

Edetate (disodium edetate) has been reported to be highly effective in the treatment of digitalis intoxication. The solution must be diluted (see below) before injection. The recommended daily dose is 50 mg/kg of body weight. Clinical reports appear to indicate that there is little danger from toxic effects if the adult does not receive 3 Gm. in 24 hours.

The required volume of disodium edetate solution from an ampoule should be diluted with 500 mg of dextrose, pyridoxine or with sodium chloride injection. This dilute solution should be administered by intravenous infusion during a period of five and a half hours. A usual dose is 3 Gm. to 4 Gm. Present evidence indicates that toxicity is dependent on both total dose and speed of administration. Therefore, it is recommended that administration must not be rapid.

The total number of days of treatment will depend on the individual case. The usual regimen is daily intravenous infusion for five days, followed by two days without edetate. This cycle is repeated three times over a total disodium edetate has been given for a total of 15 days. Intravenous administration should be continued for several weeks while the results are being assessed. Further courses of treatment may be indicated to maintain or increase the degree of improvement.

CLINICAL REPORT.

Collier, and more recently Herrmann,¹ have provided excellent surveys on the EDTA literature. Clinical studies, pharmacology, investigation and theoretical applications are discussed in these reviews.

Schaefer, et al.,² and his associates,³ have reported results obtained using disodium edetate in 23 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 treatment, nine patients showed improvement in functional tests. Esophageal motility tests and overall clinical evaluation also revealed improvement.

Reynolds, et al.,⁴ studied three patients of scleroderma (sclerosing) treated with disodium edetate. Three Gm. daily was infused intravenously during a four-hour period, for five consecutive days. This procedure was repeated the two weeks following. Symptoms were extensively reduced, and skin turgor was minimal.

Pico and his associates⁵ studied the same 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 metabolic ions (e.g., Ca, Mg, Zn) interfere with the normal function of pyridoxine, and that is why their removal by means of disodium edetate potentiates the action of pyridoxine.

Morse⁶ reported two cases of scleroderma which were greatly improved after administration of 3 Gm. of disodium edetate daily, five days a week, for three weeks. These two cases had been generally unresponsive to other methods of treatment.

Klein and Harris⁷ described the use of EDTA to treat a patient with scleroderma, sclerodactylia, calcinosis and arthritis. Disodium edetate was employed in a dosage of 3 Gm. dissolved in 500 ml. of 5% dextrose in water. Intravenous infusion lasted about three and a 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 to the affected joints.

Neldner⁸ and his associates have reported a follow-up 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: Gubner and Gubner⁹ reported the treatment of digitalis intoxication by the use of EDTA. They concluded, "The use of EDTA has several advantages over potassium administration in the treatment of digitalis toxicity. Its action is very rapid and is safer than intravenous potassium. The response is slow in effect and large doses are required which may not be well tolerated." The treatment was effective in abolishing bradycardia and ventricular arrhythmias caused by digitalis. The usual dosage employed was 500 mg. of disodium edetate administered intravenously in 240 ml. of dextrose injection, 5%.

Rosenbloom, et al.,¹⁰ employed 3 Gm. of disodium edetate intravenously in 5% glucose solution in control of digitalis toxicity in six patients. The drug was administered in from 20 to 30 minutes. Beneficial effects were seen in five of the six patients. Soffer, et al.,¹¹ used from 0.5 to 4 Gm. of disodium edetate in 500 to 1000 ml. of 5% glucose solution over a period ranging from 30 minutes to 4 hours. Highly infusions were made in 4 patients with complete arrhythmias. In 6 of 11 patients, an arrhythmia caused by digitalis toxicity, disodium edetate produced beneficial effects.

Surawicz¹² and his colleagues employed disodium edetate in 46 patients with a variety of cardiac arrhythmias. Atrial ectopic beats were corrected in 7 of 14 cases. Ventricular ectopic beats were corrected in 10 of 24 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 infrequent in nature.

Collier, et al.,¹³ 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 a broad index of digitalis toxicity since false positive and false negative results were obtained in patients with ventricular arrhythmias. Supraventricular arrhythmias were not corrected by disodium edetate whether they were caused by digitalis or not. The response did not correlate well with

the dose of disodium edetate or its influence on serum calcium.

