dysphoric changes) but not on the MBG group (a measure of euphoria) whereas transnasal butorphanol was not distinguished from placebo on any of the scales (Preston et al., 1992; Preston et al., 1994). Butorphanol i.v. increased scores on the PCAG and LSD scales and decreased scores on the MBG scales in healthy volunteers (Zacny et al., 1994; Walker et al., 2001a). In one study, butorphanol did not produce ratings on the LSD scale of the ARCI whereas the comparison κ agonist endoline did produce ratings on this scale (Walsh et al., 2001b). Overall, butorphanol appears to share more subjective effects with hydromorphone than endoline. However, whether μ or κ-like subjective effects are observed depends on the subject's drug use history, degree of opioid dependence, as well as other drugs used in the study for comparison. As more selective κ agonists are available for study in humans, a better profile of κ agonist subjective effects will be obtained.

Generally, in humans, subjective effects measures are collected in the same studies as drug discrimination studies. Overall, the reinforced behavioral discrimination measures appear more sensitive than the non-reinforced self-report visual analog scales to subtle opioid agonist effects (Preston et al., 1989; Jones et al., 1999; Comer et al., 2005). However, both sets of studies are required to fully understand the intereoceptive and subjective effects of butorphanol.

3. Self-administration – In contrast to the preclinical laboratory data in rodents and rhesus monkeys described above, neither κ agonist enadoline nor butorphanol modified cocaine self-administration although enadoline did modify some of the positive subjective effects produced by cocaine. Although there did not seem any evidence of clinically meaningful therapeutic actions between butorphanol and cocaine on behavioral outcomes, the investigatros also found that acute doses of butorphanol were administered safely in combination with cocaine. No evidence of synergistic effects that may pose safety risks (Walsh et al., 2001a).

4. Dependence – Butorphanol did not precipitate abstinence in morphine-dependent subjects (Jasinski et al., 1975). Large doses of nalorphine precipitated abstinence in subjects physically dependent on butorphanol, 48 mg daily (Jasinski et al., 1976).

   In the mid-1980s, two case report of Stadol dependence were reported in hospital staff with ready access to intravenous and intramuscular Stadol (Brown, 1985; Evans et al., 1985). Both individuals initially took Stadol for post-operative pain or migraine. Daily Stadol usage increased to 16 mg (approximately 8 mg every 12h) in one individual and to 42 mg (approximately 6-8 mg every 2-3 h beginning at noon) in the other individual. Upon withdrawal from butorphanol, both individuals exhibited the flu-like withdrawal symptoms associated with opiate withdrawal including tachycardia, rhinorrhea, nausea, vomiting, abdominal cramping, diarrhea, myalgia, diaphoresis, dilated pupils, irritable mood, and malaise. These cases demonstrate that although the incidence of butorphanol i.m. dependence is infrequent, the withdrawal symptoms are very similar to those observed for morphine and buprenorphine (Jasinski, 1977).

   In regards to the different formulations of butorphanol, the transnasal preparation of butorphanol does not appear to differ in its abuse liability from the parenteral preparations from a pharmacological viewpoint. However other nonpharmacological factors such as availability and pattern of use can play critical roles (Preston et al., 1994).

5. Epidemiology of use and abuse with an estimate of the abuse potential

In a controlled clinical trial, patients receiving repeated butorphanol nasal spray for chronic pain for 6 months, overuse was reported in 2.9% of patients. Abrupt discontinuation of butorphanol may result in withdrawal symptoms similar to that observed for opioid agonists (e.g., chills, tremulousness, diarrhea, hallucinations) (AHFS, 2005). In a retrospective case study, 22% of patients had overused or become addicted to Stadol NS. These users had a history of anxiety and depression (Robbins, 2002).

The relative occurrence of adverse effects from the UMC database was out of 8114 adverse effect reports: 3.5 % (283) for withdrawal symptoms, 0.01 % (1) for withdrawal convulsions, 0.05 % (4) for withdrawal headache, 1.5 % (120) for increased tolerance, 42.9 % (3482) for drug dependence and 1.0 % (81) for drug abuse (unpublished, communication to WHO, 2005).

The Canadian Adverse Reaction Monitoring Programme (CADRMP) in 1997 received 48 reports of adverse drug reactions associated with butorphanol nasal spray in a period of 14 months. Fifteen of these reports indicated suspected drug-seeking behavior, drug abuse, and addiction. Original prescriptions were for migraine headache. One patient has used 257 bottles of nasal spray over a period of nine months. Doctor shopping was noted. There were 53 cases of butorphanol thefts (48 B & E; 5 armed robberies).

