

Draft Guidelines for Grave's Tx Stress Options

BY JOYCE FRIEDEN

New draft hyperthyroidism treatment guidelines from the American Thyroid Association and the American Association of Clinical Endocrinologists emphasize that although radioactive iodine is a good treatment for the disorder, patients need to consult with their physicians about all three available treatment options: radioactive io-

dine, surgery, and antithyroid medications, according to Dr. Rebecca Bahn.

"Physicians in the United States have long considered radioactive iodine [RAI] be the preferred treatment for Grave's disease," Dr. Bahn, chair of the guideline task force, said in an interview. "We're recommending that the patient and the physician have a careful and clear discussion about the three treatment options, and that any of the three options

are viable. It's really a decision between the patient and the physician." Dr. Bahn presented the draft guidelines in September at the annual meeting of the American Thyroid Association in Palm Beach, Fla.

That is not to say that there aren't some situations in which one procedure is preferable to another, said Dr. Bahn, professor of medicine and a consultant in endocrinology at the Mayo Clinic,

Rochester, Minn. For example, "pregnant women should not receive radioactive iodine, and patients with medical problems that put them at high risk for surgery should not choose surgery. But our overall recommendation is that the patient and the physician should make the decision following a careful discussion."

Another major change in the guidelines deals with antithyroid drug thera-

Important Safety Information (contd)

- EMBEDA™ is contraindicated in patients with a known hypersensitivity to morphine, morphine salts, naltrexone, or in any situation where opioids are contraindicated
- EMBEDA™ is contraindicated in patients with significant respiratory depression in unmonitored settings or the absence of resuscitative equipment
- EMBEDA™ is contraindicated in patients with acute or severe bronchial asthma or hypercapnia in unmonitored settings or the absence of resuscitative equipment
- EMBEDA™ is contraindicated in any patient who has or is suspected of having paralytic ileus
- EMBEDA™ may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, and profound sedation or coma may result
- Respiratory depression is the chief hazard of all morphine preparations such as EMBEDA™. Respiratory depression occurs more frequently and is more dangerous in elderly and debilitated patients, and those suffering from conditions accompanied by hypoxia, hypercapnia, or upper airway obstruction (when even moderate therapeutic doses may significantly decrease pulmonary ventilation)
- EMBEDA™ should be used with extreme caution in patients with chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve (e.g., severe kyphoscoliosis), hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of morphine may increase airway resistance and decrease respiratory drive to the point of apnea. In these patients, alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose
- The respiratory depressant effects of morphine with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. EMBEDA™ can produce effects on pupillary response and consciousness, which may obscure neurologic signs of further increases in pressure in patients with head injuries. EMBEDA™ should only be administered under such circumstances when considered essential and then with extreme care
- EMBEDA™ may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has already been compromised by a reduced blood volume or a concurrent administration of drugs such as phenothiazines or general anesthetics. EMBEDA™ may produce orthostatic hypotension and syncope in ambulatory patients
- EMBEDA™ should be administered with caution to patients in circulatory shock, as vasodilation produced by the drug may further reduce cardiac output and blood pressure
- EMBEDA™ should be used with caution and in reduced dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result
- EMBEDA™ should not be given to patients with gastrointestinal obstruction, particularly paralytic ileus, as there is a risk of the product remaining in the stomach for an extended period and the subsequent release of a bolus of morphine when normal gut motility is restored
- Patients taking EMBEDA™ who are scheduled for cordotomy or other interruption of pain transmission pathways should have EMBEDA™ ceased 24 hours prior to the procedure and the pain controlled by parenteral short-acting opioids. In addition, the post-procedure titration of analgesics for such patients should be individualized to avoid either oversedation or withdrawal syndromes
- EMBEDA™ may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis
- Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are common during chronic opioid therapy
- EMBEDA™ should be administered with caution and in reduced dosages in elderly or debilitated patients; patients with severe renal or hepatic insufficiency; Addison's disease; myxedema; hypothyroidism; prostatic hypertrophy or urethral stricture
- Caution should also be exercised in the administration of EMBEDA™ to patients with CNS depression, toxic psychosis, acute alcoholism, and delirium tremens
- All opioids may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings

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py. "It used to be that propylthiouracil (PTU) or methimazole could be used interchangeably, but there's now good evidence that there's a very serious hepatic necrosis associated with PTU; it's rare, but it's not at all associated with methimazole," she said. "So our guidelines will say that if you're going to use antithyroid drugs you should use methimazole except in certain instances."

On the other hand, women who have Grave's disease that is diagnosed in the first trimester of pregnancy should be started on PTU, because methimazole is associated with certain birth defects, Dr.