Ureteral Dissection. Clarke, et al.,²⁰ have employed disodium edetate in a large number of patients with symptomatic ureteral calculi and vascular disease. The usual dose was 1.5 Gm. in 100 ml. of 5% glucose solution administered intravenously over a period of 2 to 3 hours. This was repeated five days a week for three weeks. Symptomatic improvement was seen in 22 of 26 patients with angina. Relief of rest pain and easier walking was produced in 11 patients with intermittent claudication. Symptoms of vascular calcification were reduced in 24 patients.

In an earlier report by these investigators,²⁰ 20 patients with a definite degree of angina pectoris were treated with intravenous disodium edetate. 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 level or showed progressive increase. For 11 of the patients, the abnormal electrocardiographic picture returned to normal during or after treatment. Seven patients showed a definite history of myocardial infarction, but treatment with disodium edetate alleviated their anginal symptoms, and their electrocardiograms remained relatively stable. It was the opinion of these investigators that the beneficial action of the drug concerned for a considerable period after treatment ceased.

In this same paper, the authors mention two cases of suspected calcium atherosclerosis and one case of proved calcium embolism following disodium edetate therapy. The investigators emphasize that the drug must be used with special caution when there are large areas of metastatic calcification involving the internal wall of the heart or the arteries.

In a more recent report, Kitchell and his colleagues²¹ stated that the influence of disodium edetate on the anginal syndrome is slight and that the drug does not significantly alter the natural history of coronary disease. Transient improvement was seen in the elec-

trocardiogram in 47% of the 28 patients. In 16 patients with peripheral vascular disease associated with diabetes, three grams of the drug in 10% levulose 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 16 patients were relieved of arterial vascular insufficiency. Three patients with diabetic retinopathy 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 of insulin requirements. Meltzer²² and his colleagues, having marked by polyglycolic the use of disodium edetate in diabetic patients on maintaining insulin but did not affect blood glucose levels in normal subjects or diabetic not receiving insulin. This effect was considered to be due to a chelation of zinc. Insulin requirements were also reduced in these diabetic patients.

Arteriosclerosis Conditions Favoring Calciosis: Clarke, et al.,²⁰ have described the treatment of a variety of conditions associated with calcinosis. Disodium edetate was infused intravenously as a solution of 5 Gm. in 500 ml. of dextrose injection, 5%, or sodium chloride injection. Administrations during periods of maximal activity in three hours. Infusions were given daily for 12 to 20 days, followed by two or three weeks of no infusions. The 22 cases reported in the study included cases of peripheral vascular disease, severe angina pectoris, indolent ulcer with extensive calcium infarctosis in the feet, calcified mitral stenosis, and atherosclerosis.

The most frequent side effect noted in this series of cases was a local burning sensation, particularly when the small veins of the hand 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 in a number of five patients exhibited a toxic reaction, which first occurred in the nasal check folds as an erythematous type of dermatitis. At a later stage this also developed at the corners of the mouth and on the chin and on the forehead. In one case, a bullae appeared on the oral mucosa membrane. The skin reactions subsided rapidly when the drug was discontinued. The incidence and the severity of toxic reactions were markedly reduced by oral administration of 25 to 50 mg. of pyridoxine daily.

Davis and Mac²³ have reported favorable results following disodium edetate in a 12-year-old girl with calcinosis universalis. Pollock²⁴ similarly obtained beneficial results in a patient with dermatomyositis without soft tissue calcification. Cappio²⁵ employed disodium edetate with favorable results in a patient with paraneuritic calcinosis. Intense calcinosis usually appeared following the second day of treatment and improvement was confirmed radiologically.

Although Evans²⁶ (disodium edetate) has been reported to produce some beneficial effects in "psoriasis" and also in "arthritis," there does not appear to be sufficient evidence to warrant its use in these conditions.

PHARMACOLOGICAL STUDIES

Foreman and Trujillo²⁷ studied metabolism of C¹⁴-labeled EDTA in human subjects. When the drug was given intravenously or intramuscularly, about 60% 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 both glomerular filtration and tubular secretion. It was found that the parenterally administered drug mixes 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 (a maximum of 6 percent) when given by mouth, and practically not at all when applied to the skin.

Foreman, et al.,²⁸ performed studies with calcium disodium EDTA using rats weighing approximately 400 Gm. each. It was found that high doses given for

A sufficient time could cause nephrosis equivalent of severe hyaline degeneration of the proximal tubules. 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 500 mg./kg./day did not develop lesions at all. The investigators concluded that the E.D.₅₀ (the amount of the drug required to produce the first histological evidence of damage in 50 percent of animals treated daily for 10 days) was 203 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

EDIMATE 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).

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