SOME CLINICAL OBSERVATIONS ON THE PROPHYLACTIC AND THERAPEUTIC USE OF PROGUANIL IN MACKINNON ROAD

BY

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In 1944, Curd, Davey and Rose [1] selected Proguanil as a chemical substance worthy of a clinical trial as an antimalarial drug. This clinical trial was carried out by MacGraith et al. [2] on Service personnel recently returned from West and East Africa and suffering from malignant tertian malaria. It was concluded that proguanil was completely effective in the treatment of malignant tertian malaria. With a similar trial on personnel suffering from benign tertian malaria we are not here concerned.

An extensive investigation into the prophylactic and therapeutic effects of proguanil was carried out at Cairns, Australia, by Fairley [3] using a New Guinea strain of Plasmodium falciparum. He concluded that, as far as malignant tertian malaria is concerned, proguanil is a complete causal prophylactic; that it acts most effectively upon the pre-erythrocytic forms of the parasite and that 50–100 mg. of the drug taken between 39 to 131 hours after being bitten will afford complete protection; that it is also a powerful schizonticide and prevents nuclear division and the formation of merozoites; and that 300 mg. given daily for ten days will result in a 99 per cent radical cure rate.

As a result of these experiments, proguanil began to supersede mepacrine in the prophylaxis and treatment of malaria in many parts of the world during 1946 and 1947. Since then reports from different parts of the world have been published tending to show that proguanil is not so efficient as it was originally thought to be. Field and Edeson [4] working in Malaya have reported that in the Tampin area increasing doses are needed each year for the radical cure of malarial patients. And they have briefly discussed the possibility of the natural development of resistant strains. Covell, Nicol, Shute and Maryon [5] working with a Lagos strain of Plasmodium falciparum found that proguanil was a complete causal prophylactic but that it failed to effect a radical cure when used alone in patients suffering from malaria experimentally induced with this strain. Bruce-Chwatt and Bruce-Chwatt [6] working in Nigeria confirm these findings with regard to the therapeutic effect of proguanil on the Lagos strain and are also convinced that cases have occurred in which proguanil has failed as a causal prophylactic.
Proguanil has been in use as a prophylactic and therapeutic agent in Mackinnon Road since October 1948—during the period from October 1948 to September 1950 there were 185 cases of malignant tertian malaria in British personnel who were supposed to be taking prophylactic proguanil in doses of 100 mg. daily. During the six months from October 1948 to March 1949 these cases came under the care of Major Hugh Droller, R.A.M.C., and totalled 44. The remaining 141 cases came either directly or indirectly under my care.

Before he left Mackinnon Road, Droller [7] wrote a report on his experiences with proguanil. He claimed that overt attacks of malignant tertian malaria had occurred in patients who had been conscientiously taking 100 mg. of proguanil daily; that trophozoites of *Plasmodium falciparum* could be found in the blood stream of some people who were conscientiously taking 100 mg. of proguanil daily, although these people were free from symptoms of malaria; that trophozoites could be found in the blood stream of patients admitted to hospital for other reasons, such as, for example, dysentery; and that out of 15 cases, treated for malignant tertian malaria with 100 mg. of proguanil eight-hourly, 3 cases had relapsed.

In presenting the additional data which accumulated during my tour of duty in Mackinnon Road, I have selected the year from the beginning of September 1949 to the end of August 1950 for detailed review, because during this period the population of Mackinnon Road remained fairly constant with a mean of 1,200 and a range of ± 200. Furthermore, subdivision into quarterly periods gives for the most important quarter a mean population of 1,100 with a range of ± 20.

<table>
<thead>
<tr>
<th>Quarterly period</th>
<th>Mean population</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>September 1, 1949-November 30, 1949</td>
<td>1,200</td>
<td>± 150</td>
</tr>
<tr>
<td>December 1, 1949-February 28, 1950</td>
<td>1,100</td>
<td>± 20</td>
</tr>
<tr>
<td>March 1, 1950-May 31, 1950</td>
<td>1,200</td>
<td>± 50</td>
</tr>
<tr>
<td>June 1, 1950-August 31, 1950</td>
<td>1,350</td>
<td>± 60</td>
</tr>
</tbody>
</table>

During the period September 1949 to August 1950, 122 cases of malignant tertian malaria were treated: ring forms of *Plasmodium falciparum* were found in the blood stream of 118 patients; in 4 patients the diagnosis was made on clinical grounds only. 74 of these cases occurred during the quarter from December 1, 1949 to February 28, 1950. This gives an incidence of 100 per 1,000 per annum for the whole period with a peak of 268 per 1,000 per annum during the quarter December 1949 to February 1950.

