The effect of sodium bicarbonate on a single dose of diethylcarbamazine therapy in patients with bancroftian filariasis in Kenya

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Abstract

An attempt was made to examine the effect of a combination of diethylcarbamazine citrate (DEC-C) and sodium bicarbonate (NaHCO₃) on the pharmacokinetics of diethylcarbamazine (DEC), side-reactions and reduction of the microfilarial density of patients with Wuchereria bancrofti infection at a hospital in Nairobi, Kenya. The microfilariae carriers received DEC-C at 6 mg/kg or 3 mg/kg with or without NaHCO₃ at 75 mg/kg body weight. The patients treated with a combination of drugs showed alkaline urine for 4 h post-treatment, while patients treated with DEC-C alone showed acidic urine. Although no significant difference was detected in the DEC half-life value and other pharmacokinetic parameters between patients treated with DEC-C (6 mg/kg) plus NaHCO₃ (75 mg/kg) and those treated with DEC-C (6 mg/kg) alone, the general tendency was that in patients receiving NaHCO₃, the first-order elimination rate constant decreased and serum elimination half-life and area under the serum concentration–time curve values increased. There was a significant difference between the mean values of the first-order absorption rate constant, the first-order elimination rate constant, and the time to maximum serum concentrations for the patients receiving DEC-C at 3 mg/kg plus NaHCO₃ at 75 mg/kg and those for the group receiving DEC-C at 6 mg/kg alone. There was no difference in frequency and severity of the side-reactions between patients receiving DEC-C at 6 mg/kg plus NaHCO₃ at 75 mg/kg, DEC-C at 3 mg/kg plus NaHCO₃ at 75 mg/kg, and DEC-C at 6 mg/kg alone.

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During the initial 5 days post-treatment, there was no significant difference in reduction of microfilarial density among these three groups. In the field, an attempt was made to examine the possibility of increased antifilarial effect using a combination of DEC-C and NaHCO₃. The patients were examined for microfilariae, given DEC-C at 6 mg/kg with or without NaHCO₃ at 75 mg/kg, and examined for microfilariae again 1 year later. Although the cure rate was the same among the groups, the percentage reduction in microfilarial density of the patients receiving DEC-C plus NaHCO₃ was significantly greater than those of patients receiving DEC-C alone. A combination of DEC-C with NaHCO₃ will be of practical value in a single dose of DEC-C for the mass-treatment of bancroftian filariasis.

Keywords: Bancroftian filariasis; Mass treatment; Combination; Diethylcarbamazine; Sodium bicarbonate

1. Introduction

Filariasis control programmes are based primarily on mass-chemotherapy. Diethylcarbamazine citrate (DEC-C) is the only available drug in use at present, until ivermectin becomes registered for use. The currently recommended regimens for mass-chemotherapy are DEC-C-medicated salt or a single dose of DEC-C administered annually or semi-annually. However, community acceptance is a prerequisite to the success of the medicated salt and 5–10 years may be necessary for the success of the single annual dose strategy [1].

Edwards et al. [2] have shown that the plasma half-life of diethylcarbamazine (DEC) after a single oral dose is significantly prolonged when an alkaline urine is maintained by administration of sodium bicarbonate (NaHCO₃) as compared to the situation when an acidic urine is produced. Thus, they treated patients infected with *Wuchereria bancrofti* by a combination of DEC-C and NaHCO₃ and reported that the NaHCO₃-treated group achieved a significantly greater reduction in skin microfilarial counts than the control group as assessed 1 week after completion of therapy. However, there was no effect of DEC on adult worms, and the Mazzotti reaction, i.e. the side-reaction of DEC, was higher in the NaHCO₃-treated patients [3].

Thus, by careful manipulation of urinary pH there is a possibility of developing more effective dosage regimens, especially for community-based intervention programmes, where the most successful drug interventions are those that can be administered in a single oral dose of DEC-C, induce a few serious side-effects, and result in a sustained, profound suppression of microfilariae.

In this article, we report the effect of a combination of DEC-C and NaHCO₃ on urinary pH, pharmacokinetics of DEC, side-reactions and the reduction of microfilarial density at the initial 5 days and 1 year after DEC-C administration.

