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Review of Butorphanol For Inclusion within Alberta's Triplicate Prescription Program

July 30, 2002

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Scope And Objectives

1. Provide relevant information on butorphanol to the Triplicate Prescription Program (TPP) Steering Committee to aid in making a decision as to whether to include it within the Alberta TPP.
2. Provide a basic overview of butorphanol with special focus on its indications, potential for abuse, alternative drugs used for the same indications, and cost.
3. Provide information related to the non-medical use of butorphanol in Alberta.
4. Provide the volume of butorphanol used in Alberta as a means of assessing the impact on workload for the TPP.

Executive Summary

A Pub Med literature search was performed to gather data on butorphanol, specifically its indications, including non-Health Canada approved indications, potential for abuse, and alternative therapies that are used for the same indications. Addiction centres in Alberta were surveyed as well as was the RCMP and the EPS (Edmonton Police Service) regarding butorphanol's non-medical use. Finally, the manufacturers of the drug were contacted to glean the volume of drug issued to Alberta for a specified time period. This information, together with consultation with physicians specializing in the areas in which this drug is used, should help clarify whether butorphanol merits addition to Alberta's TPP. The information enclosed is referenced and the written references are supplied. The information enclosed is limited by the short time frame given to perform this project. Blue Cross was not able to provide the number of prescriptions dispensed for butorphanol which has left the assessment of workload, should the drug be added to the TPP, relatively difficult. Nevertheless, the information presented, in conjunction with consultation with specialists, should be sufficient to form a consensus on the merits of adding butorphanol to Alberta's TPP.

Butorphanol

(Stadol NS[®], Apo-Butorphanol[®], PMS-Butorphanol[®])

OVERVIEW

Pharmacology/Pharmacokinetics

Butorphanol tartrate is a narcotic agonist-antagonist analgesic.(1) It acts as an agonist at kappa-opioid receptors and as a mixed agonist-antagonist at mu-opioid receptors in the central nervous system to alter the perception of pain.(2) Butorphanol has approximately 4 to 8 times the analgesic potency of morphine, 30 to 40 times that of meperidine and 16 to 24 times that of pentazocine.(3) Pharmacologically, butorphanol is similar to pentazocine and nalbuphine.(4) Like other mixed agonist-antagonists with a high affinity for the kappa receptor, butorphanol causes disagreeable psychotomimetic effects in some individuals.(2) Butorphanol is administered intranasally and therefore has a rapid onset of action (15 minutes).(3) The nasal spray formulation has an onset of action and systemic bioavailability similar to those achieved following parenteral administration of butorphanol.(4)

Indications

Butorphanol nasal spray is indicated for the relief of moderate to severe acute pain.(2) It has been utilized for post-operative pain, acute migraine pain, and for musculoskeletal pain.(5) Its efficacy for periods longer than 3 days has not been established.(2)

Dosage

Butorphanol is supplied as a nasal solution in a 10 mg/mL concentration.(2) The usual initial dose for adults is 1 spray in one nostril or 1 mg.(2) If pain relief is not adequate within 60-90 minutes, an additional 1 mg dose may be given.(2) The initial dose sequence may be repeated in 3 to 4 hours, as required.(1,2) Maximum daily dose is 16 mg.(2) More severe pain may be treated with an initial 2 mg dose or one spray in each nostril in patients who can remain recumbent in case drowsiness or dizziness occurs.(1,2) However, additional doses should not be given in 3 to 4 hours.(1,2) Dosage adjustments are required in renal or hepatic impairment and for the elderly.(2) After priming, each metered spray delivers 1 mg of butorphanol.(2) Each 2.5 mL bottle will deliver an average of 14 to 15 metered doses, if no priming is necessary.(2) If not used for 48 hours or longer, the unit must be reprimed.(1) With repriming before each dose, the unit will deliver only an average of 8 to 10 doses.(1)