These 122 cases may, in the first place, be divided into: (a) Those with satisfactory prophylactic histories; (b) those with unsatisfactory prophylactic histories; (c) those in whom the prophylactic history is unknown.

<table>
<thead>
<tr>
<th>Prophylactic History</th>
<th>Satisfactory</th>
<th>Unsatisfactory</th>
<th>Unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>74</td>
<td>27</td>
<td>21</td>
<td>122</td>
</tr>
</tbody>
</table>
In taking the prophylactic history, it was explained to the patient that no disciplinary action was envisaged, if he had failed to take proguanil regularly, and that the information was required solely for research purposes. By this means a frank admission of gross irregularity in the ingestion of proguanil was obtained in 27 cases. The 74 patients who are recorded as having satisfactory prophylactic histories were carefully cross-examined and in some cases minor irregularities were revealed; for example, failure to take proguanil on Sundays or during weekend leave in Mombasa. But these minor irregularities could not be correlated with the incubation period and were shorter in duration than would appear necessary from Fairley's work for the establishment of the erythrocytic cycle, and consequently they have not been regarded as justifying the relegation of the cases to the unsatisfactory group.

In the second place, these 122 cases may be divided into: (d) Those who developed malaria without any apparent precipitating factor; (e) those in whom a precipitating factor was present.

No precipitating factor  | Precipitating factor
---|---
Dysentery and diarrhoea | Tonsillitis | Infective hepatitis | Sundry | Total
63 | 10 (5) | 5 (2) | 8 | 122

During the period September 1949-August 1950, the number of cases of dysentery and diarrhoea, of tonsillitis and pharyngitis, and of infective hepatitis was as follows:

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysentery and diarrhoea</td>
<td>253</td>
</tr>
<tr>
<td>Tonsillitis and pharyngitis</td>
<td>48</td>
</tr>
<tr>
<td>Infective hepatitis</td>
<td>15</td>
</tr>
</tbody>
</table>

These figures have been submitted to mathematical treatment and the probabilities for the chance coincidence of these diseases with malaria have been calculated and are shown in brackets in Table above.

If, instead of taking the figures for the whole year, we take these for the quarter December 1949 to February 1950, we get the following results:

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysentery and diarrhoea</td>
<td>31 (5)</td>
</tr>
<tr>
<td>Tonsillitis and pharyngitis</td>
<td>8 (1)</td>
</tr>
<tr>
<td>Infective hepatitis</td>
<td>3 (1)</td>
</tr>
</tbody>
</table>

The calculated figures for the chance coincidence of these diseases with malaria are shown in brackets. It is concluded that these diseases have a true causal effect in precipitating overt attacks of malaria.

When we combine the two subdivisions shown in first and second Tables we get the following results:

<table>
<thead>
<tr>
<th>Prophylactic History</th>
<th>Satisfactory</th>
<th>Unsatisfactory</th>
<th>Unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysentery and diarrhoea</td>
<td>26</td>
<td>3</td>
<td>7</td>
<td>36</td>
</tr>
<tr>
<td>Tonsillitis and pharyngitis</td>
<td>7</td>
<td></td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Infective hepatitis</td>
<td>5</td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Sundry</td>
<td>8</td>
<td></td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>No precipitating factor</td>
<td>28</td>
<td>24</td>
<td>11</td>
<td>63</td>
</tr>
</tbody>
</table>

| Total                                           | 74           | 27             | 21      | 122   |
From this table, it is clear that there were 28 cases in which the prophylactic history was satisfactory and in which no precipitating factor was present. In other words, 23 per 1,000 of the population at risk developed overt malignant tertian malaria for no apparent reason. Droller's initial finding that overt attacks of malignant tertian malaria may occur in people who are conscientiously taking 100 mg. of proguanil daily is thus confirmed.

