

Uses of Some Opiates Limited in HIV Patients

BY ROBERT FINN
San Francisco Bureau

SAN FRANCISCO — Opiates are often the best choice when treating pain in patients with HIV, but some of the available drugs can have limitations, Dr. Robert V. Brody said at a meeting on HIV management sponsored by the University of California, San Francisco.

Meperidine (Demerol), for example, is an opiate whose time has come and gone.

“If you know a physician who still uses intramuscular Demerol for the management of pain like we did 30 years ago, you’re in the presence of Tyrannosaurus rex,” said Dr. Robert V. Brody of San Francisco General Hospital.

In fact, this agent was removed from the San Francisco General Hospital formulary about 15 years ago. The problem is that although meperidine is a short-acting opiate, one of its metabolites accumulates. As patients continue to use

the drug, they tend to get irritable, experience myoclonus, or, in some cases, develop seizures, he said.

Similarly, mixed agonist-antagonists like pentazocine or butorphanol (Stadol) have little use. They’re difficult to titrate, and if a patient gets too high a dose, agitation and psychotomimetic effects can appear. Furthermore, since these drugs are part antagonist, it’s difficult to simply discontinue them and give the patient something stronger, Dr. Brody said.

Tramadol, although not a bad drug, also has its limitations. Not chemically an opiate, tramadol occupies the μ opiate receptor and also has properties similar to SSRIs. It’s prone to abuse and can be quite expensive, he said.

Buprenorphine is usually thought of in the context of opiate detox, but it’s also mildly effective against pain. Its major limitation is that it binds so tightly, if the patient turns out to need something stronger, nothing is going to work very well. It’s also quite expensive, Dr. Brody said.

Physicians often use fentanyl patches inappropriately. They should be used only for chronic, stable pain and never for postoperative or unpredictable pain. The onset of analgesia can take more than 12 hours, and fentanyl’s effects can last more than 18 hours after the patch is removed. Adding another opiate to a fentanyl patch can easily result in an overdose, he noted. ■

Weight Changes

In placebo-controlled studies (6-8 weeks), the incidence of patients who experienced 5% weight gain or weight loss is shown in Table 3.

Table 3. Incidence of Weight Gain and Weight Loss in Placebo-Controlled Trials with EMSAM (selegiline transdermal system)

Weight Change	EMSAM (N=757)	Placebo (N=614)
Gained 5%	2.1%	2.4%
Lost 5%	5.0%	2.8%

In these trials, the mean change in body weight among EMSAM-treated patients was -1.2 lbs compared to +0.3 lbs in placebo-treated patients.

Laboratory Changes

EMSAM and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with EMSAM.

ECG Changes

Electrocardiograms (ECGs) from EMSAM (N=817) and placebo (N=668) groups in controlled studies were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for clinically significant changes from baseline in these variables.

No clinically meaningful changes in ECG parameters from baseline to final visit were observed for patients in controlled studies.

Other Events Observed During the Premarketing Evaluation of EMSAM

During the premarketing assessment in major depressive disorder, EMSAM was administered to 2036 patients in Phase III studies. The conditions and duration of exposure to EMSAM varied and included double-blind and open-label studies.

In the tabulations that follow, reported adverse events were classified using a standard COSTART-based dictionary terminology. All reported adverse events are included except those already listed in Table 1 or elsewhere in labeling, and those events occurring in only one patient. It is important to emphasize that although the events occurred during treatment with EMSAM (selegiline transdermal system), they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body as a Whole: Frequent: Chest pain, neck pain. Infrequent: Bacterial infection, fever, cyst, fungal infection, chills, viral infection, suicide attempt, neck rigidity, pelvic pain, photosensitivity reaction, face edema, flank pain, hernia, intentional injury, neoplasm, generalized edema, overdose. Rare: Body odor, halitosis, heat stroke, parasitic infection, malaise, moniliasis.

Cardiovascular System: Frequent: Hypertension. Infrequent: Vasodilatation, tachycardia, migraine, syncope, atrial fibrillation, peripheral vascular disorder. Rare: Myocardial infarct.

Digestive System: Frequent: Constipation, flatulence, anorexia, gastroenteritis, vomiting. Infrequent: Increased appetite, thirst, periodontal abscess, eructation, gastritis, colitis, dysphagia, tongue edema, glossitis, increased salivation, abnormal liver function tests, melena, tongue disorder, tooth caries. Rare: GI neoplasia, rectal hemorrhage.

Hemic and Lymphatic System: Frequent: Ecchymosis. Infrequent: Anemia, lymphadenopathy. Rare: Leukocytosis, leukopenia, petechia.

Metabolic and Nutritional: Frequent: Peripheral edema. Infrequent: Hyperglycemia, increased SGPT, edema, hypercholesterolemia, increased SGOT, dehydration, alcohol intolerance, hyponatremia, increased lactic dehydrogenase. Rare: Increased alkaline phosphatase, bilirubinemia, hypoglycemic reaction.

