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An Enzymatic Electrocardiographic Study on Toxicity of Dehydroemetine*

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Over half a century has elapsed since the introduction of emetine as an amœbicide, and it has been almost that long since the first report of cardiotoxicity due to the drug; yet considerable controversy still exists as to the nature, frequency, and usual severity of this seemingly capricious side-effect of a widely used agent. The occasional fatality (Kattwinkel, 1949) reported and the difficulty in determining beforehand which patients are likely to have trouble with the drug have led to attempts to modify both the structure of the compound (Osbond, 1959; Brossi *et al.*, 1959a; Brossi, Baumann, and Schnider, 1959b; Child *et al.*, 1964) and the activity of patients before and after treatment (Lepeschkin, 1951). Some of the suggested lists of therapeutic precautions, e.g. that of Dack and Moloshok (1947), have been rigid enough to be challenged (Kent and Kingsland, 1950) or ignored, particularly in those parts of the world where there is a great deal of amœbiasis and few hospital beds.

Electrocardiographic progress has been to some degree responsible for confusing the assessment of the toxic qualities of emetine. The proportion of patients reported as showing electrocardiographic changes during treatment increased (Hardgrove and Smith, 1944; Cottrell and Hayward, 1945) until it reached 100 per cent (Dack and Moloshok, 1947; Kent and Kingsland, 1950). An exception to this upward spiral was the report of Awwaad, Attia, and Reda (1961) who found that only one-third of their patients showed electrocardiographic changes after emetine, with the changes being minor and transient. Significantly, the Awwaad series was confined to children.

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These high proportions of patients reported as showing electrocardiographic change contrasted with the paucity of clinical evidence of cardiac difficulty in the great majority of patients receiving their first course of emetine, leading some clinicians to ascribe the changes usually seen to harmless, temporary, intracellular ionic shifts. Turner (1963) expressed the belief that "a study of the serum transaminase of patients on treatment . . . might provide further evidence of myocardial injury". The present report concerns such a study on Egyptian villagers before, during, and after treatment with very large doses of dehydroemetine for schistosomiasis.

Dehydroemetine (DHE), a racemic isomer of emetine, was introduced in 1959 by Osbond and Brossi *et al.* (a, b). It has a shorter period of biological activity than its parent. The electrocardiographic changes associated with its use are similar in type to those produced by emetine but are less marked and are of shorter duration (González di Cossío, 1960). It is consequently believed to be safer then emetine when given parenterally in the same dosage. It is less emetic than emetine and can be given orally as a resinate. Since its absorption from the intestinal tract is known to be incomplete, the amount of the base given as resinate must be greater than the amount given parenterally as hydrochloride in order to achieve good results in the treatment of amœbiasis (Salem and Abd-Rabbo, 1964a, b).

The present study is an extension of the work of one of us (H.H.S.) in using large doses of DHE in an attempt to cure or control the schistosomal infections of some of the patients in an amœbiasis study, whose schistosomal hæmaturia disappeared while they were being treated with DHE for their amœbic dysentery. Electrocardiograms were obtained (H.H.S.) on 15 of the first schistosomal patients treated with "excessive" doses of DHE, and no frightening changes were noted. It was decided to study the toxic effects of the drug on the next group

of such patients as closely as possible. The drug was being administered in higher doses than had ever been given before, and it was felt that general as well as specific toxicological information might be gathered.

Subjects and Methods

The 37 patients in this study ranged in age from 10 to 34 years with 29 of them being under 20 years of age. Twenty-five were male and 12 were female. Such age and sex ratios are considered typical for schistosomiasis treatment clinics in Egypt.

Of the patients, 24 received parenteral treatment with DHE hydrochloride given by subcutaneous injections daily for 12–18 days; 13 were treated with DHE resinate given orally in three divided doses daily for from 12–31 days (12–21 days with one exception). The oldest patient treated with the oral drug was 25 years of age, whereas 4 of the patients treated with DHE HCl by injection were over 25 years old.

The *total doses* of DHE base given as HCl ranged from 22 to 52 mg./kg. of body weight with a mean of 38 mg./kg. The total doses of DHE base given as resinate ranged from 100 to 294 mg./kg. of body weight with a mean of 152 mg./kg. All but a few patients had total doses that clustered closely around their respective means.

