THE EFFECTS OF EMETINE ON THE MYOCARDIUM

BY

PETER P. TURNER*

From the Coast Province General Hospital, Mombasa, Kenya

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A number of drugs have achieved notoriety for their toxicity to the myocardium. Of those used in tropical medicine antimony and emetine are outstanding examples. Both are valuable therapeutic agents and have yet to be supplanted by equally effective yet less toxic drugs. The fact that they affect the electrocardiogram has been known for some years, but there has been a recent renewed interest in the changes produced by antimony in both its older and newer chemical forms (Honey, 1960; Davis, 1961; and Somers and Rosanelli, 1962).

Emetine has been used extensively since it was first advocated by Sir Leonard Rogers in 1912. Its dangerous effects on the cardiovascular system were rapidly recognized. The effects of the drug administered intravenously on the electrocardiograms of animals were studied by Boyd and Scherf (1941): they found widening of the QRS complexes, P–R prolongation, T wave changes, and extrasystoles. In man, Hardgrove and Smith (1944) found cardiographic changes in 53 per cent of 72 patients after a 10-grain course of intramuscular emetine hydrochloride, chiefly in the T waves. There have been a number of studies since then (Dack and Moloshok, 1947; Klatskin and Friedman, 1948; Kent and Kingsland, 1950; Gonzalez de Cossio, 1952; Sodeman, D'Antoni, and Doerner, 1952; Cera, 1956; Awaad, Attia, and Reda, 1961), but some of these have lacked electrocardiograms before treatment, some have used only a few leads, and some have failed to follow the patients until the cardiograms became normal.

A number of deaths from the toxic effects of emetine on the myocardium have been reported (Kattwinkel, 1949; Gonzalez de Cossio, 1952; and Brem and Konwaler, 1955) and some of these deaths have been associated with ventricular tachycardias.

CASE REPORT

A Mkamba woman, 32 years of age, had had undoubted amebic dysentery one year before being seen at this hospital. She had been given 10 grains of emetine hydrochloride intramuscularly and two months later had complained of palpitations on exertion and at rest, dyspnea on exertion and at night, and precordial pain. The palpitation began suddenly, lasted about three hours, and then gradually faded away. During the few weeks before her admission she had been given at least two further courses of intramuscular emetine. On examination she looked collapsed and unwell. Her pulse was regular at a rate of 110 a minute. The blood pressure was 85/70 mm. Hg. There were no other abnormal findings. No evidence of amoebiasis was found. Chest radiographs showed the heart of normal size. On rest in bed the pulse rate fell to about 80 a minute and the blood pressure rose to 130/90 mm. Hg. The symptoms disappeared. An electrocardiogram on admission showed widespread T wave changes with inversion over the right precordial leads and flattening over the left, but on discharge a month later it was normal. As a result of this experience it was decided to determine the electrocardiographic effects of a standard course of intramuscular emetine hydrochloride.

* Present address: Department of Medicine, Mulago Hospital. Box 351, Kampala, Uganda.

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PETER P. TURNER

SUBJECTS AND METHODS

Twenty-five patients were studied; 14 had amebic hepatitis and 11 intestinal amebiasis. Twenty-two were men and three were women. This is a much greater preponderance of men than would be expected from the hospital medical admission ratio of 2.8 to 1, but it is quite close to the usual sex distribution of amebiasis in in-patients (Turner, 1962). The assessed age range was from 17 to 53 with a mean of 33 years. Apart from one Arab and one Somali, the patients were all Africans from various Kenya tribes. Mombasa is a port and has a population drawn from far and wide and therefore tribes from all over Kenya were represented. Less than half of the patients were of coastal origin and the others followed the distribution that has been seen previously in this hospital (Turner, 1962), with both Mkamba and Kikuyu each representing 20 per cent of the total. There was no clinical evidence of heart disease in any of these patients, and their blood pressures were all normal. They were all given emetine hydrochloride, one gram intramuscularly, once daily for ten days. In those in whom it seemed indicated treatment was continued with emetine bismuth iodide, entamidine, or chloroquine. The immediate response of the disease was satisfactory in all instances.

Electrocardiograms were recorded under standard conditions with a Philips' Cardioulux direct writing, single channel recorder. They were all recorded in the same room, on the same couch, in the semi-reclining position, and with the same machine. In all instances the three limb leads, the three augmented unipolar limb leads, six precordial leads, together with V4R and CR1, were recorded. The two latter leads were not analysed in the study. A record was taken before treatment and immediately after treatment in all the cases. After this an attempt was made to take records weekly until normality was reached. However, because of the difficulties inherent in persuading African patients to return to hospital, the time intervals were more varied than this, and some patients were lost sight of before they had achieved normal electrocardiograms.

