

Practice parameter: Appropriate use of ergotamine tartrate and dihydroergotamine in the treatment of migraine and status migrainosus

(Summary statement)

Report of the Quality Standards Subcommittee of the American Academy of Neurology

Mission statement. The Quality Standards Subcommittee (QSS) will seek to develop scientifically sound and clinically relevant parameters for the practice of neurology. Practice parameters are strategies for patient management developed to assist physicians in clinical decision making. They may include standards, guidelines, or practice options or advisories. QSS focuses on established aspects of neurological practice and is directed toward enhancing quality of care by helping physicians make practice decisions based on expected health outcomes.

Justification. Headache is a common reason for medical consultation, accounting for about 18 million outpatient visits per year in the United States. Although most headache sufferers who seek care are treated in the primary care setting, migraine is a leading reason for neurologic consultation. Ergotamine tartrate (ET) and dihydroergotamine (DHE) are medications commonly used for acute migraine, but they are often misused. Underutilization can needlessly prolong a migraine attack and overutilization can produce ergotism and, in the case of ET, chronic daily headaches refractory to abortive or preventive treatments.

The working panel for this practice parameter was made up of members of the Headache and Facial Pain Section of the American Academy of Neurology. These experts in the field of headache exhaustively reviewed the literature as it pertains to the efficacy and toxicity of ET and DHE in headache treatment. The following practice parameter provides guidance to maximize the outcome of treatment (ablation or reduction of the pain and as-

sociated symptoms) in acute migraine and status migrainosus, with minimum adverse effects and toxicity.

Overview. ET, originally derived from a rye fungus (*Claviceps purpurea*), is an ergopeptide that consists of a natural D-lysergic acid linked to a tricyclic peptide moiety by a peptide bond. It possesses alpha-adrenergic antagonist and serotonergic agonist activities and vasoconstricting actions, stimulating arterial smooth muscle through serotonin receptors. It also constricts venous capacitance vessels. DHE is a derivative of ET that has been reduced at the 9-10 double bond on the D-lysergic acid moiety. Both ET and DHE are agonists at the serotonin 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors. In addition, they interact with 5-HT₂, adrenergic, and dopaminergic receptors. DHE differs from ET in that DHE is a less potent arterial vasoconstrictor, but it is almost equipotent as a venoconstrictor. Clinically, ET is available as a sublingual preparation and, in combination with caffeine, as an oral tablet, and also as a suppository. The ET inhaler and ET/barbiturate/belladonna alkaloid combinations are no longer commercially available. DHE is currently available only in 1 mg/ml ampules, which can be administered intramuscularly (IM), subcutaneously (SC), or intravenously (IV). A nasal spray preparation has been formulated and is awaiting approval from the US Food and Drug Administration.

Process. A literature search was conducted using the Medline database, covering the years 1966 to 1991. Search topics included treatment of migraine,

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Approved by the Quality Standards Subcommittee May 3, 1994. Approved by the AAN Practice Committee May 4, 1994. Approved by the AAN Executive Board May 6, 1994.

Received June 2, 1994. Accepted in final form August 9, 1994.

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ET overuse, ergotism, side effects of analgesics and ergots, chronic daily headache, chronic tension headache, transformed migraine, abortive headache treatment, acute headache treatment, ET, and DHE. Only references in English and dealing with humans were abstracted and reviewed. Standard textbooks of neurology and headache were reviewed for additional references. Abstracts were reviewed and articles pertaining to the outcomes of efficacy of treatment as well as to toxicity were selected. One hundred fifty-six articles and abstracts were divided into prospective studies, retrospective studies, case reports, and outcome studies. They were then subdivided into class I, class II, and class III studies (see boxed Definitions at right). Appropriate evidence tables were prepared for ET efficacy, adverse effects of ET, and adverse effects of DHE. The appropriate literature was distributed to subgroups of the committee for critical review, evaluation, and completion of the evidence tables. A meeting was convened of all the subgroups and the evidence was reviewed. Outside experts were consulted. The following conclusions and recommendations were prepared on the basis of the long, detailed report of the headache subgroup.

Conclusions. Most of the evidence supporting the efficacy of ET in migraine comes from class II and class III studies although there were several class I studies. The incidence of nausea and vomiting is high. Reducing the dosage or adding antiemetics may improve tolerance to the drug.

Twenty-one studies concerning DHE efficacy were reviewed; these studies were difficult to interpret because they did not use the International Headache Society (IHS) classification, many were open and unblinded, and few compared DHE with placebo. There were only a few class I studies. There was no definition of improvement. Side effects were either not mentioned or not emphasized. From analysis of this evidence, DHE IM or IV is very effective for acute migraine attacks. Repetitive IV DHE, given for 3 to 7 days at doses of up to 20 mg per week, is helpful to break chronic daily headache, including transformed migraine, analgesic or ET rebound headache, status migrainosus, and cluster headache. Nearly all studies were done in a hospital setting. There are insufficient data at this time to determine whether IV DHE given for 2 or more consecutive days in an outpatient setting is safe or effective.