Musculoskeletal System: Frequent: Myalgia, pathological fracture. Infrequent: Arthralgia, generalized spasm, arthritis, myasthenia, arthrosis, tenosynovitis. Rare: Osteoporosis.

Nervous System: Frequent: Agitation, paresthesia, thinking abnormal, amnesia. Infrequent: Leg cramps, tremor, vertigo, hypertension, twitching, emotional lability, confusion, manic reaction, depersonalization, hyperkinesias, hostility, myoclonus, circumoral paresthesia, hyperesthesia, increased libido, euphoria, neurosis, paranoid reaction. Rare: Ataxia.

Respiratory System: Frequent: Cough increased, bronchitis. Infrequent: Dyspnea, asthma, pneumonia, laryngismus. Rare: Epistaxis, laryngitis, yawn.

Skin and Appendages: Frequent: Pruritus, sweating, acne. Infrequent: Dry skin, maculopapular rash, contact dermatitis, urticaria, herpes simplex, alopecia, vesiculobullous rash, herpes zoster, skin hypertrophy, fungal dermatitis, skin benign neoplasm. Rare: Eczema.

Special Senses: Frequent: Taste perversion, tinnitus. Infrequent: Dry eyes, conjunctivitis, ear pain, eye pain, otitis media, parosmia. Rare: Mydriasis, otitis externa, visual field defect.

Urogenital System: Frequent: Urinary tract infection, urinary frequency, dysmenorrhea, metrorrhagia. Infrequent: Urinary tract infection (male), vaginitis, cystitis (female), hematuria (female), unintended pregnancy, dysuria (female), urinary urgency (male and female), vaginal moniliasis, menorrhagia, urination impaired (male), breast neoplasm (female), kidney calculus (female), vaginal hemorrhage, amenorrhea, breast pain, polyuria (female).

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

EMSAM is not a controlled substance.

Physical and Psychological Dependence

Several animal studies have assessed potential for abuse and/or dependence with chronic selegiline administration. None of these studies demonstrated a potential for selegiline abuse or dependence.

EMSAM has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of EMSAM misuse or abuse (e.g., development of tolerance, increases in dose, or drug-seeking behavior).

OVERDOSAGE

There are no specific antidotes for EMSAM. If symptoms of overdose occur, immediately remove the EMSAM system and institute appropriate supportive therapy. For contemporary consultation on the management of poisoning or overdose, contact the National Poison Control Center at 1-800-222-1222.

EMSAM is considered to be an irreversible, MAOI at therapeutic doses and, in overdose, is likely to cause excessive MAO-A inhibition, and may result in the signs and symptoms resembling overdose with other non-selective, oral MAOI antidepressants (e.g., tranylcypromine [Parnate[®]], phenelzine [Nardil[®]], or isocarboxazide [Marplan[®]]).

Overdosage With Non-Selective MAO Inhibition

NOTE: The following is provided for reference only; it does not describe events that have actually been observed with selegiline in overdose. No information regarding overdose by ingestion of EMSAM is available.

Typical signs and symptoms associated with overdose of non-selective MAOI antidepressants may not appear immediately. Delays of up to 12 hours between ingestion of drug and the appearance of signs may occur, and peak effects may not be observed for 24-48 hours. Since death has been reported following overdose with MAOI agents, hospitalization with close monitoring during this period is essential.

Overdosage with MAOI agents is typically associated with CNS and cardiovascular toxicity. Signs and symptoms of overdose may include, alone or in combination, any of the following: drowsiness, dizziness, faintness, irritability, hyperactivity, agitation, severe headache, hallucinations, trismus, opisthotonos, convulsions, coma, rapid and irregular pulse, hypertension, hypotension and vascular collapse, precordial pain, respiratory depression and failure, hyperpyrexia, diaphoresis, and cool, clammy skin. Type and intensity of symptoms may be related to extent of the overdose.

Treatment should include supportive measures, with pharmacological intervention as appropriate. Symptoms may persist after drug washout because of the irreversible inhibitory effects of these agents on systemic MAO activity. With overdose, in order to avoid the occurrence of hypertensive crisis (“cheese reaction”), dietary tyramine should be restricted for several weeks beyond recovery to permit regeneration of the peripheral MAO-A isoenzyme.

DOSAGE AND ADMINISTRATION

Initial Treatment

EMSAM (selegiline transdermal system) should be applied to dry, intact skin on the upper torso (below the neck and above the waist), upper thigh or the outer surface of the upper arm once every 24 hours. The recommended starting dose and target dose for EMSAM is 6 mg/24 hours. EMSAM has been systematically evaluated and shown to be effective in a dose range of 6 mg/24 hours to 12 mg/24 hours. However, the trials were not designed to assess if higher doses are more effective than the lowest effective dose of 6 mg/24 hours. Based on clinical judgment, if dose increases are indicated for individual patients, they should occur in dose increments of 3 mg/24 hours (up to a maximum dose of 12 mg/24 hours) at intervals of no less than two weeks. As with all antidepressant drugs, full antidepressant effect may be delayed.