RESULTS

One hundred and twenty electrocardiograms from the 25 patients were analysed. Some abnormalities were seen in the recordings taken before any treatment was given. Sinus tachycardia occurred in 8 (32%). One patient was seen with a mean QRS axis of 0° which did not alter significantly over a period of 11 weeks, and one with a mean axis of −23° which moved rightwards to +30° and was still at this position six weeks later. The QTc (Taran and Szilagyi, 1947) was prolonged in four patients to 0.43, 0.43, 0.46, and 0.47 seconds. More interesting was the finding of the so-called "Bantu" pattern in four (16%) of the patients. One of these was a woman, and, of the three men, one was the only Arab in the series. This pattern is well known in otherwise normal subjects in East Africa and has previously been reported (Turner, 1959). These four examples were well marked and were all of the right precordial leads with inversion and biphasic (+−) T waves (Fig. 1, 2, and 3).

After treatment electrocardiographic abnormalities were seen in all of the 25 patients (100%). They are summarized in Table I. The changes were mostly of the T waves but other lesser abnormalities were observed. This is in contrast to the fact that no abnormal physical signs appeared on clinical examination and only one patient specifically complained of the effects of the drug; he developed nausea and vomiting. East African patients are notoriously stoical in their reaction to medication and seldom refuse drugs because of their unpleasant side-effects. In 23 (92%) of the patients cardiographic effects appeared at once, as soon as the course of emetine was completed: in 2 there was a delay before they appeared of 8 days and of 17 days respectively. The maximum changes were apparent immediately after the course in 9 (36%), one week later in 5 (20%), two weeks later in 6 (24%) and three weeks later in 5 (20%). The cardiogram was followed until it became normal in 17 (68%) of the patients. Of the 8 who were lost to further follow-up 4 disappeared early, but 3 still had abnormal cardiograms three weeks after the completion of the course of emetine and 1 nine weeks after. Of the 17 observed to return to normality 1 was normal one week after the completion of the course, 4 after three weeks, 4 after four weeks, 3 after seven weeks, 1 after nine weeks, 1 after ten weeks, 1 after twelve weeks, 1 after thirteen weeks, and 1 after eighteen weeks. The mean time required to reach normality was seven weeks after the completion of the course.

The mean QRS axis remained the same in most patients, but in 5 it was rotated leftwards and
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Fig. 1.—Serial cardiogram changes after emetine. The initial record shows inversion of the T waves over the right precordial leads. The intermediary changes are so gross as to suggest myocardial infarction. The last record shows that nearly five months later the original right precordial inversion has not returned.

TABLE I

<table>
<thead>
<tr>
<th>Electrocardiograph changes</th>
<th>No. of patients</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>P waves—lower voltage and widening</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>T waves—lower voltage</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>iso-electric inverted</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>inverted more than 3 mm.</td>
<td>12</td>
<td>48</td>
</tr>
<tr>
<td>J point shift</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>S-T segment changes</td>
<td>9</td>
<td>36</td>
</tr>
<tr>
<td>QTc prolonged</td>
<td>11</td>
<td>44</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>80</td>
</tr>
</tbody>
</table>

in 7 rightwards. The mean rotation was 19° and 18° respectively. It seems likely that this is within the limits of the normal changes that might be expected in serial electrocardiograms. P wave changes were not conspicuous. In 5 (20%) changes were seen. There was a tendency to lower
FIG. 2.—Two examples of the effect of emetine on inverted right precordial T waves. The first is partially corrected and then returns to inversion. The second remains unaffected despite the changes in the other leads.

FIG. 3.—Showing deep inversion of right precordial leads ("Bantu" pattern) lessened after emetine.

