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WHO/Ma1/291 ✓
23 May 1961

ORIGINAL: ENGLISH

THE CONCURRENT WEEKLY ADMINISTRATION OF CHLOROQUINE AND
PRIMAQUINE FOR THE PREVENTION OF KOREAN VIVAX MALARIA¹

A PRELIMINARY REPORT OF A FIELD TRIAL
CONDUCTED BY THE EIGHTH UNITED STATES ARMY

by

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¹ From the Eighth United States Army in Korea. These investigations are supported by the US Army Medical Research and Development Command, Office of The Surgeon General, Department of the Army.

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INTRODUCTION

The standard method used by the United States Armed Forces for the chemoprophylaxis of malaria is as follows. While in a malarious area 300 mg chloroquine base is administered once a week. Upon leaving the malarious area 600 mg chloroquine base plus 15 mg primaquine base is administered on the first day of departure followed by 15 mg primaquine for the next 13 days. This regimen has been highly successful in the prevention of malaria (Archambeault, 1954, and Health of the Army Reports). However, a better method of malaria chemoprophylaxis is desirable because the present method requires the strict control of all individuals for a period of two weeks after leaving the area of exposure to insure adherence to schedule. This is particularly difficult administratively when persons are transported by air or return home by sea if the voyage is less than 14 days.

Numerous investigators have reported on the haemolytic effect of primaquine associated with a glucose-6-phosphate dehydrogenase deficiency of the erythrocytes (review by Carson, 1960). The administration of 15 mg primaquine base daily has not resulted in any significant haemolysis among primaquine sensitive American Negroes (Archambeault, 1954; Alving, et al., 1960). However, the possibility that daily doses greater than 15 mg primaquine base are required to cure radical infections with certain strains of vivax malaria, and the finding that primaquine sensitive Caucasians have a more severe enzymatic deficiency in their erythrocytes and are more susceptible to haemolysis than the American Negroes (Marks et al., 1959; Ramot et al., 1959a; Ramot et al., 1959b) emphasize the need for a method of malaria chemoprophylaxis better than that presently used by the US Armed Forces.

Alving and co-workers (1960) have studied the toxicity and therapeutic time-dosage curve of primaquine [6-methoxy-(8-(4-amino-1-methylbutylamino) quinoline)] administered once a week with chloroquine. On the basis of carefully controlled preliminary clinical trials, they reported that the weekly administration of 300 mg chloroquine base and 45 mg primaquine base proved highly effective as a prophylactic against severe P. vivax infections with the Chesson strain and did not produce clinical haemolysis even among primaquine sensitive American Negro adult volunteers. This method resulted in markedly diminished toxicity and more effective prophylaxis of P. vivax malaria (Chesson strain) infections than with the US Armed Forces standard method.

Early in 1960, the Surgeon General, Department of the Army, requested the medical personnel of the Eighth United States Army in Korea to conduct a large-scale field trial of combined chloroquine-primaquine in weekly doses throughout the year to obtain answers to these questions:

1. Is such a programme administratively feasible in the US Army?
2. Will any toxicity be observed in such a large group under field conditions?
3. Will any malaria occur in returnees who have been subject to this regimen?

This is a preliminary report concerned with the first two questions and based on observations over the first 22 weeks of the field trial.

MATERIALS AND METHODS

In mid-September 1960, the Eighth United States Army directed that over 50 000 adult US military and civilian personnel in Korea, among whom there was a considerable percentage of American Negroes, take one tablet¹ containing chloroquine phosphate (300 mg base) and primaquine phosphate (45 mg base) each Monday throughout the year at the noon meal beginning the programme during the first week of October 1960. Orders were issued that any toxic reactions were to be reported to the Preventive Medicine Officer along with the following information:

1. Name, rank, serial number and organization of the individual.
2. Ethnic background of the individual.
3. Haemoglobin or haematocrit data of the individual.
4. Number of weeks during which medication had been taken and whether intentional overdose of drugs had been employed.

¹ The tablets were manufactured by Winthrop Laboratories and purchased and made available to Eighth United States Army by the US Army Medical and Development Command, Washington 25, DC, United States of America

5. Presence of any disease.
6. Additional information considered relevant.

The 14-day primaquine treatment upon departure from Korea was terminated four weeks after the field trial began, i.e., on 1 November 1960.

In view of the sensitivity to primaquine which has been reported among Caucasians of the Mediterranean area by several investigators (Marks et al., 1959; Ramot et al., 1959a; Ramot et al., 1959b) on 5 December 1960, a special study was initiated among 250 Turkish troops of the United Nations Command. On the day this study began and once weekly thereafter, each man ingested one tablet of the combined drugs.

Since 139 of these men were stationed in one small area, it was possible to study these men in some detail. They took the first dose of combined drugs at 9 a.m. on 5 December 1960. Between 2 and 3 p.m. on the same day, a voided specimen of urine was obtained from each man and 5 ml of venous blood was obtained from each third man (44 altogether). The syringes were coated with mineral oil and rinsed with heparin immediately prior to use. On 10 December, five days after the ingestion of the tablet, between 11 a.m. and 2 p.m., a voided specimen of urine was again collected from 130 of the same group of 139 men and 5 ml of venous blood collected as before from the first 94 of the men.

The samples of urine collected on both days were tested for haemoglobin using benzidine. Haematocrit and plasma haemoglobin determinations (modified benzidine method of Crosby et al., 1956) were done on the blood samples collected on 5 December 1960. Haematocrit and plasma haemoglobin determinations were again done on the blood samples collected on 10 December 1960 and a Heinz body in vitro incubation test with acetylphenylhydrazine (Beutler et al., 1955) was carried out.