2. Materials and methods

2.1. Patients studied

Two groups of patients were studied:

(1) Subjects for the study of the effect of a combination of drugs on the pharmacokinetics, side-reactions and reduction of microfilarial density at the initial 5 days post-treatment.

These studies were carried out at the Clinical Research Center wards, Kenya Medical Research Institute (KEMRI), Nairobi. Twelve healthy Kenyan adults, four males and eight females, aged between 15 and 65 years with light to moderate microfilarial density and with no obvious gastrointestinal, hepatic or renal disease were admitted to the Clinical Research Center. All the subjects were from Malindi and they gave their informed consent. The study was approved by the Ethical Committee of KEMRI. Pretreatment examinations included parasitological and clinical examination of filariasis according to the WHO standard protocol [4], and routine biochemical analysis. The patients were given the standard hospital diet during the observation period of 6 days.

(2) Subjects for the study of the effect of a
combination of drugs on the reduction of microfilarial density at 1 year post-treatment.

The study was carried out in three villages in Kwale, where bancroftian filariasis is endemic. One-hundred and thirty-five villagers, 60 males and 75 females, with light to heavy microfilarial density and no obvious disease signs were enrolled in the study, after obtaining their informed consent. Each sample was determined by the urinalysis reagent strip (Uropaper-Hg-2, Eiken Chemicals Company, Japan). The mean weight, age and geometric mean of microfilarial density of each group were: Group 1, 47.8 kg, 51.5 years and 9.2 microfilariae/60 cm of blood; Group 2, 47.8 kg, 45.5 years and 14.6 microfilariae/60 cm of blood; and Group 3, 52.0 kg, 19.5 years and 18.5 microfilariae/60 cm of blood.
paper as geometric means. Differences between study groups were assessed by \( \chi^2 \)-test or Student's t-test.

The association of demographic and parasitological parameters with treatment outcomes were assessed by multiple regression analysis using variables, such as gender, age treatment and pre-treatment microfilarial density.

2.7. Side-effect

In the hospital, any events physically observed or experienced by the patients were recorded. In the field, the patients were requested to report any side-effects they may have experienced for 1 week post-treatment.

3. Results

3.1. Urinary pH

The variation in mean urinary pH over 24 h in the patients in the hospital is described in Fig. 1. All patients who received NaHCO\(_3\) showed alkaline urine and maintained a urinary pH > 7.2 during the initial 4 h post-treatment. The pH of urine of these patients returned to baseline acidic level after 8 h.

3.2. Pharmacokinetics

The mean serum concentration–time profiles for DEC are shown in Fig. 2. The first-hand data on all 12 patients fitted into a one-compartment pharmacokinetic model with first-order absorption characteristics. The mean values of the standard pharmacokinetic parameters are summarized in Table 1. There was no significant difference between the mean values of all parameters in Group 1 (DEC-C 6 mg/kg) and those in Group 2 (DEC-C 6 mg/kg + NaHCO\(_3\) 75 mg/kg). However, the general tendency was that in patients receiving NaHCO\(_3\), \( K_e \) decreased, whereas serum elimination half-life (\( T_{1/2} \)) and AUC values increased. Interestingly there was a significant difference between the mean of the first-order ab-
Fig. 2. Mean serum concentration–time profile of DEC: O, DEC-C 6 mg/kg alone; ●, DEC-C 6 mg/kg plus NaHCO₃ 75 mg/kg; □, DEC-C 3 mg/kg plus NaHCO₃ 75 mg/kg. Each point represents the mean ± S.E. This study was done at the Clinical Center wards.

