EDRATE DISODIUM
NDA 11355
LOG 1205

Panel on Cardiovascular Drugs (I)

INDICATIONS

Cardiac arrhythmias associated with digitalis toxicity, as follows:

A. Ventricular arrhythmias secondary to digitalis.

EVALUATION: Effective.

B. Supraventricular arrhythmias secondary to digitalis.

EVALUATION: Possibly effective.

C. First, second, and advanced degrees of heart block secondary to digitalis.

EVALUATION: Probably effective.

COMMENTS: See General Comments.

DOCUMENTATION:

1. Cohen, B. D., N. Spritz, G. D. Lubash, and A. L. Rubin. Use of a calcium chelating agent (NaEDTA) in cardiac arrhythmias. Circulation 19:918-927, 1959.
2. Gubner, R. S., and H. Kallman. Treatment of digitalis toxicity by chelation of serum calcium. Amer. J. Med. Sci. 234:136-144, 1957.
3. Rosenbaum, J. L., D. Mason, and M. J. Seven. The effect of disodium EDTA on digitalis intoxication. Amer. J. Med. Sci. 240:77-84, 1960.
4. Soffer, A. Chelation therapy for cardiovascular disease, pp. 15-33. In Chelation Therapy. Springfield: Charles C Thomas, 1964.
5. Soffer, A., T. Toribara, D. Moore-Jones, and D. Weber. Clinical applications and untoward reactions of chelation and cardiac arrhythmias. Arch. Intern. Med. (Chicago) 106:824-834, 1960.

II. Cardiac arrhythmias, including supraventricular arrhythmias, ventricular arrhythmias, and atrioventricular conduction defects in the absence of digitalis.

EVALUATION: Possibly effective.

COMMENTS: Experience seems to indicate better results in supraventricular arrhythmias in this category on non-digitalis-induced arrhythmias, but further study is needed (1,2).

DOCUMENTATION:

1. Soffer, A., T. Toribara, D. Moore-Jones, and D. Weber. Clinical applications and untoward reactions of chelation and cardiac arrhythmias. Arch. Intern. Med. (Chicago) 106:824-834, 1960.

2. Surawicz, B., M. G. MacDonald, V. Fuller, and J. C. Bettinger. Treatment of cardiac arrhythmias with disodium ethylenediamine tetraacetic acid (EDTA). Amer. Heart J. 58:493-503, 1959.

III. Occlusive vascular disorders, including angina pectoris, peripheral vascular disease, cerebrovascular disease, diabetic retinopathy, and calcareous valvular disease.

EVALUATION: Possibly effective.

COMMENTS: Although the insert states that this agent "is not recommended for the treatment of generalized arteriosclerosis associated with advancing age," it appears, nevertheless, that such claims are strongly implied in the "Clinical Reports" section of the insert.

There have been no adequately controlled studies to evaluate the effect of Endrate Disodium in any of the above conditions. Meltzer et al. (6) concluded that, although transient improvement may occur with EDTA therapy in patients with angina pectoris, it did not alter the natural history of the disease nor offer any protection against repeated infarction or death. They state that "at present we believe that chelation as used in this study did not benefit patients more than other commonly used therapeutic methods. It is not a useful clinical tool in the treatment of coronary disease at the present." Soffer (8) was unable to produce significant changes in a small group of patients with peripheral vascular disease, nor could he show any change in patients with scleroderma heart disease or calcific aortic stenosis. An additional study by Kitchell et al. (3) also failed to demonstrate any significant benefit, other than a possible short-lived effect in patients with coronary artery disease and angina pectoris. Investigations by other authors (1,2,4,5,7) are little more than testimonials.