Droller's second finding—that parasites may be found in the blood streams of healthy individuals who are conscientiously taking 100 mg. of proguanil daily—has recently been investigated by Captain D. G. Rushton, R.A.M.C., Pathologist at the Military Hospital, Mackinnon Road. With the assistance of Headquarters, Mombasa Area, arrangements were made for 200 British personnel to take 100 mg. of paludrine daily under the supervision of an officer. Their blood was examined for parasites before the start of the experiment and again on the sixteenth days of the experiment. Rushton [8] obtained the following results:

<table>
<thead>
<tr>
<th>Date of collection</th>
<th>Positive slides</th>
<th>Negative slides during previous month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mid December 1949</td>
<td>1</td>
<td>199</td>
</tr>
<tr>
<td>Mid January 1950</td>
<td>5</td>
<td>155</td>
</tr>
<tr>
<td>Mid February 1950</td>
<td>Nil</td>
<td>118</td>
</tr>
</tbody>
</table>

Droller's second finding is thus confirmed. It is interesting to note that in Mid January 1950, Rushton found an incidence of positive films of 32 per 1,000 as this figure is comparable to the incidence of 23 per 1,000 previously found for patients developing overt malaria for no apparent reason.

Droller's third finding—that parasites may be found in the blood streams of patients admitted for other diseases—has also been confirmed. During the period September 1949 to August 1950 malarial parasites were found in the blood streams of 25 patients who were admitted to hospital for other reasons and in whom the entire absence of symptoms suggestive of malaria precluded a subsidiary diagnosis of this disease being made.

No attempt was made to confirm Droller's fourth finding—that relapses occurred when patients were treated with proguanil alone—as this had already been confirmed by Covell et al.

The two standard courses of treatment used were as follows:

**Course “A”**: Mepacrine alone.
- Total 4.2 grammes.
- 4 tablets t.d.s. on day 1
- 3 tablets t.d.s. on day 2
- 2 tablets t.d.s. on days 3–4
- 1 tablet t.d.s. on days 5–7

**Course “B”**: Mepacrine and Proguanil.
- Mepacrine 0.9 gramme on day 1; Proguanil 0.6 gramme daily for 10 days.

53 cases received Course A and 59 cases received Course B.
Of the remaining 10 cases, 7 received intravenous quinine or intramuscular mepacrine in addition to one of the standard courses, and 3 cases, having failed to respond to Course B, were treated successfully with Course A.

It was impossible during the period September 1949 to August 1950 to obtain any objective data about the relative efficacy of the two standard therapeutic courses. It was originally intended to use length of stay in hospital as a means of contrasting the two standard courses. But so many extraneous factors were found to affect length of stay in hospital that it was abandoned as a thoroughly unsatisfactory measurement. The rate at which parasites were cleared from the blood stream was considered as a possible measurement, but this was not implemented owing to the additional burden that it would have placed on an understaffed laboratory. Reliance had, therefore, to be placed on the patient’s statements about their symptomatology and on the clinical impressions of the medical officers. These impressions confirmed the views expressed by other workers; that mepacrine leads to the abatement of fever and other symptoms in 48 to 60 hours, while proguanil takes 72 to 96 hours to produce the same result.

As far as the therapeutic use of proguanil is concerned our results are in conformity with those of other workers in many parts of the world, and discussion of them is unnecessary. But with regard to the prophylactic use of proguanil, our results apparently disagree with the experimental evidence produced by workers on this subject. It is therefore useful to consider the possible explanations.

The most obvious explanation is that the 74 people, whom we regarded as having satisfactory prophylactic histories, had not, in fact, been taking proguanil regularly. According to Fairley, 100 mg. of proguanil taken 39 to 131 hours after being bitten will afford complete protection. This means that one must omit to take proguanil for four successive days before the erythrocytic cycle can be established. But once this cycle has been established it may well remain suppressed for many weeks by the schizonticidal action of the daily 100 mg. of proguanil although this dose is inadequate to produce radical cure. This explanation fits well the 46 cases in which the prophylactic history was satisfactory and overt malaria appeared to be precipitated by other diseases. It fits less well the 28 cases with satisfactory prophylactic histories in which overt malaria developed in the absence of any precipitating factor. It also serves to explain Rushton’s findings. Against this explanation it may be said that 78 people is a large number to brand either as deliberate deceivers or as having such poor memories that they were unable to recall the omission to take proguanil for four successive days.