Table 1
Pharmacokinetic values of DEC in four patients after a single dose of DEC-C (6 mg/kg or 3 mg/kg) with or without NaHCO₃ (75 mg/kg) derived from a one-compartment model

<table>
<thead>
<tr>
<th>Parameters*</th>
<th>DEC-C 6 mg/kg alone</th>
<th>DEC-C 6 mg/kg plus NaHCO₃ 75 mg/kg</th>
<th>DEC-C 3 mg/kg plus NaHCO₃ 75 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_max (µg/ml)</td>
<td>0.899 ± 0.570</td>
<td>1.334 ± 0.386</td>
<td>0.803 ± 0.103</td>
</tr>
<tr>
<td>T_max (h)</td>
<td>4.88 ± 1.41a</td>
<td>3.86 ± 1.65</td>
<td>2.56 ± 0.78a</td>
</tr>
<tr>
<td>K_a (1/h)</td>
<td>0.348 ± 0.279f</td>
<td>1.147 ± 1.358</td>
<td>1.505 ± 0.666f</td>
</tr>
<tr>
<td>K_e (1/h)</td>
<td>0.152 ± 0.048b,d</td>
<td>0.074 ± 0.052b</td>
<td>0.049 ± 0.011d</td>
</tr>
<tr>
<td>T_(1/2) (h)</td>
<td>4.94 ± 1.57c,h</td>
<td>16.11 ± 15.62c</td>
<td>14.38 ± 3.13b</td>
</tr>
<tr>
<td>V_d/f (l)</td>
<td>4.987 ± 4.557</td>
<td>3.398 ± 1.104</td>
<td>3.352 ± 0.488</td>
</tr>
<tr>
<td>AUC (µg h/ml)</td>
<td>12.304 ± 6.369d</td>
<td>37.033 ± 25.122c</td>
<td>19.213 ± 6.589</td>
</tr>
</tbody>
</table>

* C_max, maximum serum concentration; T_max, time to maximum serum concentration; K_a, first-order absorption rate constant; K_e, first-order elimination rate constant; T_(1/2), half terminal elimination life; V_d/f, apparent volume of distribution; AUC, area under the serum concentration–time curve.

a,b,c,dP < 0.1.

fP < 0.05.
b,c,dP < 0.01.

This study was done at the Clinical Center wards, KEMRI.
sorption rate constant \( (K_a) \), \( K_r \), \( T_{1/2} \) and time to maximum serum concentration \( (T_{\text{max}}) \) values for the patients receiving DEC-C at 3 mg/kg plus NaHCO\(_3\) at 75 mg/kg and those of the control group receiving DEC-C at 6 mg/kg alone.

### 3.3. Side-reactions

The general reaction pattern is shown in Table 2. This was similar in all the three groups. All the side-reactions experienced by the patients were mild and tolerable, and they did not last more than 2 days. In the field only one patient reported headache in a 7-day period.

### 3.4. Effect on microfilariae

The reduction of microfilarial density during the initial 5 days post-treatment is shown in Fig. 3. Following 36 h post-treatment the mean microfilariae counts had fallen to 11.8–22.7% of initial count in all groups. However, at 60 h for the control group and 84 h for the NaHCO\(_3\)-treated groups, microfilarial density began to increase. Although the control group showed strong increasing tendency of microfilarial density, there was no significant difference between the NaHCO\(_3\)-treated group and the control group at 132 h.

Tables 3 and 4 show the cure rate and reduction of microfilariae density of the patients given DEC-C at 6 mg/kg, with or without NaHCO\(_3\) at 75 mg/kg, respectively, 1 year post treatment in the study community. Overall, the parasitological cure rate of the patients receiving DEC-C with or without NaHCO\(_3\) is the same. However, the difference in cure rate of patients with moderate microfilarial density (21–100 microfilariae/ml of blood) was significant. The reduction of microfilarial density for the NaHCO\(_3\)-treated group was 95.3% and those for the control group was 86.2%. Multiple regression analysis of the percentage reduction of microfilarial density indicated that treatment and pre-treatment microfilarial density were, together, significantly associated with reduction of microfilarial density after treatment. Gender and age were not associated with reduction of microfilarial density after treatment. The difference in the percentage reduction of microfilarial density between the patients receiving DEC-C plus NaHCO\(_3\) and those receiving DEC-C alone is significant. Again for the patients with moderate intensity the higher reduction was observed in those receiving NaHCO\(_3\).