DOCUMENTATION:

1. Bolick, L. E., and D. H. Blankenhorn. A quantitative study of coronary arterial calcification. Amer. J. Path. 39:511-519, 1961.
2. Clarke, N. E., Sr., N. E. Clarke, Jr., and R. E. Mosher. Treatment of occlusive vascular disease with disodium ethylene diamine tetraacetic acid (EDTA). Amer. J. Med. Sci. 239:732-744, 1960.
3. Kitchell, J. R., F. Palmon, Jr., N. Aytan, and L. E. Meltzer. The treatment of coronary artery disease with disodium EDTA; a reappraisal. Amer. J. Cardiol. 11:501-506, 1963.
4. Lamar, C. P. Chelation therapy of occlusive arteriosclerosis in diabetic patients. Angiology 15:379-395, 1964.
5. Lamar, C. P. Chelation endarterectomy for occlusive atherosclerosis. J. Amer. Geriat. Soc. 14:272-294, 1966.
6. Meltzer, L. E., M. E. Ural, and J. R. Kitchell. The tr atment of coronary artery disease with disodium EDTA, pp. 132-136. In M. J. Seven, Ed. Metal-Binding in Medicine. Philadelphia: J. P. Lippincott Co., 1960.
7. Pullman, T. N., J. R. Lawrence, and M. Packland. Synthetic chelating agents in clinical medicine, pp. 175-194. In A. C. DeGraff, Ed. Annual Review of Medicine. (Vol. 14) Palo Alto, California: Annual Reviews, Inc., 1963.

8. Soffer, A. Chelation therapy for cardiovascular disease, pp. 15-33. In Chelation Therapy. Springfield: Charles C Thomas, 1964.

GENERAL COMMENTS

It appears that the onset of action of Endrate Disodium is rapid. The effect is transient. Therefore, other agents with longer duration of action may be needed in the treatment of arrhythmia if the arrhythmia is not terminated or if it recurs.

Further investigation is necessary to determine the effectiveness, safety, and appropriate dosages of Endrate Disodium as applied to cardiac arrhythmias in man. It does not appear to be the drug of choice in the treatment of arrhythmias produced by digitalis toxicity. However, its possible usefulness in decreasing the degree of atrioventricular block may merit further exploration. This may apply especially to digitalis-induced atrioventricular block, but may also pertain to atrioventricular block not caused by digitalis.

The statement in the insert that "the use of the drug in any particular clinical entity is recommended only when the severity of the disease justifies the aggressive measures associated with this type of therapy" deserves special emphasis.

Endrate Disodium has been used by some investigators for assessment of the degree of digitalization and for protective effect in pushing digitalis to a maximally effective dose (3,8). Inasmuch as it has been demonstrated in normal man and in digitalis-toxic dogs that Endrate Disodium has a negative inotropic effect (4,7,9), the drug may actually negate the desired action of digitalis and should not be used for this purpose. For example, Cohen et al. (2) described two patients who seemed to show a reversal of digitalis effect after receiving Endrate Disodium; one patient developed pulmonary edema shortly after treatment. Other isolated cases have been noted in which there was clinical deterioration or death within hours of the infusion of Endrate Disodium. This may have resulted from a negative inotropic effect in patients with congestive heart failure. Certainly, further study is necessary to observe the incidence and severity of the negative inotropic effect of this agent, especially in patients with limited cardiac reserve.

Contraindications:

1. Because of reports of convulsions thought to be induced by hypocalcemia, the drug should not be used in patients with seizure disorders or a history of a suspected intracranial lesion (brain tumor, CVA, etc.) that may predispose to convulsions (7,11).

2. The drug should not be given to patients with known or suspected hypocalcemia.

Warnings, Precautions, and Adverse Experiences:

1. Periodic BUN and creatinine determinations, as well as frequent urinalyses, should be done on patients receiving the drug over a long period.

2. Patients should remain in bed for a short period after the infusion of Endrate Disodium because of the possibility of postural hypotension, which can develop during and for a short time after infusion.

3. The possibility of an adverse effect on myocardial contractility previously noted should be considered when administering the drug to patients with heart disease.

4. It has been recommended that calcium gluconate be available during therapy to combat any serious effects resulting from depletion of serum calcium. However, Eliot and Blount (5) recommend great caution in the use of intravenous calcium in the treatment of tetany, especially in digitalized patients, citing an adverse experience of their own and one from the literature.

5. Because of its irritant effect on the tissues and the danger of serious side effects in undiluted form, the vial containing 150 mg/ml of solution should be diluted to at least a 3% solution before infusion.

