Electrocardiogram after Chloroquine and Emetine


In the treatment of hepatic amebiasis emetine is still considered the drug of choice which cannot be supplanted. Chloroquine is also used for hepatic amebiasis. The recommended treatment consists of intramuscular injection of emetine in doses of 1 grain daily for 10 days followed by oral administration of chloroquine for 2 to 4 weeks, and aspiration of pus from the liver when necessary. No serious toxic effects on the cardiovascular system have been found after chloroquine administration orally in therapeutic doses although single large oral doses of chloroquine have caused deaths from cardiac arrest and acute cardiorespiratory failure. Emetine has been considered a protoplasmic poison. Serious toxic effects on the heart have been demonstrated in animal experiments, and deaths attributed to emetine toxicity on the heart have been reported in human beings. Myocardial effects of emetine, including electrocardiographic abnormalities, have been attributed to myocardial degeneration, necrosis, or interstitial myocarditis due to deposit of emetine in the myocardium. There is, however, no agreement on the question of emetine toxicity on the heart. Even in recent reports absolute rest in bed during the period of therapy and stoppage of the drug when the electrocardiographic changes appear have been recommended; it has also been stated that the drug does not cause serious toxic effects, is relatively harmless, and that the electrocardiographic abnormalities do not seem to warrant abandoning this valuable remedy.

Electrocardiographic abnormalities after chloroquine have been reported only once in the literature. It was also thought that combined use of emetine and chloroquine may produce more severe electrocardiographic changes than either drug alone. Again the problem of extremely divergent views on emetine toxicity on the myocardium may be solved if the electrocardiographic abnormalities are found to be reversible by potassium administration and therefore functional in character. The present investigation was undertaken to determine (1) the electrocardiographic abnormalities after chloroquine, emetine, and emetine followed by chloroquine, and (2) the effects of oral potassium administration on these abnormalities. The latter investigation was prompted by the dramatic improvement after oral potassium administration of severe muscular paralysis and electrocardiographic abnormalities which occurred in a patient with amebic hepatic abscess after emetine and chloroquine therapy.

Case Report

A 34-year-old man was admitted on January 18, 1962, with the complaints of fever and pain in the lower part of the right chest and right hypochondrium for 3 months, and cough with a large quantity of blood-mixed expectoration for 2 months. He gave a history of having been treated with penicillin, streptomycin, and tetracycline for pulmonary tuberculosis and lung abscess without improvement in his condition. Sputum was chocolate colored and measured 240 ml in 24 hours. Roentgenogram of the chest showed a diffuse opacity in the lower part of the right lung. Diagnosis of liver abscess rupturing into the right lung was made, and from January 20 the patient was given emetine hydrochloride intramuscularly in doses of 1 grain daily for 12 days, achromycin in doses of 250 mg. four times a day for 7 days, and diiodoquine in doses of 2 tablets three times a day for 3 weeks. Chloroquine was given orally from February 1, in doses of 250 mg. three times a day for 2 days and then twice daily. On February 11, he complained of gener-

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alized muscular weakness, which increased rapidly, and 3 days later he was completely paralyzed and could not move his extremities or sit up in bed. He was otherwise well, and there was no fever, cough, or expectoration, and the opacity in the right lung had cleared up. Chloroquine was therefore stopped on February 14. Examination revealed paralysis of all four extremity muscles with flaccidity, areflexia of tendon jerks, and absence of sensory changes. Emetine neuritis was diagnosed and he was given thiamine in 100 mg. doses daily intravenously. There was no improvement in his condition, and an electrocardiogram taken on February 18 showed severe ST-segment and T-wave changes and a pattern compatible with hypokalemia (fig. 1). The patient was therefore given potassium chloride orally in doses of 15 grains three times a day. There was dramatic improvement of the muscular weakness. On February 22, he was well except for a tired feeling; the electrocardiogram showed considerable improvement of pattern. The muscular power and the electrocardiogram were normal on February 27.

**Figure 1**

Serial electrocardiograms of the reported case showing severe abnormality after emetine and chloroquine and reversal to normal pattern after oral administration of potassium chloride.

