ENDRATE®
DISODIUM EDATATE, ABBOTT

**ENDRATE® Disodium (disodium edetate) is the disodium salt of a synthetic chelating agent, ethylenediaminetetraacetic acid (EDTA). Its structural formula is as follows:**

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\text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_2\text{CH}_2\text{CH}_2\text{NH}_2\text{CH}_2\text{COOH} + \text{H}_2\text{O} \rightarrow \text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_2\text{CH}_2\text{CH}_2\text{NH}_2\text{COONa}_2
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**Intravenous chelation therapy is indicated in patients with high serum calcium levels.** It has also been used in a variety of conditions associated with hypercalcemia, including kidney stones, multiple myeloma, and metastatic bone disease. EDTA forms complexes with metal ions, such as calcium, and is then excreted by the kidneys. The mechanism of action involves the formation of a chelate, which is less stable than the original complex and is thereby excreted more rapidly.

**Precautions and Side Effects:**

- Hypercalcemia represents a theoretical danger to the patient under treatment with disodium edetate, but no death has been reported to date. Injection of undissociated, insoluble salts, such as calcium, may result in hypocalcemia and neurological disorders. Possible effects from the depuration of body calcium may readily be reversed by administration of calcium gluconate, which should be available during therapy.

- It should be noted that the use of disodium edetate may result in renal dysfunction if large doses are given. Repeated urinalysis during the course of therapy may indicate renal insufficiency, and any further disodium edetate should not be administered until the condition has been reversed.

**Administration and Dosage:**

The physician is advised to follow the dosage recommendations carefully, and the preceding section on "Precautions and Side Effects" should be consulted before therapy begins.
Endure (disodium edetate) is highly soluble and is injected intravenously. The solution must be diluted (see below) before injection. The recommended daily dosage is 50 mg./kg. of body weight. Clinical reports appear to indicate that there is little danger from toxic effects if the adult dose does not exceed 3 Gm. in 24 hours.

The required volume of disodium edetate solution from an ampoule should be diluted with 500 ml. of 5% dextrose injection or with sodium chloride injection. This dilute solution should be administered intravenously during a period not less than two and a half hours. The usual intravenous injection is 5 to 10 hours. Present evidence indicates that toxicity is dependent on both speed of injection and speed of administration. Therefore, it is recommended that administration must be slow.

The total number of days of treatment will depend on the individual. The usual treatment is daily intravenous injection for five days, followed by two days without further treatment. This cycle is repeated three times (total 6 dosages of edetate has been given for the total 18 days). Intravenous administration should be continued for several weeks while the results are being observed. Further courses of treatment may be indicated to maintain or increase the degree of improvement.

CLINICAL REPORT

So far, and more recently Berryman, have provided excellent surveys of the EDTA literature. Clinical studies, pharmacologic investigations, and theoretical applications are abundant in these reviews.

Schaffer and his associates have reported results obtained using disodium edetate in 25 patients with scleroderma of varying degrees. The drug was administered intravenously at a dose of 50 mg./kg. of body weight. This dose was repeated for five days followed by a two-day rest period, after which the routine was repeated. After three weeks, or fifteen days of the drug treatment, nine patients showed improvement of functional tests. Endoscopic and roentgenographic examinations as well as clinical evaluation also revealed improvement.

Ravenel et al. studied three cases of scleroderma (malar rash) treated with disodium edetate. Three Gm. daily was infused intravenously during a fourhour period, for five consecutive days. This procedure was repeated the two weeks following. Symptoms were entirely reduced, and the disease was halted.

Price and his associates studied the three cases of scleroderma from a metabolic standpoint. It was found that all three patients had abnormal tryptophan metabolism, which became normal or nearly so after administration of disodium edetate or pyridoxine or both. These investigators suggest that metallic ions (e.g., Ca, Mg, Zn) interfere with the normal function of pyridoxine, and that this is why their removal by means of disodium edetate potentiates the action of pyridoxine.

Munz reported two cases of scleroderma which were greatly improved after administration of 3 Gm. of disodium edetate daily, three times a week, for three weeks. These two cases had been generally unresponsive to other methods of treatment.