### 4. Discussion

It has been previously reported that at alkaline pH, re-absorption of DEC through the renal tubules is facilitated [7]. Based on their studies on

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**Table 2**

Observed side-reactions in patients who were treated by DEC-C alone and DEC-C plus NaHCO\(_3\).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>DEC-C 6 mg/kg alone</th>
<th>DEC-C 6 mg/kg plus NaHCO(_3) 75 mg/kg</th>
<th>DEC-C 3 mg/kg plus NaHCO(_3) 75 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects examined</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>No. of patients with any complaints</td>
<td>2(^{a,b})</td>
<td>1(^c)</td>
<td>1(^d)</td>
</tr>
</tbody>
</table>

\(^{a,b}\)Signs and symptoms reported.

\(^a\)Abdominal discomfort.

\(^b\)Fever, chest pain, headache.

\(^c\)Joint pain, headache.

\(^d\)Abdominal discomfort.

This study was also done at the Clinical Center wards.
Fig. 3. Microfilaria density after DEC-C administration: ○, DEC-C 6 mg/kg alone; ●, DEC-C 6 mg/kg plus NaHCO₃ 75 mg/kg; □, DEC-C 3 mg/kg plus NaHCO₃ 75 mg/kg. This study was done at the Clinical Center wards.

Table 3.
Comparison of efficacy of DEC-C (6 mg/kg) alone and DEC-C plus NaHCO₃ (75 mg/kg) by cure rate

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mf density (Mf/ml)</th>
<th>No. of subjects</th>
<th>No. Mf-negative after treatment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEC-C alone</td>
<td>1-20</td>
<td>14</td>
<td>11 (78.6)</td>
</tr>
<tr>
<td></td>
<td>21-100</td>
<td>19</td>
<td>16 (84.2)*</td>
</tr>
<tr>
<td></td>
<td>101-500</td>
<td>28</td>
<td>7 (25.0)</td>
</tr>
<tr>
<td></td>
<td>501-</td>
<td>17</td>
<td>3 (17.6)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>78</td>
<td>37 (47.4)</td>
</tr>
<tr>
<td>DEC-C plus NaHCO₃</td>
<td>1-20</td>
<td>14</td>
<td>11 (78.6)</td>
</tr>
<tr>
<td></td>
<td>21-100</td>
<td>19</td>
<td>16 (84.2)*</td>
</tr>
<tr>
<td></td>
<td>101-500</td>
<td>28</td>
<td>7 (25.0)</td>
</tr>
<tr>
<td></td>
<td>501-</td>
<td>17</td>
<td>3 (17.6)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>78</td>
<td>37 (47.4)</td>
</tr>
</tbody>
</table>

*P < 0.05 (x²-test).

This study was undertaken at three villages in Kwale. Efficacy of treatment was evaluated 1 year after the treatment.

The clinical pharmacology of DEC-C, Awadzi et al. [3] attempted to examine the effect of the combination of DEC-C and NaHCO₃ on the microfilarial density and clinical reactions for onchocerciasis patients. Although the NaHCO₃-treated group achieved a greater reduction in skin microfilarial counts than the control group, as assessed 1 week after completion of therapy, these patients reported unacceptable side-reactions which were consistently higher than in the control group. Therefore combination of DEC-C with NaHCO₃ is not of practical value in onchocerciasis chemotherapy.

Roychowdhury et al. [8] reported that no difference in reduction of microfilarial density occurred between the microfilariae carriers of W. bancrofti who were treated with DEC-C plus NaHCO₃ and those with DEC-C alone, although pharmacokinetics of DEC in these patients was not studied. In their study, the patients received DEC-C at 6 mg/kg daily for 12 days and NaHCO₃ at 7.5 g daily for 7 days before and during the 12 days of DEC-C administration. The absence of a significant difference in the reduction of microfilarial density may be due to the fact that the microfilarial density had drastically fallen to the lower level even in the control group.

