Plasma Paludrine Levels – Some Observations in Commonwealth Troops in The Far East 1970

Brig D E Worsley,
OHP, FFCM, FFOM, L/RAMC

Consultant Adviser in Community and Occupational Medicine

SUMMARY: Some information on plasma Paludrine levels in troops on various dose-regimes and conditions of activity is recorded. Some observations on Paludrine dose-regimes are made. The use of Paludrine in the Army is very briefly reviewed and a preliminary report on recent experience included.

Introduction

In 1969 AMD Research Project 149 was initiated to study the incidence of chloroquine-resistant falciparum malaria in Commonwealth troops operating in the Far East. The findings were reported by McKelvey et al¹ in 1971. In association with this work an investigation into the levels of Paludrine (proguanil hydrochloride ICI) in the plasma of troops on various dose regimes was undertaken. The results of this study have never been published and this belated report has been stimulated by two facts:

- the Army continues to use Paludrine as its standard chemoprophylactic, and
- there has been a resurgence of interest in this drug^{2,3,4}

The Army adopted Paludrine, first synthesised in November 1944, as a prophylactic, and, alone or in combination, therapeutic drug in 1946/7 following the studies of Maegraith⁵ and Fairley⁶. It replaced Mepacrine in these roles. It was more effective, safer, being almost free from side-effects, and was potentially cheaper.

Within four years there were reports in this Journal⁷ and elsewhere of failures in prophylaxis. By 1956 the Army standard dose of 100mg/day had been doubled for personnel serving in West Africa in view of the apparent ineffectiveness of the lower dose in this area. Paludrine became increasingly unpopular in the world at large due to the reported incidence of drug-resistance and drugs such as chloroquine, with its alleged advantages of weekly dosage, were adopted by many. The Army continued to employ Paludrine as a prophylactic wishing to use different drugs for prophylaxis and therapy and in view of the importance of using a safe drug in mass-medication. Regular reviews of the situation were instituted.

The history of chloroquine is well-known and it was to characterise chloroquine resistance in falciparum malaria according to the WHO protocol⁸ that AMD Research Project 149 was undertaken. In addition as all personnel were under orders to take 100mg of Paludrine

a day it was a logical step to study the levels of this drug actually present in the plasma under a variety of conditions, to some extent repeating the work of Maegraith et al⁹

Aims

The study set out to measure the plasma Paludrine levels in two groups of Servicemen:

- a group taking various dose regimes under strict supervision, (Phase I)
- a sample of the troops participating in a large field exercise (Bersatu Padu) who were instructed to take 200mg/day under unit arrangements (Phase II). This exercise was held on the east coast of West Malaysia.

In this way the levels would be characterised under optimum and realistic field conditions.

It was also anticipated that some of the Phase I subjects might subsequently develop malaria at a time which would permit some estimate of the minimum plasma levels providing protection against the *Plasmodium* species to which they were exposed.

Methods

Assay was performed by the Central Pathology Laboratory Far East Land Forces (FALELF) Singapore, using the method of Spinks and Tottey¹⁰, for which 10ml of plasma are required, and was supported by a grant from ICI. The technique is considered accurate to $\pm 5\mu\text{g/l}$ at plasma levels in excess of $10\mu\text{g/l}$. To obtain repeated blood samples in excess of 20ml called for a degree of dedication on the part of the subjects, but with one small exception, entire subunits as desired to minimise selection bias, volunteered to a man. In the Phase I study blood was taken at standard intervals, often every 24hr immediately before the next dose of Paludrine was due. The Phase II exercise activities made access to the volunteers difficult, but samples were obtained within an acceptable time frame. The blood was centrifuged as soon as possible and plasma samples stored in a freezer if necessary before assay. During Phase II a hand centrifuge was used and

plasma stored in the ice-box of a domestic refrigerator until it could be flown to Singapore. There were other demands on the refrigerator.

Basic data on each subject, age weight, medical history and length of time in the theatre was recorded before sampling commenced. At the time of bleeding the subject was interrogated regarding his activity levels, any gastro-intestinal disturbance, fluid and alcohol intake and any other noteworthy event during the previous 24hr. Phase II subjects were asked when they had last taken Paludrine.

Results

253 volunteers participated in Phase I, including Australian, British, Gurkha, Malay, New Zealand and Singaporean troops. Phase II involved approx 100 British Army and Royal Marine personnel.

Phase I

A number of dose regimes were studied in Phase 1 but only the most relevant and interesting are considered here:

a. Individual day-to-day variation.

22 men taking 100mg under supervision at the same time each day were bled on four successive days immediately before the next dose was due, at the time of the lowest plasma level within the 24hr period. This may be considered the plateau level⁹. Fig 1 demonstrates the wide individual variation which could not be correlated with activity, medical history or fluid intake, and the relation to body weight is barely detectable.

b. Regular 100mg/day build-up and decay.

A total of 47 men, none of whom had taken any chemoprophylaxis for at least a fortnight, commenced a supervised dose of 100mg at the same time each morning, continued for a minimum of seven days and then ceased. Blood was taken before each daily dose and on four days after administration stopped. Fig 2 shows

Fig 1

the build-up to the plateau of $80\mu\text{g/l}$ (sd 14), which was reached at the end of the second day. The decay when the drug was withdrawn is rapid, the level falling to about $40\mu\text{g/l}$ some 48hr after the last dose.

c. Regular 200mg/day.

A similar study to the above at twice the dose. The plateau level was $130\mu\text{g/l}$ (sd 20) in a group of 41 men. The build-up and decay rates are in Fig 3.

d. Regular 100mg twice a day.