If this first explanation is not excepted, one may postulate that in Mackinnon Road there is a mixture of strains of Plasmodium falciparum and that these 78 cases were infected by a strain in which the pre-erythrocytic stage was resistant to proguanil. Against this explanation, it should be pointed out that in only 3 cases were we unsuccessful when using proguanil in thera-
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Therapeutic doses. Had a resistant strain been present, one would have expected to find a steady increase in the number of cases developing malaria and a similar increase in the number unsuccessfully treated with therapeutic doses of proguanil. This was not so.

A third explanation remains. The experimental evidence is based on experiments involving a relatively small number of people. Our data are based on a population of 1,200 which is probably greater than the total number of people involved in all the experiments added together. It is, therefore, reasonable to suggest that our results reveal a natural variation in individuals to proguanil and to postulate that in the 78 cases with satisfactory prophylactic histories there was some inborn variation either in the absorption or the metabolism of proguanil which prevented the drug exerting its effect upon the pre-erythrocytic forms of *Plasmodium falciparum*. Against this explanation, it can be argued that people with such an inborn variation should tend to have repeated attacks. And this in fact they did not do.

Our results are equivocal: they can be explained in at least three different ways and arguments can be adduced both for and against each explanation. Our object in publishing these results is to bring the problem to the notice of as many medical officers as possible, because we believe that the solution of the problem may well lie in the hands of an enthusiastic Regimental Medical Officer.

To solve the problem the following data are required:

(a) Evidence that at the start of a period of observation the personnel involved are free from infection with malarial parasites. The most satisfactory method of providing this evidence is to give the personnel involved a therapeutic course of either mepancrine or chloroquine during the first week of any experimental period.

(b) Evidence that the personnel involved are actually ingesting their proguanil. This can only be satisfactorily obtained if the investigator personally supervises the taking of the proguanil.

(c) Evidence that the personnel involved are absorbing proguanil. This can be obtained from analysis of either blood samples or urine samples.

(d) In the event of any of the personnel developing overt malaria, evidence that the strain of *Plasmodium* is or is not susceptible to proguanil. This can only be obtained by isolating the strain and then inoculating it into non-immunes.

These data can be gathered in two ways: One may take, as Rushton did, a large group of men and observe them over a given period. Or one may take every man, in a given unit, who develops malaria and observe them over a given period after their blood stream has been sterilized by a therapeutic antimalarial course. Whichever method is adopted, the ideal person to carry out the investigation is the Regimental Medical Officer. The laboratory investigations required could easily be performed for him by the nearest
I, R. M. Johnstone, pathologist. It is in the hope that some suitably placed Regimental Medical Officer may be inspired to carry out such an investigation that we have submitted our results for publication.

SUMMARY

(1) 122 cases of malignant tertian malaria occurred at Mackinnon Road during the year September 1949 to August 1950 in a population of 1,200 supposedly taking prophylactic proguanil.

(2) In 74 cases the prophylactic history was satisfactory; in 27 cases it was unsatisfactory; and in 21 cases it was unknown.

(3) In 59 cases precipitating factors were present; in 63 cases no precipitating factors were present.

(4) In 28 cases, the prophylactic history was satisfactory and no precipitating factors were present.

(5) 200 healthy soldiers took prophylactic proguanil under supervision for 60 days. On the 30th day, malarial parasites were present in the blood stream of 5 of these soldiers.

(6) Three possible explanations of these results are advanced and the arguments for and against each explanation are discussed.

(7) An outline plan is suggested for a further attack upon this problem.

I am greatly indebted to Captain D. G. Rushton, R.A.M.C., for his generous permission to make full use of the results of his investigation.

I am also greatly indebted to Lieutenant-Colonel J. L. Gordon, O.B.E., R.A.M.C., A.D.A.H., Headquarters, East Africa Command, for his stimulating suggestions and criticisms and for his kindness in subjecting the results to statistical analysis.

I have been privileged to discuss these results with Sir Neil Hamilton Fairley, K.B.E., M.D., D.Sc., F.R.C.P., F.R.S., and Dr. D. G. Davey, O.B.E., and I wish to thank them for their clarification of many of the points involved.

REFERENCES