In April 1961 a study was performed on 104 men from this same Turkish unit in Korea. Fifteen ml of venous blood was collected in acid-citrate-dextrose solution. The blood was immediately placed in a thermos with wet ice and within 24 hours a methemoglobin reduction test by the spectrophotometric method (Brewer et al., 1960) was performed on each sample. Then the blood was transported on ice to the 406th Medical General Laboratory in Japan, where the cresyl violet dye reduction test (Motulsky et al., 1959) and a specific assay for glucose-6-phosphate dehydrogenase, based on the method of Glock & McLean (1953) were performed on each sample.

RESULTS

United States Forces

During the 22 weeks covered by this report the programme has been shown to be administratively feasible. No commander raised any objections to the continued administration of the tablets in Korea after the termination of the malaria transmission season.

No instance of haemolytic reaction has been observed among the over 50 000 adult United States personnel including a considerable number of American Negroes. An occasional individual has experienced intestinal cramps and one or two loose bowel movements several hours after the ingestion of a tablet. However, the incidence of these complaints has been no higher than it was with the previous programme consisting of 300 mg chloroquine base weekly.

Turkish Forces

The results of the special study involving the Turkish troops are especially significant:

1. All 139 samples of urine collected between five and six hours after the initial ingestion of the combined chloroquine-primaquine tablets and all urine samples collected five days later were negative for haemoglobin by the benzidine test.
2. The 44 blood samples collected between five and six hours after the initial ingestion of the drugs and the 94 samples collected five days later had haematocrit findings of 45 or above and plasma haemoglobin determinations were negative. Thus, no drug induced haemolysis was observed among the Turkish subjects.
3. Of the 94 blood samples collected on 10 December 1960, thirteen (14%) had positive Heinz body tests. Of the 104 bloods collected in April 1961, only one was positive for enzyme deficiency. The three tests performed on each sample (the methemoglobin reduction test, the cresyl violet dye reduction test, and the enzymatic assay for glucose-6-phosphate dehydrogenase) were in agreement on all 104 samples.
4. The one G-6-P-D enzyme deficient man had no detectable erythrocyte glucose-6-phosphate dehydrogenase activity by the Glock & McLean method.
5. After 14 weekly doses of the combined drugs, no clinical toxic reactions were observed among the 250 Turkish soldiers in the United Nations Command in Korea, including the one man known to be totally deficient in the enzyme. After four and one-half months of weekly drug administration, this man had a normal haemogram.

DISCUSSION AND CONCLUSIONS

Results of previous studies indicated that combined chloroquine and primaquine given in eight weekly doses was effective in producing radical cure in volunteers infected with the Chesson strain of Southwest Pacific P. vivax malaria and that the amount of primaquine given weekly, in doses as high as 60 mg base, proved less haemolytic than 15 mg given once daily for 14 days.

A large-scale field trial, in which over 50 000 adult and civilian personnel of the Eighth United States Army in Korea participated, was initiated in early October 1960. All personnel took weekly one tablet which contained 300 mg chloroquine base and 45 mg primaquine base.

Experience through the first 22 weeks of this trial has shown that this programme is safe and administratively feasible. No greater toxic reactions have been encountered among these personnel than previously observed with chloroquine alone.

The incidence of primaquine-sensitivity in the Turkish soldiers was initially thought to be approximately 14 per cent. based on the Heinz body tests performed 10 December 1960. However, in April 1961 it was demonstrated that the incidence of this trait in the Turkish troops was relatively low, probably around one per cent. This discrepancy cannot be ascribed to sampling differences and is undoubtedly due to false positive results with the Heinz body test. This may be due to the thalassaemic trait, which occurs frequently in Mediterranean peoples and is known to be associated with Heinz body formation (Sansone et al., 1958), or to other factors, such as the administration of primaquine five days previously. Because of its lack of specificity it is probably best to avoid using the Heinz body test for diagnosing primaquine-sensitivity, since more reliable methods, just as easily performed, are available.

The clinical experience through the first 14 weeks of this trial among the 250 Turkish soldiers in the United Nations Command in Korea, has shown that the described drug administration programme is safe in this group. The one known primaquine-sensitive individual has taken 45 mg primaquine base and 300 mg chloroquine base weekly throughout this time with no apparent ill-effects.

REFERENCES

- Alving, A. S., Johnson, C. F., Tarlov, A. R., Brewer, G. J., Kellermeyer, R. W. & Carson, P.E. (1960) Bull. Wld Hlth Org. 22, 621
- Archambeault, C. P. (1954) J. Amer. med. Ass. 154, 1411
- Beutler, E., Dern, R. J. & Alving, A. S. (1955) J. Lab. clin. Med. 45, 40
- Brewer, G. J., Tarlov, A. R. & Alving, A. S. (1960) Bull. Wld Hlth Org. 22, 633
- Carson, P. E. (1960) Fed. Proc. 19, 995
- Crosby, W. H. & Furth, F. W. (1956) Blood 11, 380
- Glock, G. E. & McLean, P. (1953) Biochem. J. 55, 400
- Health of the Army Reports, Monthly Reports, Office of the Surgeon General, Department of the Army, 1952-1960
- Marks, P. A. & Gross, R. T. (1959) J. clin. Invest. 38, 2253
- Motulsky, A., Kraut, J., Thieme, W. & Musto, D. (1959) Clin. Res. Proc. 7, 89
- Ramot, B., Fisher, S., Szeinberg, A., Adam, A., Sheba, C. & Gafni, D., (1959a) J. clin. Invest. 38, 2234
- Ramot, B., Szeinberg, A., Adam, A., Sheba, C. & Gafni, D. (1959b) J. clin. Invest. 38, 1659
- Sansone, G., Borrone, C. E. & Rovei, S. (1958) Boll. Soc. ital. Biol. sper. 34, 22