**Material and Methods**

Eighty-one patients admitted to the hospital for treatment of chronic amebic dysentery, hepatitis, or liver abscess were studied. Twenty-five patients received chloroquine alone, 28 received emetine alone, and 28 received emetine followed by chloroquine. Emetine was given intramuscularly in doses of 1 grain daily for 8 to 12 days for an average of 10 days. Chloroquine was given orally in doses of 250-mg. tablets (150 mg. of base) two or three times daily for a period of 14 to 32 days, with an average dose of 48 tablets and average duration of 20 days. Potassium chloride was given in doses of 40 grains daily in three divided doses. In some patients it was given after cessation of antiamebic therapy to determine the effect on electrocardiographic abnormalities and in some others it was given simultaneously with antiamebic therapy, from its onset to its cessation, to find out the effect on the appearance of abnormalities. In a few patients it was administered in single large doses of 5 Gm. each of potassium citrate and bicarbonate. A 12-lead electrocardiogram was obtained before onset
of therapy in each case, and subsequently at intervals of 5 to 10 days in most of the cases. It was obtained before and after 60 and 90 minutes of ingestion of a single large dose of potassium. Serum potassium levels were determined in 26 patients before and after antiamebic therapy.

Results

The results are summarized in tables 1 to 3.

Chloroquine

The abnormalities (fig. 2) included inversion of T wave in lead V1–3 in three cases, and in V5–6 in one case. The inversion in precordial leads other than V1 was of the terminal type. Abnormality was seen after 10 days from onset of chloroquine in 12 cases and after 14 to 21 days in six cases. Maximum abnormality was noted at the end of chloroquine therapy. In 12 cases a follow-up electrocardiogram was obtained after 10 days of cessation of chloroquine. It was normal in two cases, showed improvement of pattern in four, and no change in six. Potassium was given for 3 days in four of the last six cases, and immediately after cessation of chloroquine in five others, and the electrocardiogram became normal in seven on stoppage of potassium and in two 4 days later.

Emetine

Abnormality was present on admission in one case in which it increased further and potassium administration subsequently failed to produce a normal pattern. Abnormality was seen at the end of emetine in nine cases. Maximum abnormality occurred in four cases at the end of emetine. Abnormalities included inversion of T wave in lead V1–2 in two cases, in V1–3 in one, in V1–4 in two and in V1–5 in one.

Table 1

<table>
<thead>
<tr>
<th>Percentage of cases with abnormalities</th>
<th>Chloroquine</th>
<th>Emetine</th>
<th>Emetine and Chloroquine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cases</td>
<td>No potassium</td>
<td>Simultaneous potassium</td>
<td>No potassium</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>No. with abnormality</td>
<td>90</td>
<td>60</td>
<td>93</td>
</tr>
<tr>
<td>T-wave changes: total</td>
<td>90</td>
<td>60</td>
<td>86</td>
</tr>
<tr>
<td>T-wave lower voltage</td>
<td>45</td>
<td>60</td>
<td>7</td>
</tr>
<tr>
<td>T-wave inversion: total</td>
<td>45</td>
<td>0</td>
<td>78</td>
</tr>
<tr>
<td>Limb leads</td>
<td>15</td>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>Precordial leads</td>
<td>35</td>
<td>0</td>
<td>64</td>
</tr>
<tr>
<td>Prolonged QTe (0.04 sec. or more)</td>
<td>50</td>
<td>0</td>
<td>57</td>
</tr>
<tr>
<td>ST depression</td>
<td>10</td>
<td>0</td>
<td>36</td>
</tr>
<tr>
<td>Premature beats</td>
<td>0</td>
<td>0</td>
<td>21</td>
</tr>
</tbody>
</table>

Table 2

Mean Serum Potassium Levels before and after Antiamebic Therapy in 22 Patients with Abnormality