The recommended dose of DHE HCl is the same that obtains for emetine itself, i.e. 10 to 20 mg./kg. body weight total dose. Thus the smallest dose of DHE HCl given in this series exceeded the highest recommended dose of the drug and the mean dose was twice the highest recommended dose and thrice the usual dose.

The recommended total dose of DHE given orally as resinate in treating amœbiasis is 50–55 mg./kg. body weight. The 13 patients in this series who received their DHE orally got doses of the base that were from 2 to 6 times that much, and the mean total dose given was 3 times that amount.

Thus in both the patients treated by injections and in those given oral medication the amount of DHE base received was 3 times the usual (i.e. the amœbicidal) dose.

With two exceptions all patients remained in hospital for one week following the completion of treatment. They were not confined to bed, and in keeping with standard parasitological egg-harvesting practice were encouraged to be active in the mornings before obtaining stool and urine specimens for egg counting. Cardiograms and blood samples were obtained on each patient before treatment, half-way through the treatment course, at the end of treatment, and at the time of discharge from the hospital one week later. Electrocardiograms were recorded on 24 patients and blood was drawn on 19 patients at the time of the next follow-up visit one to three weeks after discharge. Some selection occurred at this point in the follow-up since it was those patients whose studies were known to be abnormal at time of discharge from the hospital who were most diligently followed as outpatients, even to the extent of going after some of them in their villages.

The *electrocardiograms* consisted of the usual 12 leads with a standardization made with each lead. All of them were read by one interpreter (J.J.D.). In addition to the usual mensurations, the height of the QRS complex in lead II and of the T wave in lead V4 (or V5 if V4 was transitional) were recorded. All voltage changes seen were in the direction of diminution. To avoid over-reading, decline in T voltage of less then 50 per cent was not considered significant. T voltage drop of over 50 per cent was called 1+ change provided the T wave remained even the slightest bit upright. If the T wave became flat, diphasic, or inverted then the change was called 2+.

The *biochemical tests* performed on the sera of all patients included the measurement of: blood urea nitrogen, total serum bilirubin, direct acting serum bilirubin, thymol turbidity, alkaline phosphatase, SGOT, and SGPT. One-half of the patients also had serial potassium levels determined, and three-quarters of the patients had serial calcium levels done. The transaminase levels were measured in Sigma-Frankel units/ml., with the upper limits of normal being 50 for the SGOT and 45 for the SGPT.

Results

(A) *Clinical Evidence of Toxicity:* All the patients had some side-effects from taking dehydroemetine in such doses. Among those taking the medicine *orally*, the effects were limited to diarrhœa (present to some extent in all patients on oral medication), nausea, and weakness. Among the group taking the medicine *parenterally* pain at the site of the injection was a universal complaint. Nausea, abdominal cramping, diarrhœa, and generalized muscle weakness were frequent complaints in the group on injections. One patient, at 34 the oldest in the series, had chest pain during therapy. Another patient, at 30 the second oldest patient in the group, developed marked weakness, persistent tachycardia, and a loud diastolic summation gallop. He was the only patient whose therapeutic course was stopped because of side-effects, and his total dose of 22 mg./kg. was the lowest in the series.

(B) *Biochemical Evidence of Toxicity:* The blood urea nitrogen levels, the thymol turbidity determinations, the levels of both total and direct acting serum bilirubin, and the alkaline phosphatase determinations were not affected by therapy with the parenteral or oral forms of DHE. No significant changes in serum K^+ and Ca^{++} occurred.

The SGPT levels rose slightly following therapy and the SGOT levels rose conspicuously after therapy. The respective averages of these two enzymes taken before, during, and after treatment are shown in Fig. 1. There were 8 patients whose post-treatment SGPTs were in the abnormal range and 23 patients whose post-treatment SGOTs were abnormally raised.