Patients should be informed that tyramine-rich foods and beverages should be avoided beginning on the first day of EMSAM 9 mg/24 hours or 12 mg/24 hours treatment and should continue to be avoided for two weeks after a dose reduction to EMSAM 6 mg/24 hours or following the discontinuation of EMSAM 9 mg/24 hours or 12 mg/24 hours (see WARNINGS).

Special Populations

No dosage adjustment is required for patients with mild to moderate renal or hepatic impairment. The recommended dose for elderly patients (65 years) is EMSAM 6 mg/24 hours daily. Dose increases, in the elderly, should be made with caution and patients should be closely observed for postural changes in blood pressure throughout treatment.

How to Use EMSAM

- EMSAM should be applied to dry, intact skin on the upper torso (below the neck and above the waist), upper thigh or the outer surface of the upper arm. A new application site should be selected with each new patch to avoid re-application to the same site on consecutive days. Patches should be applied at approximately the same time each day.
- Apply the patch to an area of skin that is not hairy, oily, irritated, broken, scarred or calloused. Do not place the patch where your clothing is tight which could cause the patch to rub off.
- After you have selected the site for your patch, wash the area gently and thoroughly with soap and warm water. Rinse until all soap is removed. Dry the area with a clean dry towel.
- Just before you apply the patch, remove it from the pouch. Remove half of the protective backing and throw it away. Try not to touch the exposed side (sticky side) of the patch, because the medicine could come off on your fingers.
- Press the sticky side of the patch firmly against the skin site that was just washed and dried. Remove the second half of the protective liner and press the remaining sticky side firmly against your skin. Make sure that the patch is flat against the skin (there should be no bumps or folds in the patch) and is sticking securely. Be sure the edges are stuck to the skin surface.
- After you have applied the patch, wash your hands thoroughly with soap and water to remove any medicine that may have gotten on them. Do not touch your eyes until after you have washed your hands.
- After 24 hours, remove the patch. Do not touch the sticky side. As soon as you have removed the patch, fold it so that the sticky side sticks to itself.
- Throw away the folded patch so that children and/or pets cannot reach it.
- Wash your hands with soap and water.
- If your patch falls off, apply a new patch to a new site and resume your previous schedule.
- Only one EMSAM patch should be worn at a time.
- Avoid exposing the EMSAM application site to external sources of direct heat, such as heating pads or electric blankets, heat lamps, saunas, hot tubs, heated water beds, and prolonged direct sunlight.

Maintenance Treatment

It is generally agreed that episodes of depression require several months or longer of sustained pharmacologic therapy. The benefit of maintaining depressed patients on therapy with EMSAM at a dose of 6 mg/24 hours after achieving a responder status for an average duration of about 25 days was demonstrated in a controlled trial (see Clinical Efficacy Trials in Full Prescribing Information and INDICATIONS AND USAGE). The physician who elects to use EMSAM for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

DISTRIBUTED BY:

Bristol-Myers Squibb Company
Princeton, NJ 08543 U.S.A.

MANUFACTURED FOR:

Somerset Pharmaceuticals, Inc.
Tampa, FL 33607 USA

Somerset
PHARMACEUTICALS, INC.
Tampa, FL 33607 USA

Issued February 2006
EM-B0001A-02-06

EMSAM:PIR2

Use of Intranasal Lidocaine May Relieve Migraine

SOUTH LAKE TAHOE, CALIF. —

The next time you see a patient with a migraine headache, you might want to try intranasal lidocaine, Dr. John Richards said at an emergency medicine conference sponsored by the University of California, Davis.

“It’s a very easy block, and it doesn’t involve a needle,” said Dr. Richards of the department of emergency medicine at the UC Davis Medical Center, Sacramento. “So it’s worth a try.”

The literature on lidocaine treatment for migraine is not extensive, and at least one study found it to be of no benefit. But in some studies, lidocaine successfully resolved the migraine in 30%-50% of patients, with a relapse rate of about 20%.

Dr. Richards said he has had good experience with lidocaine. “I’ve had success with it for migraines, cluster headaches, and just headaches in general,” he said.

With cluster headaches, there usually is not complete relief, “but it does help them quite a bit,” he said.

The technique for treatment is to apply 4% lidocaine jelly to a long cotton swab, then aim the swab straight down the nasal canal all the way until it stops, on the side of the headache, or bilaterally if the headache is bilateral. The target is the sphenopalatine ganglion, which is located in the pterygopalatine fossa, posterior to the middle turbinate and inferior to the maxillary nerve. “It is covered by a small amount of mucous membrane [1.5 mm thick], so it is actually pretty easy to get to,” Dr. Richards said.

A second technique is to lay the patient back, with the head over the edge of the table at a 45-degree angle, and administer lidocaine drops, which will pool in the appropriate area. In one successful randomized trial, 10 drops were used, and the patients remained in their positions for 30 minutes, he said.

—Timothy F. Kirn