Klein and Harris described the use of EDTA to treat a patient with scleroderma, spondylitis, calcific tendinitis, and arthralgia. Disodium edetate was employed in a dosage of 3 Gm. dissolved in 200 ml. of 5% dextrose in water. Intravenous infusion lasted about three and one half hours, and was repeated daily for one week. In a later course of treatment, the patient received a similar dosage on alternate weeks for two months. Following therapy, articular and cutaneous calcium deposits were markedly reduced, histological examination showed regression of the sclerodermatous changes in the skin, and mobility was restored in the affected joints.

Neller and his associates have reported a followup study of 60 patients who had received disodium edetate for both localized and systemic scleroderma. They found that improvement was usually temporary and that the course of the disease was not significantly altered by therapy. Because of the potential side effects of disodium edetate, these investigators felt that the routine use of the drug in scleroderma is not warranted.

Cardiac Arrhythmias: Guinan and others reported the treatment of digitalis intoxication by the administration of sodium pyruvate. They concluded that the use of EDTA was effective in abolishing both atrial and ventricular arrhythmias caused by digitalis. The usual dosage employed was 100 mg. of disodium edetate administered intravenously in 200 ml. of dextrose 5% over a period of 20 to 30 minutes. Beneficial effects were seen in all except for six patients.

Soffer et al. described the use of disodium edetate in 50 to 100 ml. of 5% glucose in water over a period ranging from 20 minutes to 1 hour. Slowly infusions were made in 45 patients with cardiac arrhythmias. In 46 cases, digitalis toxicity was demonstrated by digitalis toxicity, disodium edetate produced beneficial effects.

Surawicz and his colleagues employed disodium edetate in 46 patients with a variety of cardiac arrhythmias. Atrial ectopic beats were corrected in 7 of 11 cases. Ventricular ectopic beats were corrected in 10 of 25 cases. Disodium edetate was not effective in controlling atrial flutter or fibrillation. The presence of digitalis toxicity did not appear to influence the results with disodium edetate. Side effects were minor in nature.

Colton et al. employed disodium edetate in 14 patients with cardiac arrhythmias. In five patients with ventricular tachycardia caused by digitalis, disodium edetate produced beneficial effects. The drug was not effective in cases of digitalis toxicity since false positive and false negative results were obtained in patients with ventricular arrhythmias. Supraventricular arrhythmias were not affected by disodium edetate whether they were caused by digitalis or not. The response did not correlate well with
the dose of diastemolide or its influence on serum calcium.

Internal Dosage: Clarke, et al., have employed diastemolide in a large number of patients with coronary artery disease or vascular disease. The usual regimen was 4 Gm in 500 ml of 5% glucose solution administered intravenously over a period of 5 to 10 hours. This was repeated two to three times. Symptomatic improvement was noted in 20 patients with coronary artery disease. Electrocardiograms showed definite evidence of myocardial damage in 14 cases, and suggestive evidence in three. Most of the electrocardiograms had been taken at intervals for periods of two months to two years prior to therapy, and in all cases the abnormalities were either present or showed progressive increase. For the patient with the abnormal electrocardiogram the drug was returned to normal during or after treatment.

Seven patients showed a definite history of coronary infarction, but treatment with diastemolide alleviated their original symptoms, and their electrocardiograms remained relatively stable. It was the opinion of these investigators that the beneficial action of the drug continued for a considerable period after treatment ceased.

In this same study, the authors mention two cases of suspected calcification of the portion of the coronary artery disease with diastemolide therapy. The investigators emphasize that the drug must not be used with special care when there are acute symptoms involving the internal wall of the heart or its branches.

In a more recent report, Kitchell and his colleagues stated that the influence of diastemolide on the arterial syndrome is slight and that the drug does not significantly alter the natural history of coronary disease. Permanent improvement was seen in the electrocardiographic tracings of 4 of the 28 patients in the study.

Irregular Dosage: Clarke, et al., have employed diastemolide intravenously in 10 patients with peripheral vascular disease associated with diabetes. Three grams of the drug in 5% dextrose was administered for five days a week and this regimen was repeated for three weeks following which there was a drug-free interval of 10 days. A total of thirty to forty infusions were usually given, rarely more. All 15 patients were relieved of incipient vascular insufficiency. Three patients with diabetic neuropathy obtained dramatic objective and subjective benefit. Objective improvement was demonstrated by periodically taken color retinal microphotographs. Seven of these patients have also shown a reduction in insulin requirements.