electron voltage and widening, and in 4 of the 5 the P wave became notched. The widest P wave seen was 0·12 seconds. Recovery occurred in all of these. The P–R interval was always within normal limits and no changes became apparent after emetine. There was a tendency for the voltages of the R and S waves in the precordial leads to increase after emetine, but it is doubtful whether these are of any significance. No deformities of the QRS complex were seen and Q waves did not appear. U waves were seen in 14 of these patients and in 4 (16%) of them became larger, but it is doubtful if these changes are of any significance. S–T segment changes were not uncommon and were sometimes striking. They occurred in 11 (44%) of the patients: in 2 there was a flat segment of 0·2 sec. or longer over the left precordial leads and in leads II and III, in 2 (Fig. 4) there was a considerably raised segment with an upward concavity and raised J point reminiscent of the pattern of epicardial injury associated with pericarditis, in 2 there were raised segments in the precordial leads; in 1 there was a raised segment in I and AVR with reciprocal depression in III and AVF; in 1 there were depressed and flat segments in II, III, and AVF; in 1 depressed segments in all the precordial leads; and in 1 sagging segments in III and AVF. The most dramatic change was of raised segments in I and AVL and deeply depressed segments in the right precordial leads associated with deeply inverted T waves, very suggestive of the pattern of myocardial infarction but for the absence of Q waves (Fig. 5).
There was a shift of the J point in the præcordial leads in 9 (36%) instances. In 1 there were reciprocal changes, in 2 it was displaced downwards, and in 6 it was displaced upwards. In 2 instances (Fig. 4) a pattern reminiscent of acute pericarditis was produced, but this became normal without going on to produce the pattern of chronic pericarditis.

The corrected Q–T interval was calculated by the formula of Taran and Szilagyi (1947). The QTc was prolonged after treatment in 20 (80%) of the patients. The mean of the 25 patients before treatment was 0.40 sec. (range 0.32 to 0.47), that after treatment was 0.46 sec. (range 0.39 to 0.62), and in the last cardiograms taken it was 0.41 sec. (range 0.34 to 0.52). The greatest prolongation seen was by 0.23 seconds.

**Fig. 4.**—Two examples of raised J points and S–T segments in the præcordial leads after emetine.

T wave changes (Fig. 6) were much the most common finding, being seen in 23 (92%) of these patients, in the limb leads in 18 (72%), in the unipolar limb leads in 20 (80%), and in the præcordial leads in 23 (92%). No particular one of the limb or unipolar leads was more affected than another. They occurred with equal frequency and severity in all of the præcordial leads. On two occasions the changes were greater on the left than on the right and on two occasions greater on the right than on the left. Likewise, changes were seen only in the left præcordial leads twice and only in the right præcordial leads twice. When T waves were normally inverted as in AVR and occasionally in III, AVL, AVF, and VI, they tended to become flattened and then upright after emetine. An attempt was made to grade the severity of the T wave
changes. There were no changes in 2 (8%), lower voltages in 4 (16%), iso-electric waves in 5 (20%), inverted waves in 12 (48%), and deeply inverted waves greater than 3 mm. in depth in 2 (8%). There was a gradation of T wave changes from lower voltage through notching to biphasic (+ − or − +) to inversion and finally to deep inversion (Fig. 6), although the whole range was not seen in all of the patients.

In 2 of the 25 patients the electrocardiograms were so grossly abnormal as to suggest, but for the absence of Q waves, acute myocardial infarction (Fig. 1 and 5).
The so-called "Bantu" pattern occurred in 4 of the original records (Fig. 1, 2, and 3). In all of these the right precordial leads only were affected. This pattern is notoriously unstable and may be seen on some occasions and not on others (Turner, 1959). It has recently been shown (Somers and Rankin, 1962) that it may be partially or completely corrected by exercise. In 3 of those in this series the inverted T waves became less inverted or upright after the drug, much as do the inverted T waves in AVR, but in the other one the pattern seemed most resistant and remained unaffected, while the left precordial leads became inverted and then upright again (Fig. 2). This is in contrast to the findings in the 'Bantu' pattern with antimony where the inverted T waves become more inverted after treatment (Davis, 1961). It is of particular interest that in one of these the corrected 'Bantu' pattern persisted and the right precordial leads all showed upright T waves almost five months later (Fig. 1). The only effect of exercise at this time was to increase further the amplitude and to produce "peaking" of the T waves over the right precordium as far as V4.

**Discussion and Conclusions**

Hardgrove and Smith (1944) found electrocardiographic changes in 53 per cent of 72 cases, Dack and Moloshok (1947) in 38 per cent of 21, Klatskin and Friedman (1948) in 53 per cent of 93, Kent and Kingsland (1950) in 100 per cent of 26, González de Cossio (1952) in 100 per cent of 45, Sodeman et al. (1952) in 26 per cent of 38, Cera (1956) in 100 per cent of 7, and Awwaad et al. (1961), who studied children only, in 33 per cent of 33. In the series reported here changes occurred in 100 per cent of the 25 patients. The abnormalities that have been described include low voltage P waves, prolonged P–R intervals, slurring and notching of the QRS complexes, small shifts of the S–T segments with changed contours, prolonged Q–T intervals, T wave changes, extrasystoles, wandering pacemaker, and nodal rhythm. The T wave changes were most prominent in all of these series.