6. Endrate Disodium therapy has been shown to cause a lowering of blood sugar and insulin requirements in patients with diabetes who are treated with insulin. It has been theorized that this occurs because of chelation of zinc in the exogenous insulin, causing it to be more rapidly soluble and thereby producing hypoglycemia (5).

Side Effects:

1. Gastrointestinal symptoms, such as nausea, vomiting, and diarrhea, are fairly common.

2. Transient symptoms, such as circumoral paresthesias, numbness, and headache, can occur.

3. Exfoliative dermatitis and febrile reactions have been described.

4. One case of anemia that responded to cessation of therapy has been noted.

5. A drop in both systolic and diastolic blood pressure can occur transiently.

6. There is suggestive evidence that Endrate Disodium infusion produces an early and transient rise in uric acid. One case of gout may have been precipitated by this therapy (6).

Dosage and Administration:

1. Endrate Disodium is supplied in a solution of 150 mg/ml only for intravenous use. It should not be administered in a concentration of greater than 3%.

2. The usual dose for the treatment of cardiac arrhythmias in adults is 3 g of Endrate Disodium as a 1.2% solution in 5% dextrose and water over a 30-min period. Some authors have given this amount over shorter periods, in dosages of 0.5-4.0 g in ½-4 hr. Arena (1) recommended a 2% solution over a period of 1-2 hr in children, with a total dose of 36 mg/kg twice daily. On a weight basis, in adults the usual recommended dose is 50 mg/kg in 24 hr.

3. Toxicity is probably related to both total dose and rate of infusion. There is considerable debate as to the proper dosage in the treatment of arrhythmias. For example, Eliot and Blount (5) suggested a minimum of 3 g of trisodium EDTA to be given in 12 min before a therapeutic test is discontinued in the treatment of arrhythmias.

DOCUMENTATION:

1. Arena, J. M. General considerations of poisoning, p. 16. In Poisoning. Springfield, Illinois: Charles C Thomas, 1963.
2. Cohen, B. D., N. Spritz, G. D. Lubash, and A. L. Rubin. Use of a calcium chelating agent (NaEDTA) in cardiac arrhythmias. Circulation 19:918-927, 1959.
3. Cohen, S., A. M. Weissler, and C. D. Schoenfeld. Antagonism of the contractile effect of digitalis by EDTA in the normal human ventricle. Amer. Heart J. 69:502-514, 1965.
4. Cook, J. R., J. W. Pollard, and J. C. Cooley. Myocardial contractile force in the treatment of ouabain intoxication with disodium EDTA, potassium chloride, and magnesium sulfate. J. Lab. Clin. Med. 69:292-303, 1967.
5. Eliot, R. S., and S. G. Blount, Jr. Calcium, chelates, and digitalis; a clinical study. Amer. Heart J. 62:7-21, 1961.
6. Lamar, C. P. Chelation therapy of occlusive arteriosclerosis in diabetic patients. Angiology 15:379-395, 1964.
7. Landry, A. B., Jr., and A. V. N. Goodyer. Experimental study; rate of rise of left ventricular pressure; indirect measurement and physiologic significance. Amer. J. Cardiol. 15:660-664, 1965.
8. Leitch, J. L., and T. J. Haley. The effect of ethylenediamine tetra-acetic acid and other chelating agents in the isolated mammalian heart. Arch. Internat. Pharmacodyn. 95:234-242, 1953.
9. Nalbandian, R. M., S. Gordon, R. Campbell, and J. Kaufman. A new, quantitative digitalis tolerance test based upon the synergism of calcium and digitalis. Amer. J. Med. Sci. 233:503-512, 1957.
10. Nalbandian, R. M., S. Gordon, and J. Kaufman. Calcium-digitalis tolerance test; a clinical report of the first 24 trials. Amer. J. Med. Sci. 234:291-302, 1957.

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11. Soffer, A., T. Toribara, D. Moore-Jones, and D. Weber. Clinical applications and untoward reactions of chelation and cardiac arrhythmias. Arch. Intern. Med. (Chicago) 106:824-834, 1960.

Approved by _____

Chairman