Melvin and his colleagues employed diastemolide with insulin for patients with diabetic neuropathy. The drug was given intravenously in the absence of dosage schedule in diabetic patients unresponsive to insulin. No blood glucose levels in normal subjects or diabetics were obtained. This effect was considered to be due to a correction of the diabetic condition. Insulin requirements were reduced in these diabetic patients.

Muscular cramps (diastemolide): Clarke, et al., have described the treatment of a variety of conditions associated with calcinosis. Diastemolide was infused intravenously in a solution of 4 Gm in 500 ml of dextrose injection, 5%, or sodium chloride injection. Administered during periods of convalescence in three-hour infusions were given daily for 15 to 20 days, followed by two or three weeks of no infusions. The 22 cases reported in the study included cases of hypercalcemia, peripheral vascular disease, and angina pectoris, incident ulcer with extensive calcification metastatic in the juxta-

The most frequent side effect noted in this series of cases was a local burning sensation, particularly when the small veins of the hands were used. There were also several complaints of mild nausea and diarrhea. These were usually controlled without interruption of therapy.

Following a prolonged course of therapy, two of the patients developed abdominal cramping pains, which disappeared promptly when administration of the drug was discontinued. The skin and mucous membrane of five patients exhibited a toxic reaction which first occurred in the usual cheek folds as an erythematous type of dermatitis. At a later stage, this also developed on the corners of the mouth and on the forehead. In one case, small bullae appeared on the oral mucous membranes. The skin reactions subsided rapidly when therapy was discontinued. The incidence and the severity of the skin reactions were markedly reduced by oral administration of 25 to 50 mg of pyridoxine hydrochloride.

Nevus and hair: We have reported favorable results following diastemolide in a 12-year-old girl with calcinosis universalis. Pollock similarly obtained beneficial results in a patient with dermatomyositis without soft tissue calcification. Cappel employed diastemolide with favorable results in a patient with periarteritis nodosa. Intravenous administration appeared following the second day of treatment and improvement was confirmed pathologically.

Although Enzyme: (diastemolide) has been reported to produce some beneficial effects in porphyria and also in gout, there does not appear to be sufficient evidence to warrant its use in these conditions.

PHARMACOLOGICAL STUDIES

Forman and Trujilo studied metabolism of C-labeled EDTA in human subjects. When the drug was given intravenously or intramuscularly, almost all of it could be accounted for in the urine within 24 hours.

The investigators concluded that calcium EDTA passes through the body unchanged, and leaves the kidney by glomerular filtration and tubular secretion. It was found that the parenterally administered drug mixtures with almost all the body water, except that it enters the spinal fluid relatively slowly, and does not enter the red cells. The drug was shown to be absorbed poorly (5% of the dose) when given by mouth, and practically not at all when applied to the skin.

Forman, et al., performed studies with calcium EDTA using rats weighing approximately 400 Gm each. It was found that high doses given for
suflcient time could cause nephrosis consisting of severe hydropnephrosis of the bilateral kidneys. Animals receiving 3 Gm/kg/day developed lesions in 48 hours; those receiving 1 Gm/kg/day showed the first signs of kidney damage after four days. Animals given 500, 250, or 125 mg/kg/day developed lesions between 4 and 16 days, and some given 62.5 mg/kg/day developed lesions after 16 days. Lesions cleared, however, within a few days after administration of the drug was discontinued. Some animals receiving as much as 600 mg/kg/day did not develop lesions at all. The investigators concluded that the E.D.I. (the amount of the drug required to produce the first histologic evidence of damage in 50 percent of animals treated daily for 16 days) was 205 mg/kg/day. This investigation, although showing that chelation must be exercised in the use of calcium disodium EDTA, also shows that the drug can be used safely - as prolonged administration of large doses was required to produce lesions, and the lesions were reversible.

HOW SUPPLIED

EDTA Disodium (disodium edetate), 150 mg per ml. (List No. 6940), is supplied in 20-ml ampoules, in boxes of 6 (pH adjusted with sodium hydroxide).

REFERENCES