<table>
<thead>
<tr>
<th>Therapy</th>
<th>No. cases</th>
<th>Serum K (mEq./L.)</th>
<th>Before therapy</th>
<th>Emetine</th>
<th>After therapy</th>
<th>Chloroquine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine</td>
<td>6</td>
<td>5.2</td>
<td></td>
<td></td>
<td></td>
<td>4.7</td>
</tr>
<tr>
<td>Emetine</td>
<td>6</td>
<td>5.6</td>
<td>4.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emetine and chloroquine</td>
<td>5</td>
<td>5.6</td>
<td>5.1</td>
<td></td>
<td></td>
<td>4.8</td>
</tr>
<tr>
<td>Emetine, chloroquine, and potassium</td>
<td>5</td>
<td>5.5</td>
<td>5.1</td>
<td></td>
<td></td>
<td>4.6</td>
</tr>
</tbody>
</table>
In 14 cases potassium was given simultaneously with emetine and was continued for 10 days after stoppage of emetine. Abnormality was seen at the end of emetine in three cases and 5 days later in two cases. Abnormalities included inversion of T wave in lead V<sub>2-3</sub> in two cases, and in V<sub>3-6</sub> in one case. All five cases had inversion of T wave in lead V<sub>1</sub> at the time of admission. Maximum abnormality occurred in one case at the end of emetine. In

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Chloroquine</th>
<th>Emetine</th>
<th>No potassium</th>
<th>Simultaneous potassium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases with inverted T-wave in V&lt;sub&gt;1-5&lt;/sub&gt;</td>
<td>0</td>
<td>7%</td>
<td>56%</td>
<td>10%</td>
</tr>
<tr>
<td>Appearance</td>
<td>13(10-21)</td>
<td>12(10-20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum</td>
<td>17(14-21)</td>
<td>17(10-20)</td>
<td>28(20-48)</td>
<td>28(24-31)</td>
</tr>
<tr>
<td>Disappearance</td>
<td>—</td>
<td>27(20-37)</td>
<td>58(40-76)†</td>
<td>33(28-35)</td>
</tr>
<tr>
<td>Cessation of chloroquine</td>
<td>17</td>
<td>—</td>
<td>36</td>
<td>28</td>
</tr>
</tbody>
</table>

*Figures in parentheses are ranges and those outside are mean number of days.
†Forty-five days in patients who received potassium after cessation of chloroquine.

**Figure 2**

Electrocardiographic abnormalities after chloroquine administration in three patients. Upper tracing is before and lower one after administration of the drug.
two cases the electrocardiogram became normal on the fifteenth and twenty-fifth days, respectively, and in three others abnormality persisted in the last electrocardiogram taken on the thirtieth day, although improvement of pattern had occurred in two of them.

**Emetine and Chloroquine**

Abnormality was present on admission in two cases in which it further increased. Abnormality appeared when emetine was stopped in 13 cases and 10 to 12 days later in three cases. Abnormalities (figs. 1, 3, and 4) included inversion of T wave in lead V1 in five cases, in V1-5 in five, and in V1-4 in two. Severe electrocardiographic changes were frequently not associated with tachycardia. Maximum abnormality occurred during chloroquine therapy in five cases and at the end of chloroquine in 13 cases. In eight cases potassium was given for 4 to 10 days after cessation of chloroquine and the electrocardiogram showed marked improvement of pattern in three of them and became normal in four (fig. 3). In one case a hyperkalemic pattern (fig. 4) was observed after ingestion of a single large dose. It was therefore discontinued.

In 10 cases potassium chloride was given simultaneously with emetine and chloroquine. The electrocardiogram was abnormal in one patient on admission in whom the abnormality increased after therapy and was not corrected by further potassium administration for 10 days. Abnormalities appeared in seven cases and included inversion of T waves in V1-6 in

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**Figure 3**

Electrocardiograms of three patients showing abnormalities after emetine and chloroquine (upper tracing) and effect of oral potassium chloride administration (lower tracing).
Electrocardiograms of three patients showing effect of single large dose of potassium after 60 minutes of ingestion (lower tracing) on abnormalities (upper tracing) after chloroquine (A), and after emetine and chloroquine (B and C). Abnormalities are reversed in A and B and hyperkalemic pattern occurs in C.

one case and \( V_{1-4} \) in two cases. Abnormalities disappeared after further administration of potassium for 4 to 7 days.