23 men on a regular dose of 100mg at 0800 and 1600 1 hr each day were bled daily immediately before the

morning tablet, at 16hr after their last tablet. The plateau in this group was $156\mu\text{g/l}$ (sd 23). Build-up and decay was not studied in this population but in 25 Gurkhas on a identical regime their decay rate is illustrated in Fig 4. It is noteworthy that in this latter

Fig 4

Phase II Activity Levels

Fig 5

group the plateau at $134\mu\text{g/l}$ (sd 14) was at a lower level than in the former, Australian group.

Phase II

Conditions were less than ideal but the results from 352 blood samples drawn from almost 100 men who were under orders to take 100mg twice a day are summarised in Fig 5, which relates the levels measured to the stated number of hours since the previous tablet was taken. An attempt was made to divide the population into high and low activity groups. It is immediately apparent that throughout the plasma levels are lower than those which could be anticipated from the Phase I results. This is discussed below.

None of the troops studied in Phase II developed malaria, although an adjacent unit, which had been excluded from the study partly because of its reputation for excellent anti-malaria discipline, suffered a very high incidence.

Discussion

The salient facts which emerge from Phase I are reasonably self-evident. In the dose-regimes studied it is unlikely that men commencing administration will achieve peak plasma levels until the third day although the plateau as defined will be reached on the second day. It seems pharmacological sense to start Paludrine dosage three days before exposure, although on the grounds of establishing a regular habit there is much to be said for an earlier start, say one week.

A regime of two 100mg tablets once a day provides an increase in the plateau level from the $80\mu\text{g/l}$ achieved with a single tablet daily to some $130\mu\text{g/l}$, while on 100mg twice a day a higher plateau of almost $160\mu\text{g/l}$ is reached. Peak plasma levels were not investigated in this study but are thought likely to follow a similar pattern. These findings provide support for employing a 200mg/day regime in divided doses, certainly if it is the plateau level which is more significant than the peak. However, one is so close to limit of effectiveness that the difference between 130 and $160\mu\text{g/l}$ is critical, with a drug as safe as Paludrine there is a case for increasing the total daily dosage to 300mg.

The decay rates on the regimes studied are included for interest in the absence of any data on the minimum effective level in the strains to which the troops were exposed. The half-life appears to be about 48hr.

The levels found in Phase II are lower than anticipated. That this was due to the rigours of heavy physical work and associated sweating is not supported when the two activity groups are compared, nor is it believed that existing on field rations has some peculiar effect on pharmacology. That the conditions of storage and transport of the specimens was less than ideal cannot be denied and this may account for the differences. However the more experienced and cynical observer will find favour with the suggestion that there was a degree of poor Paludrine discipline in at least some of the troops on Bersatu Padu. The dramatic and totally unphysiological increase in plasma Paludrine levels found in the low activity group at 14 and 15hrs since stated last dose (Fig 5) may perhaps be explained by the guilty swallowing the odd tablet when the investigator transport hove in sight. These results based on the subjects recollection of when he last took a tablet, and the apparent anomalies revealed may well highlight the difficulties which arise on active service or on exercises when routine is disrupted, meals irregular and ideas of the day of the week blurred. The only fixed points, and even these may be missed, are dawn and dusk. This provides good justification for a daily or twice-daily prophylactic.

No reference has been made to other anti-malaria precautions available to troops in the field as the aims of the study were limited by the resources which could be deployed.

It has already been recorded that the British Army has continued to use Paludrine since its adoption in 1946/7, and that as a result of experience the daily dose for West Africa was doubled to 200mg/day in 1956. This increase in dosage was made world-wide in 1982. During almost 40 years the drug has served well, and has never produced side-effects of more than a trivial nature. Cases of malaria have occurred but it is fair to state that in many these were due to a failure to observe other anti-malaria precautions associated with poor compliance with the chemoprophylactic regime, perhaps most typically during the post-exposure period which is often spent on leave.

There has been much pressure to change to alternative drugs such as chloroquine, Maloprim or Fansidar, and the situation has been kept under constant review, leading to the adoption of the standard 200mg/day dose mentioned above. While the Army has far fewer permanent bases in malarious areas than in the past, (Belize and the New Territories of Hong Kong are the only two remaining), our troops do exercise in many parts of the world. Kenya is one of these and during the last four years some thousands of men have spent 4-6 weeks at a time training in different parts of that country from the highlands to the coastal strip. Their malaria experience initially on 100mg/day Paludrine and more recently 200mg/day has been monitored, including assays of plasma and urine.

Between Jan 1983 and Nov 1984 of some 2500 troops exercising four developed malaria, (3 proven falciparum and 1 clinical falciparum). In two of these there was convincing evidence of failure of compliance with chemoprophylactic discipline. In Jan 1985 a unit of about 600 men suffered 18 cases (10 falciparum, 3 vivax, 1 mixed and 4 clinical) to be followed in May by a unit of 700 who produced 23 cases (20 falciparum, 1 mixed and 2 clinical)¹¹. The reasons for this untoward incidence remain to be established and forthcoming exercises will be even more closely monitored.

It is recognised that it may be necessary for us to modify our chemoprophylactic regime by adding a drug of a different type to our standard Paludrine for certain parts of the world; Kenya may be one of these.

Whichever drug or drugs are selected it is to be hoped that they at least approach Paludrine in their margin of safety, and that the hazards of chemoprophylaxis are infinitely less than the potential hazards of the disease.

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