Significant adverse effects were absent. Contraindications to the use of ET or DHE include renal or hepatic failure; pregnancy; coronary, cerebral, and peripheral vascular disease; hypertension; and sepsis. All evidence regarding adverse effects of the ergot alkaloids is class III, ie, predominantly single case reports. Most reports concerned ET use; reports of adverse effects associated with DHE were rare. Based on class III evidence, it is likely that even small doses of ET, if taken regularly, two or three times per week or more in some

DEFINITIONS

Classification of evidence

Class I. Evidence provided by one or more well-designed randomized controlled clinical trials.

Class II. Evidence provided by one or more well-designed clinical studies such as case-control studies, cohort studies, and so forth.

Class III. Evidence provided by expert opinion, nonrandomized historical controls, or one or more case reports.

Strength of recommendations

Standards. Generally accepted principles for patient management that reflect a high degree of clinical certainty (ie, based on class I evidence or, when circumstances preclude randomized clinical trials, overwhelming evidence from class II studies that directly addresses the question at hand or from decision analysis that directly addresses all the issues).

Guidelines. Recommendations for patient management that may identify a particular strategy or range of management strategies and that reflect moderate clinical certainty (ie, based on class II evidence that directly addresses the issue, decision analysis that directly addresses the issue, or strong consensus of class III evidence).

Practice options or advisories. Other strategies for patient management for which there is unclear clinical certainty (ie, based on inconclusive or conflicting evidence or opinion).

Practice parameters. Results, in the form of one or more specific recommendations, from a scientifically based analysis of a specific clinical problem.

patients with migraine, can induce a dependency (physiologic and psychological) state.

ET is usually not recommended for children. Based on limited and anecdotal data, some pediatric neurologists are now using DHE alone or with metoclopramide or promethazine to treat migraine or intractable headache in children and adolescents.

Recommendations. Standards. On the basis of class I, class II, and class III studies, supported by extensive clinical experience, *the use of ET in the treatment of migraine in adults may be recommended as safe and effective when used in appropriate doses and when patients with contraindications are excluded.* DHE can be administered IM in the office, emergency department, and home.

On the basis of class I and class II studies, and the uniform consensus of expert opinion, *the use of DHE in the treatment of migraine in adults may be recommended as safe and effective when used in appropriate doses and when patients with contraindications are excluded.*

Guidelines. On the basis of class III evidence, one class II study, and the overwhelming consen-

sus of expert opinion, *repetitive IV DHE, given over 3 to 7 days in an inpatient setting, is effective and safe in the treatment of intractable headache in adults* (migraine status, transformed migraine, rebound headache). Longer-term use of daily IV or IM DHE cannot be recommended at this time because data on potential adverse outcomes from such treatment are not currently available.

On the basis of class III evidence, current available data, and overwhelming consensus of expert opinion, *the use of ET should be restricted to no more than 2 usage days per week, except at or around a menstrual period provided that limited or no use occurs during the remainder of the month. The total weekly dose should not exceed 10 mg.*

Recommendations for future research. Plan a prospective, double-blind, placebo-controlled, parallel or crossover study of ET and DHE for IHS migraine and possibly other headache types. Outcome measures should include quality of life, time to improvement of headache, and associated symptoms and headache recurrence.

Compare DHE with sumatriptan, neuroleptics, anti-nauseants, nonsteroidal anti-inflammatory drugs, etc, in all parenteral forms.

Plan a prospective double-blind, controlled study of repetitive IV DHE, comparing it with neuroleptics, corticosteroids, and placebo in intractable headache, with precise definitions to delineate which types of chronic daily headache will respond.

Acknowledgments

The Quality Standards Subcommittee wishes to express particular gratitude to Stephen D. Silberstein, MD, Chair of the Work-

ing Panel, which also consists of members of the AAN Headache and Facial Pain Section, for their work in preparing this practice parameter and the background paper for it. QSS also wishes to express appreciation for the work of its Chair, Jay H. Rosenberg, MD, who served as QSS facilitator of this project.

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The following medical societies were invited to comment on this practice parameter, and all of them did so: American Association of Neurological Surgeons, American Academy of Family Physicians, American College of Emergency Physicians, American College of Physicians, American Academy of Pain Medicine, American Association for the Study of Headache, and American Society for Clinical Pharmacology and Therapeutics. Thirteen members of the AAN Member Reviewer Network also reviewed the practice parameter. Members of the AAN Headache and Facial Pain Section and the Women in Neurology Section also provided comment.

This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.