In the USA it is estimated that in 2004 0.1 % of all persons of 12 years or older have used butorphanol (as Stadol) nonmedically in their lifetime. (NSDUH, 2005).

Drug Abuse Warning Network (DAWN) data:
Following the marketing approval of butorphanol nasal spray, there were 35 drug abuse-related emergency room visits involving butorphanol. In 1996, butorphanol was mentioned in 239 drug abuse-related ED visits in the United States. Following the control of butorphanol in Schedule IV of the Controlled Substances Act (CSA), butorphanol involved drug abuse-related ED visits declined to 19 in 1998. Estimates during the subsequent period of 1999 through 2002 were too unreliable for publication.

6. Nature and magnitude of public health problems

No country out of 74 reported any abuse of butorphanol or other problems related to public health except for Switzerland and the United States of America.

In Switzerland there was one case of accidental poisoning and one case of chronic abuse by a veterinarian. Both were in 2002 and in other years no cases were reported.
Some abuse is reported in the United States.

7. National controls

Butorphanol is controlled in Australia, Colombia, Ireland, Italy, the United Kingdom and United States of America as well as perhaps in other countries. In 1997, in the USA the substance was put under Schedule IV of the Controlled Substances Act after reports of abuse and diversion were given since 1992. This Schedule would be comparable to Schedule IV of the Convention on Psychotropic Substances.

8. Therapeutic and industrial use

In their answers to the WHO 2005 Questionnaire, 21 out of 74 countries answered that butorphanol is available as a medicine. Of these, in 13 countries it is available for human use only, in 3 countries for veterinary use only, and in 2 countries for both. In most countries it is imported from other countries. Not surprisingly, it is always used as an analgesic.

Of these 21 countries it is available as injections in 16, as a nasal spray in 5, and as tablets in 2.
Commercial preparations for *human use* include:

- Parenteral injection: 1 mg/mL in single dose vials or prefilled syringes; 2 mg/mL in single or multiple dose vials and prefilled syringes,
- Nasal solution in 1 mg/metered spray (10 mg/mL) with 14-15 doses of 1.0 mg butorphanol.

Commercial preparations for *veterinary use* include:

- Injection: 0.5 mg/mL in 10 mL and 10 mg/mL in 50 mL vials.
- Oral: 1 mg, 5 mg, and 10 mg tablets.

country	year of market admission	injection	nasal spray	tablet	hum use	vet use	controlled
Phillipines	?	x?	x?		x		
USA	1978	x	x	x	x	x	x
Colombia	2002	x	x		x		x
China	2002	x	x		x		
Ireland	1988	x				x	x
Moldava	1999	x?			x		
Nepal	2003	x			x		
Japan	1985	x			x		
India	?	x			x		
Georgia	2004	x			x		
Australia	1997	x			x	x	
Ukrain	2002	x					
Switzerland	1998	x				x	
Czec Republic	1996	x				x	
Austria	?	x				x	
Sweden	?	x				x	
Chile	1996		x		x		
Finland	on special licence only					x	
UAE	?			x	x		
Israel	1998				x		

Commercial preparations for veterinary use could be launched in France in the future. A few specific import authorizations have been issued.

9. Illicit manufacture, illicit traffic and related information

No countries reported illicit activities for butorphanol, except for Australia and the United States.

Australia reported only 1 relatively small seizure during the fiscal year 2004/2005.

The United States reported that before the substance was put under control, sources for nopnmedical use originated from excessive prescription refill, retail and hospital pharmacy thefts, forged and altered prescriptions, improper prescribing and inappropriate dispensing, doctor shopping, escalating use, requests for early refills, and drug seeking. Based on the evidence of significant abuse of butorphanol, the U.S. Federal government controlled butorphanol in Schedule IV of the CSA in 1997. At present the abuse has decreased. According to the System to Retrieve Information from Drug Evidence (STRIDE[1]), a DEA database to collect drug analysis results from DEA and other federal laboratories systematically, butorphanol drug items analyzed from 2000 to 2004 ranged from 1 to 5 per year.

10. International controls in place and their impact

The substance is not under international control currently.

1. System to Retrieve Information on Drug Evidence (STRIDE) is a database that maintains all drug analysis done by the U.S. DEA forensic chemists.

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