Bahn said. "Also, if the patient is found to have minor side effects with methimazole, in some cases PTU might be used. But the overall drug of choice in most instances is methimazole."

In the case of hyperthyroidism caused by nodules, "for definitive treatment we don't recommend antithyroid drugs because the patient would have to be on those essentially forever," she said. "In some instances, such as patients with a relatively short life expectancy or iodine-induced disease, these medications may be used, but in general, the treatment is surgery or RAI." In particular, the task

force is recommending that for toxic multinodular goiter, near-total or total thyroidectomy should be performed. If the toxic adenoma is in the thyroid isthmus, an ipsilateral thyroid lobectomy or isthmectomy should be performed.

The guidelines also address the treatment of hyperthyroidism in patients with Grave's ophthalmopathy. "For the 50% of Grave's patients who have evidence of mild eye disease, any [Grave's disease] treatment option is fine, but if RAI is chosen, then the physician and patient need to talk about the risk-benefit ratio of using prednisone" for 6-8 weeks

to prevent the eye disease from worsening as a result of RAI. Patients who are at higher risk of worsening eye disease include smokers and patients with high anti-TSH receptor antibodies, she said. "They are most likely to progress if not given concurrent steroids."

Dr. Bahn said she expects the task force will give a final draft of the guidelines to the boards of both the ATA and AACE for their approval in late fall and hopes that the guidelines will be ready for publication in early 2010. Dr. Bahn said she had no conflicts to declare with regard to the guidelines. ■

Important Safety Information (contd)

- EMBEDA™ may impair the mental and/or physical abilities needed to perform potentially hazardous activities such as driving a car or operating machinery. Patients must be cautioned accordingly. Patients should also be warned about the potential combined effects of EMBEDA™ with other CNS depressants, including other opioids, phenothiazines, sedative/hypnotics, and alcohol
- Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol) should be administered with caution to a patient who has received or is receiving a course of therapy with EMBEDA™. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of EMBEDA™ and/or may precipitate withdrawal symptoms in these patients
- Consuming EMBEDA™ that has been tampered with by crushing, chewing, or dissolving the extended-release formulation can release sufficient naltrexone to precipitate withdrawal in opioid-dependent individuals. Symptoms of withdrawal usually appear within five minutes of ingestion of naltrexone and can last for up to 48 hours. Mental status changes can include confusion, somnolence, and visual hallucinations. Significant fluid losses from vomiting and diarrhea can require intravenous fluid administration. Patients should be closely monitored and therapy with non-opioid medications tailored to meet individual requirements
- **Care should be taken to use low initial doses of EMBEDA™ in patients who are not already opioid-tolerant, especially those who are receiving concurrent treatment with muscle relaxants, sedatives, or other CNS active medications**
- EMBEDA™ should not be abruptly discontinued
- Serious adverse reactions that may be associated with EMBEDA™ therapy in clinical use include: respiratory depression, respiratory arrest, apnea, circulatory depression, cardiac arrest, hypotension, and/or shock
- The common adverse events seen on initiation of therapy with EMBEDA™ are dose dependent, and their frequency depends on the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as part of opioid analgesia. The most frequent of these include drowsiness, dizziness, constipation, and nausea
- Additional common adverse events reported during clinical studies include constipation, nausea, and somnolence
- EMBEDA™ should be used with great caution and in reduced dosage in patients who are concurrently receiving other central nervous system (CNS) depressants including sedatives, hypnotics, general anesthetics, antiemetics, phenothiazines, other tranquilizers, and alcohol because of the risk of respiratory depression, hypotension, and profound sedation or coma. When such combined therapy is contemplated, the initial dose of one or both agents should be reduced by at least 50%
- EMBEDA™ may enhance the neuromuscular blocking action of skeletal relaxants and produce an increased degree of respiratory depression
- Monoamine oxidase inhibitors (MAOIs) have been reported to potentiate the effects of morphine anxiety, confusion, and significant depression of respiration or coma. EMBEDA™ should not be used in patients taking MAOIs or within 14 days of stopping such treatment
- There is an isolated report of confusion and severe respiratory depression when a hemodialysis patient was concurrently administered morphine and cimetidine
- Morphine can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone. Morphine may also lead to acute retention of urine by causing spasm of the sphincter of the bladder, particularly in men with prostatism
- Anticholinergics or other medications with anticholinergic activity when used concurrently with opioid analgesics may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus

Indications and Usage

- EMBEDA™ is an extended-release oral formulation of morphine sulfate and naltrexone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time
- EMBEDA™ is NOT intended for use as a prn analgesic
- EMBEDA™ is not indicated for acute/postoperative pain or if the pain is mild or not expected to persist for an extended period of time. EMBEDA™ is only indicated for postoperative use if the patient is already receiving chronic opioid therapy prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time

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