Serum potassium levels were determined before and after antiamoebic therapy in 22 cases who showed electrocardiographic abnormalities (table 2) and in four cases who showed no abnormalities. They were determined only in cases without any history of recent diarrhea. In patients who showed no abnormality there was no significant decrease of levels. Decrease of level varying between 0.4 and 1.4 mEq./L. occurred in 15 of 16 cases who received emetine and four of six cases who received only chloroquine.

**Discussion**

There is only one report in the literature on electrocardiographic changes after chloroquine\(^9\) and the changes observed were concordant diminution in the height of the T wave in 12 of 20 cases receiving 0.3 Gm. of chloroquine base in two doses daily. In the present


study electrocardiographic changes were observed in 90 per cent of cases, and consisted of inversion or lowering of T wave, ST-segment depression, and prolongation of QTc interval. The changes were less severe and of shorter duration than after emetine.

Electrocardiographic abnormalities reported after emetine have varied greatly in their incidence, severity, and duration. The incidence of abnormality has varied between 26 and 100 per cent and incidence of inversion of T wave between 10 and 100 per cent.\textsuperscript{2, 14, 16, 25–27} In the present series in patients who received emetine without simultaneous potassium, abnormality was found in 93 per cent and included inversion of T wave in 75 per cent. Inversion of T was more frequent in precordial leads than in limb leads and occurred predominantly in right precordial leads; inversion in left precordial leads was almost always associated with inversion in right leads. This was also seen after chloroquine and after emetine and chloroquine. Awwaad et al.\textsuperscript{28} found T wave changes more in right leads, while Kent and Kingsland\textsuperscript{27} found them more in the left leads, and Turner\textsuperscript{2} observed them equally in all precordial leads. Lag of appearance of abnormality,\textsuperscript{2, 16, 19} after completion of the emetine course was noted in three of our cases. Maximum abnormality occurred at the end of emetine therapy in 31 per cent and 5 to 10 days later in others. Turner\textsuperscript{2} reported maximum changes immediately on cessation of emetine therapy in 36 per cent, and 1 to 3 weeks later in others.

Study of abnormalities in patients who received both emetine and chloroquine revealed that they were greater in severity, the occurrence of maximum abnormality was much more delayed, and the duration of abnormalities was more prolonged than after emetine alone. The maximum time for return to normal has been noted by Gonzalez\textsuperscript{17} and Turner,\textsuperscript{2} on an average of 7 weeks after cessation of emetine therapy by Turner and on an average of 53 days after onset of emetine by Gonzalez. Gonzalez\textsuperscript{17} has not mentioned the use of chloroquine, but as most of his cases were of liver abscess, it is not unlikely that some of them received chloroquine after emetine therapy. Turner\textsuperscript{2} has mentioned that some of his cases received chloroquine. It is concluded that the combined effects of emetine and chloroquine were responsible for the differences (table 3).

It was most interesting to find that oral administration of potassium after cessation of antiamebic therapy produced rapid improvement of the electrocardiographic pattern and much earlier return to a normal pattern (table 3) than in cases that received no potassium. It was also noted that induced hyperkalemia with a single large dose of potassium reversed the abnormality (fig. 4). Effect of administration of potassium simultaneously with antiamebic therapy was also noteworthy. The incidence as well as the severity of abnormality was less, the appearance of abnormality was delayed, and the electrocardiogram returned to normal earlier (tables 1 and 3) with further administration of potassium. It was noted, however, that in patients with abnormal electrocardiograms before therapy the abnormality could not be reversed by potassium, which suggested that the changes when present on admission were due to toxic myocarditis.

It is difficult if not impossible to produce potassium poisoning by oral administration except in patients with renal failure, shock, or adrenal insufficiency,\textsuperscript{20} or in patients with severe heart disease or congestive failure.\textsuperscript{24, 31} It was therefore significant that in one of our cases changes consistent with hyperkalemic pattern (fig. 4) were found after ingestion of a single large dose in the absence of any of the above-mentioned conditions and in an otherwise normal subject.