Route of administration did not affect the rise in

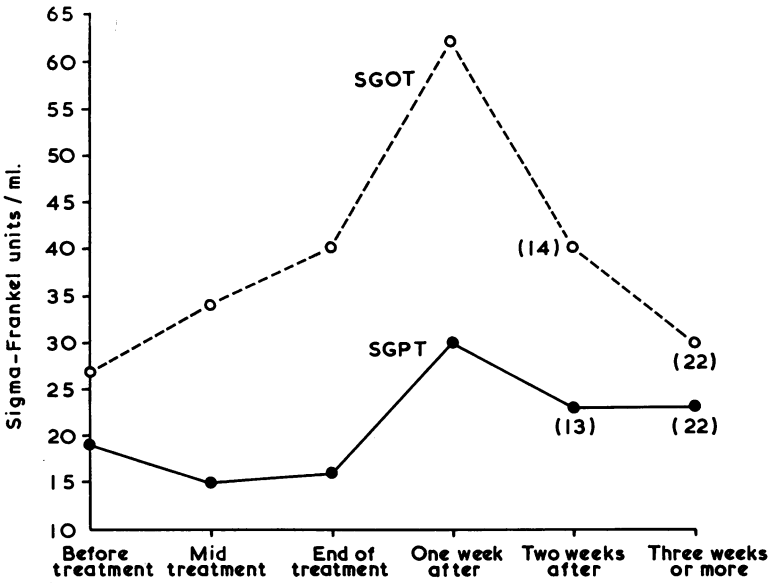


FIG. 1.—Mean SGOT and SGPT levels before during and after treatment with DHE in 37 patients. Figures in parentheses refer to number of specimens obtained at phases when not all patients were studied.

SGOT; the average rise in the 13 patients receiving DHE orally was essentially the same as that in the 24 patients receiving the drug parenterally. There was no clear-cut relation between age and increase in SGOT or between degree of electrocardiographic change and increase in SGOT. However, the two oldest patients in the series, both alluded to earlier, had significant rises in SGOT (to peaks of 122 units and 85 units); and their enzyme levels and cardiograms remained abnormal for several weeks after completing treatment.

There were 3 patients whose SGOT levels were raised before starting treatment (the patient with the highest pre-treatment value was not included in calculating average values). The serial SGOT levels in these 3 patients are given in Table I. All 3 had pre-treatment abnormalities of their other biochemical studies (bilirubin, thymol turbidity, alkaline phosphatase, SGPT) consistent with mild liver disease: these abnormalities diminished or disappeared while receiving DHE. The administration of DHE affected the biochemical tests of these 3 patients with chemical evidence of hepatitis before treatment in the same manner that it affected the tests of those patients whose pre-treatment biochemical studies were normal. In both instances the only significant change was a rise in the SGOT levels following treatment.

(C) *Electrocardiographic Evidence of Toxicity:* No patient developed either atrio-ventricular or intraventricular block while under observation nor were premature contractions noted. One patient, the oldest of the series, developed paroxymal atrial tachycardia at the end of treatment. This patient had experienced some chest discomfort during treatment. Sinus tachycardia was seen routinely among those taking the drug by injection. The averages of the cardiac rates before, during, and after treatment are shown in Fig. 2.

Analysis of the frequency and degree of post-treatment T wave change shows a difference between those patients who received the drug by injection and those who were treated orally with resinate. Table II lists the changes seen.

Of the 37 patients in the study, there were 14 who did not have significant T wave changes after treatment. Of these 11 were from the group of 13 patients treated with DHE resinate. None of the patients on

TABLE I

SERIAL SGOT DETERMINATIONS (Sigma units/ml.) DURING AND AFTER TREATMENT WITH DHE IN 3 PATIENTS WITH EVIDENCE OF PRE-TREATMENT LIVER DAMAGE

Pre-treatment	Half way	End of treatment	1 week after treatment	More than one week after treatment
560	430	62	130	50
62	36	40	62	55
65	32	25	42	—