A single dose of DEC-C has been enthusiasti-
Table 4
Comparison of efficacy of DEC-C (6 mg/kg) alone and DEC-C plus NaHCO$_3$ (75 mg/kg) by reduction of microfilarial density

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mf density (Mf/ml)</th>
<th>No. of subjects treated</th>
<th>Geometric mean of Mf count</th>
<th>% decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>DEC-C</td>
<td>1–20</td>
<td>14</td>
<td>6.3</td>
<td>1.5</td>
</tr>
<tr>
<td>plus NaHCO$_3$</td>
<td>21–100</td>
<td>19</td>
<td>47.6</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>101–500</td>
<td>28</td>
<td>223.9</td>
<td>8.3</td>
</tr>
<tr>
<td></td>
<td>501–</td>
<td>17</td>
<td>1174.9</td>
<td>38.0</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>78</td>
<td>117.3</td>
<td>5.5</td>
</tr>
<tr>
<td>DEC-C</td>
<td>1–20</td>
<td>22</td>
<td>6.8</td>
<td>2.2</td>
</tr>
<tr>
<td>alone</td>
<td>21–100</td>
<td>16</td>
<td>49.0</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td>101–500</td>
<td>13</td>
<td>218.8</td>
<td>9.3</td>
</tr>
<tr>
<td></td>
<td>501–</td>
<td>6</td>
<td>1318.3</td>
<td>138.0</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>57</td>
<td>45.7</td>
<td>6.3</td>
</tr>
</tbody>
</table>

*P < 0.01 (t-test).

This study was also undertaken in the three villages.
Efficacy of treatment was evaluated 1 year after the treatment.

cally advanced in some endemic areas of bancroftian filariasis [9]. A combination of DEC-C with NaHCO$_3$ may be of practical use in a single dose of DEC-C in the mass-treatment of *W. bancrofti* infection, because NaHCO$_3$ increases the $T_{1/2}$ and AUC of DEC [2]. The present paper confirmed the effect of NaHCO$_3$ on the pharmacokinetics of DEC.

Although there was no significant difference in all pharmacokinetic parameters between Group 1 and Group 2, $T_{1/2}$ and AUC values were likely to increase in Group 2. The absence of a significant difference is probably due to the limited power of statistical comparison within a small group of subjects and great intersubgroup variations. There was a significant difference in some parameters between Group 1 and Group 3. The present study strongly suggests that a combination of DEC-C with NaHCO$_3$ increases the absorption of DEC and decreases the elimination of DEC from the blood.

Although the general tendency was that in patients receiving NaHCO$_3$, microfilarial density began to increase gradually, the improvement in the microfilaricidal effect of the combination therapy at the initial observation period after treatment could not be confirmed. However, a combination of DEC-C with NaHCO$_3$ showed partial improvement in the reduction of the microfilarial density of patients at 1 year post-treatment. The patients with mild microfilarial density were especially susceptible to the combination therapy. However, the reason remains to be studied. These results demonstrate that a combination of DEC-C with NaHCO$_3$ is effective both to microfilariae and adult worms.

Administration of NaHCO$_3$ results in a longer mean serum DEC half-life, and may cause severe reactions in the patients. In the treatment of onchocerciasis, moderately severe reactions occurred in a total of eight out of 21 patients [3]. Roychowdhury et al. [8] reported that the frequency and nature of the side-reactions were not markedly different between the NaHCO$_3$-treated group and the control group, although the patients received DEC C and NaHCO$_3$ for 12 and 19 days, respectively. We found in our study that for the treatment of bancroftian filariasis, NaHCO$_3$ does not cause an unacceptable level of side-reaction. Moreover, the patients do not have any difficulty in taking NaHCO$_3$. A combination of DEC-C with NaHCO$_3$ appears to be more effective than a single annual dose of DEC-C for mass-treatment, and has fewer adverse reactions and compliance from patients is good. The combination therapy is as simple and as cheap as a single dose of DEC-C.

Although NaHCO$_3$ has been used as the safety
drug for the treatment of gout and other diseases, special attention should be given to the fact that NaHCO₃ permitted the induction of the disease with lower dosages of *Vibrio cholerae* [10]. Sodium bicarbonate buffers the stomach contents to pH > 5.0 for 30 min. It takes 60 min for the pH-value of gastric samples to return to a baseline acidic level. Therefore the combination of DEC-C with NaHCO₃ can not yet be recommended in areas where cholera is more likely occur.

Acknowledgements

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References