Abuse Potential

As a class, the mixed agonist-antagonist opioid analgesics are reported to have less abuse potential than that of morphine, codeine or propoxyphene(3,4); nevertheless, transnasal butorphanol has been reported to be abused. Health Canada reported in 1997 that since November of 1994, 15 reports indicated suspected drug-seeking behaviour, drug abuse or addiction.(3) These reports involved patients aged 22 to 51 years taking butorphanol nasal spray for migraine headache, headache, cluster headaches, or intractable migraine.(3) Noteworthy were reports that included the receipt by 1 patient of 257 bottles of the nasal spray in a 9 month period and the receipt by 4 patients of prescriptions from 2 or more practitioners.(3) One of the 4 patients received prescriptions from 34 practitioners and had them filled at 23 different pharmacies.(3) In addition, Health Canada's Bureau of Drug Surveillance received 41 psychoactive drug loss/theft/forgery reports for butorphanol nasal spray during a 15 month period running 1995-96.(3) In early 1997, butorphanol nasal spray was added to one provincial Prescription Practice Program in order to screen for abuse, multiple prescribers and forgeries.(3) The manufacturer of Stadol NS[®] warns of dependence: "Among 161 patients who used butorphanol for 2 months or longer, during a controlled clinical trial, there were 5 reports suggestive of possible abuse, including 3 reports of clinically significant overuse."(2) In addition, the manufacturer acknowledges that more cases of drug abuse have been reported in patients receiving butorphanol nasal solution than in those receiving the injection formulation.(4) Subsequently, the manufacturer states that, in order to minimize the risk of abuse and dependence associated with butorphanol, prescription limitations be set for this drug, in addition to careful patient selection and frequent monitoring.(2)

Alternatives

Other marketed opiate analgesics available in oral or parenteral routes of administration are all alternatives to butorphanol nasal spray. Butorphanol's unique nasal spray formulation is an alternative to oral opioid analgesics, especially in the presence of nausea or vomiting, or to parenteral opioids, when the oral route of administration is not feasible.(5) However, narcotic analgesics in general are not first-line therapy for acute migraine headache.(5) More conventionally used drugs for acute migraine include the triptans and dihydroergotamine.

Cost

Opiate Agonist-Antagonist Cost Comparison

Medication	How Supplied	Cost ⁺⁺ (\$)/Unit	Dosage	Cost ⁺⁺ (\$)/Dose	Covered on AHWDBL?
Butorphanol (Apo-Butorphanol [®] , Stadol-NS [®] , PMS-Butorphanol [®])	2.5 mL spray pump delivering 1 mg/spray	41.68 ^{**}	1-2 mg q3-4h	2.78-5.56 (assuming 15 sprays per container)	No
Nalbuphine (Nubane [®])	10 mg/mL, 20 mg/mL injectable	4.46, 5.15	10-20 mg q3-6h	4.46-5.15	Yes
Pentazocine (Talwin [®])	50 mg tablets; 30 mg/mL injectable	0.37; 0.85	50-100mg q3-4h; 30 mg q3-4h	0.37-0.74; 0.85	Yes

⁺⁺ Acquisition cost only, for July 2002; * Usual dosage for opiate-naïve 70 kg adult, assuming normal renal/hepatic function; AHWDBL=Alberta Health and Wellness Drug Benefit List; ** For Apo-Butorphanol

Most opiate agonist analgesics are available on the AHWDBL for a fraction of the cost of butorphanol.

NON-MEDICAL UTILIZATION IN ALBERTA

Butorphanol nasal spray is abused in Alberta, although the incidence of abuse appears low. The Addiction Centre affiliated with the Foothills Hospital in Calgary reports that in the last 5 years, they treated only 5 adults addicted to butorphanol and they had all obtained it by prescription.(6) The provincial Opiate Dependency Program has had no cases of butorphanol abuse.(7) The AADAC does not keep statistics on which drugs are being abused.(8) The EPS reported that butorphanol is not seen as a problem on the streets of Edmonton.(9) Likewise, the Boyle McCauley Health Centre in Edmonton reported no issues with respect to butorphanol seeking or overdose.(10) The RCMP reported no major issues with butorphanol.(11) Because butorphanol abuse appears limited, a street value is unknown.

VOLUME OF DRUG IN ALBERTA

Apotex reported that 13,537 units of Apo-Butorphanol nasal spray was sold to Alberta pharmacies and wholesalers for the 12 month period of July 2001-June 2002.(12) Bristol-Myers Squibb does not track their sales data of Stadol NS[®] provincially.(13) Pharmascience did not return calls made to them regarding PMS-butorphanol[®] sales to Alberta. No provincial data could be located as to the number of prescriptions filled for any brand of butorphanol.

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