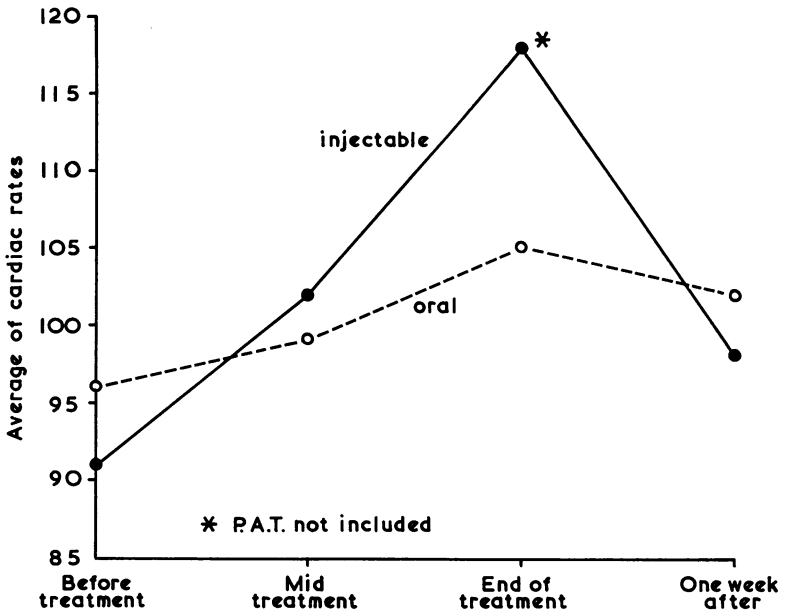


FIG. 2.—Average of cardiac rates of patients on oral and injectable DHE.

the oral form of the drug had greater than 1+ change, but one-third (8 out of 24) of the patients who received DHE HCI had 2+ change.

Those 8 patients whose cardiograms showed the greatest degree of T wave change form an interesting subgroup. Included in it are the 2 patients who showed clinical signs of cardiotoxicity and the one other male over the age of 25 (the one female patient over age 25 had 1+ change). Although there was overlap, the pulse rate increases in the group with 2+ T change (12 to 75/min. with a mean increase of 35/min.) were greater than the increases that occurred in the patients on parenteral treatment showing a lesser degree of T change; and were far greater than occurred in the group of patients receiving oral therapy.

Thus correlation existed between the presence and degree of T wave change and the following variables: mode of drug administration, age of patient, increase in cardiac rate during treatment, and clinical evidence of cardio-toxicity.

TABLE II

T WAVE CHANGES ASSOCIATED WITH DHE THERAPY (1+ MEANS OVER 50% DECREASE IN T WAVE HEIGHT, 2+ MEANS FLAT, BIPHASIC, OR INVERTED T WAVE)

Route	No.	No significant change	1+ change	2+ change
Parenteral	24	3	13	8
Oral	13	11	2	0

The most abnormal cardiogram inscribed by any particular patient was almost invariably the tracing obtained at the end of treatment. Fairly rapid reversal of the T wave change was the rule, and the cardiograms obtained two weeks after completion of treatment were usually normal.

Selected leads from the cardiograms of the two oldest patients in the series are shown in Fig. 3. Standardization was constant.

The striking QRS voltage drop that occurred in some patients during treatment is illustrated in the cardiograms of the 30-year-old patient shown in Fig. 3. Fig. 4 shows selected leads from tracings of a patient who had changes typical of those seen: considerable drop in QRS voltage, 1+ T wave change, increase in cardiac rate, and a rapid reversal to the pre-treatment pattern. All but 9 patients had a decrease of over 10 per cent in the QRS amplitude following treatment, and there were 8 patients who showed a QRS voltage drop of over 33 per cent. Of this latter group, 3 were on oral medication. No striking differences were noted between these 8 patients as a group and the other patients in the study. Three of them had no significant T wave change, three had 1+ T changes, and one had 2+ T change. The average rise in pulse rate for these patients as a group was not unusual, and the average rise in SGOT levels was similar to that seen in patients with little or no decline in QRS voltage.

QRS voltage decline, though almost routinely encountered, could not be consistently correlated

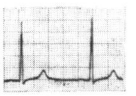
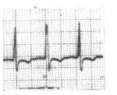
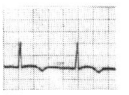
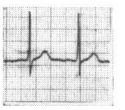
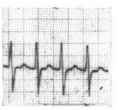
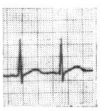
Clinical features	SGOT rise Sigma-Frankel units/ml.	V_4 Before treatment	V_4 End of treatment	V_4 Two weeks after treatment
Male, age 30 (2nd oldest patient in series). Dyspnoea, weakness, gallop rhythm	51 (34-85)			
Male, age 34 (oldest patient in series). Chest pain, dyspnoea, weakness, paroxysmal atrial tachycardia	94 (28-122)			

FIG. 3.—Summary of findings in two patients who developed clinical evidence of cardio-toxicity. Both patients had T wave inversion one week after the end of treatment.