Electrocardiographic changes after emetine have been attributed to toxic action of the drug on the heart causing myocarditis. While human deaths attributed to emetine toxicity on the heart have been reported, Brem and Konwaler\textsuperscript{15} stated that there was only one report with electrocardiographic and detailed histologic observations and reported one case of their own. They admitted, however, that the finding of myocarditis in their case as a result of emetine might be debated. In two other cases
in their series, in five cases of Kent and Kingsland, and in 11 cases of McE Lamont and Pooler\textsuperscript{20} no evidence of myocarditis was found at autopsy. Wilmot\textsuperscript{1} has stated that human fatalities have seldom been reported that are clearly attributable to emetine. It has been observed that functional or metabolic types of T-wave changes seen in a variety of noncardiac illnesses, which have been considered in the past as evidence of myocarditis, are reversed by induced hyperkalemia, and those due to acute ischemia, myocardial infarction and organic heart disease are mostly unaltered.\textsuperscript{20-24} Dodge et al.\textsuperscript{22} stated that changes described in emetine therapy may well fall in the metabolic group. Our study showed that the electrocardiographic changes due to emetine and chloroquine were usually reversed by potassium and may therefore be considered as functional in nature and not attributable to organic myocardial damage.

Muscular weakness, including actual paralysis and neuritis, has been reported to occur after emetine. Etiology of this so-called "neuritis" or muscle paralysis has remained obscure. It has been attributed to direct action of emetine on the muscles,\textsuperscript{23} or to a primary disorder of muscle, probably a myositis.\textsuperscript{26} Wilmot\textsuperscript{1} states that true polynueritis with both motor and sensory objective changes very rarely, if ever, occurs. In the case reported by us the episode of paralysis without sensory changes and the dramatic improvement of paralysis and electrocardiographic changes after potassium administration resemble family periodic paralysis or muscular paralysis which occurs in thyrotoxicosis as a result of disturbance of potassium metabolism.

Results of determination of serum potassium (table 2) in some of our cases revealed that the potassium levels decreased significantly after antiamebic therapy in almost all of the cases that showed abnormalities but not in those without abnormalities. This decrease was not attributable to diarrhea. It was clear, however, that the decrease was not so marked as to be considered to indicate hypokalemia. Question arises whether emetine causes some disturbance in the metabolism of potassium ion in the body, in the myocardium, and in the skeletal muscles, which causes shift of potassium into the skeletal muscles with decrease of potassium in serum and in cardiac muscle, which may explain both the muscle paralysis and the electrocardiographic changes. Trial of potassium therapy in cases of emetine "neuritis" and observations on concentrations of potassium in skeletal muscle and myocardium before and after emetine therapy may throw some light on the problem.

**Summary**

Electrocardiographic abnormalities have been studied after administration of chloroquine in 25 patients, of emetine in 28 patients, and of emetine and chloroquine in 28 patients.

Abnormalities after chloroquine were less in severity and of shorter duration than after emetine. They were more severe, became maximum later after cessation of emetine therapy, and were much longer in duration after emetine and chloroquine than after emetine. These differences are attributed to combined effects of the two drugs.

Serum potassium levels showed some decrease after antiamebic therapy, the decrease being more after emetine than after chloroquine.

A case is reported in which severe abnormalities and muscular paralysis occurring after emetine and chloroquine were rapidly reversed by oral potassium administration.

Administration of potassium simultaneously with emetine and chloroquine often prevented or delayed the appearance or decreased the severity of abnormalities. Subsequent potassium administration usually reversed the abnormalities except in cases in which they were present before emetine therapy. It is concluded that the abnormalities are functional in nature and not due to organic myocardial damage.

It is suggested that some disturbance of potassium metabolism in the myocardium and skeletal muscles may be the cause of electrocardiographic abnormalities and emetine neuritis, respectively.
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References
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