In the few with 12 lead electrocardiograms there is disagreement as to the relative merits of limb and precordial leads. González de Cossio (1952) found T wave changes in 100 per cent of precordial leads but in only 18 per cent of the standard leads, and Awwaad et al. (1961) found no changes in any of the limb leads. However, Kent and Kingsland (1950) found T wave changes in the limb leads of 88 per cent of their patients and in the series reported here they occurred in 80 per cent of limb and unipolar limb leads, not far short of the 92 per cent in the precordial leads. The changes were, however, greater in the precordial leads. Some authors have found the changes to occur more frequently in the right precordial leads (Awwaad et al., 1961) and others in the left precordial leads (Kent and Kingsland, 1950). In the series reported here they were equally common all across the precordium. Similar discrepancies have been reported with antimony. Honey (1960) found the changes more frequently over the left precordium, whereas Davis (1961) and Somers and Rosanelli (1962) found them more frequently over the right precordium. It appears from the series reported here that the changes from emetine are more severe than those from antimony.

The cause of the cardiographic changes due to emetine and antimony is not known, but it seems probable that the two drugs have similar effects on the myocardium. Various possibilities have been suggested for the causation of these changes and these have been discussed by Honey (1960) and Davis (1961): it seems probable that they are due to myocardial damage. It has been shown that extensive T wave inversion may occur from superficial damage to the myocardium (Brink and Goodwin, 1952). In the present series many of the patients had extensive T wave inversion across the precordium, and in 2 patients the changes were associated with gross S–T segment shifts very suggestive of acute infarction but for the absence of Q waves. In two other patients a pattern suggestive of the epicardial injury from acute pericarditis was seen. In one of the series of Dack and Moloshok (1947) deep Q waves appeared in leads II and III, and cardiographic evidence of a posterior infarction occurred in one of the series of Cera (1956). In the fatal cases reported by Kattwinkel (1949) and Brem and Konwaler (1955) there had been extensive cardiographic
changes, and at autopsy there was good histological evidence of myocarditis. Similarly with antimony, Honey (1960) reported a septal infarction proven at autopsy in a 21-year-old West African girl while on treatment, and O’Brien (1959) reported a severe ventricular dysrhythmia with Stokes-Adams attacks in a West African soldier while on treatment. In spite of the notorious instability of the T waves in the precordium in African peoples (Brink, 1951; Brink and Goodwin, 1952; Grusin, 1954; Turner, 1959) and the fact that changes occur after antimony more frequently in Africans than in Europeans (Honey, 1960), it is inescapable that both antimony and emetine may produce temporary myocardial damage and are potentially dangerous. It is of interest to note that the appearance of cardiographic abnormalities may be delayed as it was in two patients of this series, may only reach a maximum after a week or two, and may require a mean period of seven weeks to disappear. This all suggests that the effects of the drug are cumulative and that the maximum damage may be produced some while after the cessation of treatment.

Emetine is a valuable drug and cannot as yet be supplanted. Until a less toxic and equally effective drug is found it is recommended that intramuscular emetine should only be given to patients at rest in bed and under hospital supervision. Treatment should be stopped if severe toxic signs, fall of blood pressure or cardiovascular collapse occur. Likewise, a cardiogram showing severe changes indicates the need for prolonged bed-rest until it becomes more nearly normal. A study of the serum transaminases of patients on treatment with antimony and emetine might provide further evidence of myocardial injury. Some authorities still believe that the cardiographic abnormalities are from changes of repolarization brought about by ionic intracellular changes of a temporary nature, and that they are of no harmful significance.

**Summary**

Twenty-five East African patients with amoebiasis were given intramuscular emetine hydrochloride and the effects on the electrocardiograms were watched. Changes occurred in all. The changes mostly affected the T waves and Q–Tc. In two instances the changes were so gross as to suggest acute myocardial infarction, although there were no Q waves. In two patients a pattern suggestive of acute pericarditis was seen. Comparisons are made between the cardiographic changes due to antimony and emetine. It is believed that in both they are due to myocardial injury. It is recommended that intramuscular emetine is only used in patients in hospital and resting in bed.

I should like to thank Dr. Rashida Janmohamed for recording many of the electrocardiograms and for her assiduity in ensuring an adequate follow-up of many of these patients.

**References**