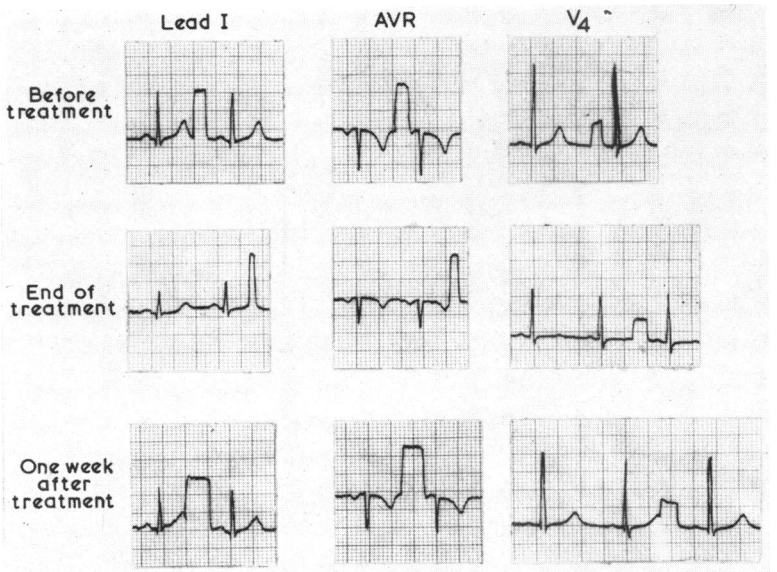


FIG. 4.—Serial electrocardiograms revealing QRS voltage drop, 1+ T wave change, increase in cardiac rate; 8 rapid reversal. Note constant standardization.

with mode of drug administration, age of patient, increase in cardiac rate, or degree of rise in SGOT level. In individual cases the diminution in QRS voltage was undoubtedly significant. In other cases, particularly when it occurred as an isolated finding, the decline probably resulted from physiological variation in the depolarization force, a phenomenon particularly common in the age-group involved in this study.

DISCUSSION AND CONCLUSIONS

The *parenteral* administration of DHE HCl, in amounts twice the maximum recommended dose to 24 patients, resulted in electrocardiographic evidence of cardio-toxicity in 21 patients and clinical evidence of cardio-toxicity in 2. This is not surprising. In fact the tolerance of the young heart for such doses was impressive. The hearts of the patients over the age of 25 were less tolerant of such doses. As mentioned by several authors, the electrocardiographic changes produced by DHE are of shorter duration than those produced by emetine itself.

Dehydroemetine was given *orally* as resinate to 13 patients. Even in very large doses it was associated with much less electrocardiographic evidence of toxicity than was seen following the parenteral administration of the drug. No doubt some of the difference is due to incomplete absorption (Child *et*

al., 1964; F. Roux, 1965, personal communication), but one of us (H.H.S.) has successfully treated amœbic hepatitis with oral DHE resinate in doses approximately one-third of the mean dose used in this series. Moreover the SGOT rises seen in this study among the patients taking the oral preparation indicates that at least a fair proportion of the orally administered drug was absorbed.

The only observed significant biochemical evidence of toxicity was a rise in the SGOT level. The question that immediately arises is whether this increase in the SGOT level was further evidence of myocardial toxicity, or whether it was a manifestation of either liver damage or of skeletal muscle disturbance from the drug ("emetine myositis", Klatskin and Friedman, 1948).

Against the liver origin of the rise are several pieces of evidence. One is that the bilirubin, thymol turbidity, and alkaline phosphatase levels were not disturbed by the treatment. The slight SGPT rise would, of course, be in keeping with muscle (cardiac or skeletal) origin of the enzymes; and the fact that the SGOT rise was greater than the SGPT rise speaks against hepatic origin. But perhaps the most telling point against the enzyme rise being due to liver damage is that no evidence of deterioration in liver function was seen in 3 patients who were given full courses of treatment though their pretreatment biochemical tests revealed evidence of mild liver damage. The abnormal liver tests in these 3 patients improved while they were receiving DHE; and the post-treatment SGOT levels were similar to those seen in the patients whose pre-treatment SGOT levels had been normal. Such a sequence would seem unlikely were the SGOT rise following DHE treatment a manifestation of liver damage.

That emetine produces a myositis is well known, and the local reaction at the site of the injection of emetine can be quite severe. Myositis from emetine (or DHE) therapy can be generalized or localized. It is reasonable to exclude local myositis as a cause of the rise of SGOT levels in this study since there was significant post-treatment rise among the patients who had received the drug orally. Most patients in both the orally and parenterally treated groups did complain of weakness and the possibility that the SGOT rise was due to a generalized myositis cannot be completely excluded; but the constantly working heart muscle would in all likelihood share disproportionately in such a process.

There are several negative aspects of the study that argue against ascribing the SGOT changes to cardio-toxicity. Although there was a difference in the incidence of electrocardiographic changes between the patients taking DHE resinate orally and DHE HCl by injection, no such difference existed in the transaminase rise. The electrocardiographic changes usually were improving by one week after the completion of treatment, the time when the SGOT level was highest. Finally, though exceptions occurred, there was no constant relationship in patients with T wave changes between the degree of that change and the SGOT rise.

These points are cogent, but it is important to remember that the electrocardiogram and the SGOT variations measure cardiac injury in very different ways. Even in such clear-cut myocardial situations as infarction there are usually temporal differences between cardiogram change and SGOT rise, and there are frequently quantitative differences as well (if such were not the case little or no need would exist for transaminase determinations in suspected cases of myocardial infarction). On theoretical grounds diffuse myocardial injury of the type that would be likely to occur from drug toxicity is the form of heart involvement that the electrocardiographer can most easily miss. This is particularly likely to be the case if, as in this study, the electrocardiograms were deliberately under-read. A final important consideration is that the blood samples and cardiograms were obtained only once weekly. Ideally in an evaluation such as this one these studies, particularly the transaminase determinations, should be made daily.

The routinely observed positive findings in these patients following the administration of dehydroemetine in large doses were the development of tachycardia and electrocardiographic changes, and a significant rise in SGOT levels. It appears likely that these findings are associated, and that the source of the rise in the circulating enzyme in these patients was their cardiac muscle mass.

Summary

Electrocardiographic and biochemical studies were carried out on patients receiving an average of three times the usual dose of dehydroemetine.

Among 24 patients receiving dehydroemetine base *parenterally* as hydrochloride, sinus tachycardia and significant electrocardiographic changes were routinely noted. The two oldest patients treated with the parenteral form of DHE developed clinical evidence of cardio-toxicity (one of these patients had received only little more than the usual dose of the drug). Among 13 patients who received dehydroemetine base *orally* as resinate, both the degree of increase in pulse rate and the frequency and degree of significant electrocardiographic changes were much less than in the parenterally-treated patients.

The electrocardiographic changes seen were the previously well-described T wave changes and a less well-discussed or understood decline in the QRS

voltage. That diminution in depolarization as well as repolarozation force might accompany any diffuse myocardial derangement seems reasonable. In future studies of this general type, attention should be given to QRS voltage as well as to T wave amplitude and direction.

The only biochemical abnormality that was noted to be routinely produced by the administration of the drug was an increase in the SGOT level. It must be assumed that the source of this rise is myocardial.

The very fact that DHE could be given in such doses to 37 patients without fatality speaks for the safety of the drug as compared to emetine. The orally administered resinate seems particularly safe from an electrocardiographic standpoint. Toxicity to dehydroemetine seems to be related to age. The fact that one of the two patients developing clinical evidence of significant cardio-toxicity received only slightly more than the recommended dose of the drug indicates that individual variation in tolerance is fairly wide, and some care needs to be exercised in giving even the conventional dose of parenteral dehydroemetine to adults.

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