The effect of drug packaging on patients' compliance with treatment for *Plasmodium vivax* malaria in China

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A study conducted in 1994 showed that the use of blister packs containing antimalarial drugs significantly increased patients' compliance, compared with traditional means of dispensing drugs in a paper envelope. The present study assessed patients' compliance and compared the difference between 3-day chloroquine and 8-day primaquine courses of treatment for vivax malaria. The level of real compliance was determined by marking the drugs with phenobarbital, and measuring its level in the blood following treatment. The results show that blister packaging significantly improved patients' compliance ($P < 0.001$) over traditional means of dispensing antimalarial drugs; there was no difference in treatment compliance between 3-day and 8-day courses when the drugs were in blister packs. However, with ordinary packaging the treatment compliance rate for an 8-day course was significantly less than for a 3-day course ($P < 0.05$).

Introduction

Hunan Province in south-central China comprises 14 prefectures and 125 counties with a population of 64 million. Since the start of the malaria control programme in this province in the 1950s, there have been three *Plasmodium vivax* malaria outbreaks with annual incidences of 1560 per 100000 in 1955, 1690 per 100000 in 1962, and 1323 per 100000 in 1971. Despite a comprehensive malaria control programme, the incidence since 1986 has risen and, for counties in the south and south-west of the province, is five times higher than the provincial average.

Chloroquine and primaquine are produced in China for the treatment of *P. vivax* malaria, and are generally dispensed by health workers from 1000-tablet bottles or tins. The current treatment regimen for adults is 4 chloroquine tablets (each containing 0.25 mg chloroquine phosphate) on day 1, 3 tablets on days 2 and 3, and 3 tablets of 13.2 mg primaquine daily from day 1 to 8. The curative dosage of each drug is dispensed by a health worker or pharmacist from the container in a paper envelope or small paper bag, and given to the patient without any identification of the drugs or written directions on their use. The doctor's or health worker's oral instructions to the patient on the number of tablets to be taken and for how many days are brief and do not include any advice or health education. Treatment is often incomplete due to its discontinuation once the symptoms have disappeared, or to disintegration or loss of the tablets. Sometimes patients take an excessive dose so as not to risk loss of the drug, and can experience unpleasant side-effects.

Over 20 years ago, compliance was assured by delivering drugs on a daily basis to patients with direct observation of therapy. While clearly effective, this was unsustainable owing to the need for large numbers of health workers. To improve compliance and use of antimalarial drugs, a pilot intervention study was undertaken to determine the effects of new packaging of drugs and written instructions on compliance.

The specific objectives of the study were as follows:

— To compare the compliance of patients in completing a full course of antimalarial treatment; a control group received medication in paper envelopes and a second group were given the improved packaging with simple, written instructions on their use.

— To determine the possible reasons for non-compliance in both groups and whether they were related to the type of packaging and instructions on use.

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— To evaluate the impact of the new packaging and of providing simple, written instructions with the medication.

— To determine the difference between reported compliance (Phase-I study, based on only patients' reports) and true compliance (Phase-II study, including use of a pharmacological marker inserted with each antimalarial tablet).

Materials and methods

Blister packs. The tablets of chloroquine and primaquine for the study were provided in two packs, one for chloroquine (with daily doses separated for three consecutive days) and the second for primaquine (with daily doses of 3 tablets for a total of 8 days). The number 8, according to Chinese beliefs, brings good luck and it was considered that a course of primaquine over 8 days would enhance compliance more than one for 14 days. Detailed oral instructions were given to the patients on the correct dosage and the need to complete the treatment.

The new blister pack was hermetically sealed, separately for each day's supply of tablets, with the name of the drug on the back of the pack. The blister packs were inserted into boxes, with the drug name on the front and dosage directions and precautions on the back; clear instructions were given on a leaflet inside the box. Each pack measured 8 × 5.5 cm and contained 10 tablets of chloroquine for use over 3 days, or 24 tablets of primaquine for 8 days.

Study sites. For the phase I study, which was conducted during the malaria season in 1994, the Health and Epidemic Prevention Stations in five counties of Hunan Province were selected as the study site. In phase II, the Health and Epidemic Prevention Stations in seven counties implemented the study in the malaria season from July till October 1996. The choice of epidemic station in the counties was made so that a sufficient number of patients could be enrolled in the study period, which would ensure that the study was carried out as designed. The qualifications of the staff at these stations were high, and each station had a good working relationship with the provincial authorities.

During the study period, millions of people from Hunan Province migrated to Guangdong and Hainan Provinces where a high level of economic development was taking place. Most workers were engaged in mining and road and house constructions in areas of high malaria endemicity. Malaria is common among the migrant nonimmune populations and when these persons return to their homes in Hunan, the disease is introduced, causing epidemics of imported malaria.

Patients. The patients in the study were consenting adults (aged >15 years) with confirmed, slide-positive vivax malaria; they were ambulatory, had no major clinical symptoms requiring hospitalization, and had not received any malaria treatment during the previous 6 months. On selection at one of the clinic sites, a patient was randomly assigned either to the new drug packaging group or to the control group prior to receiving medication. Upon entry to the study, basic data were recorded on each patient, including age, sex, occupation, suspected onset of infection, clinical symptoms, laboratory test results, and date and time of treatment. When the drug regimen was completed in phase I and phase II, information was solicited on when the first and last doses of the drug were taken, the total number of tablets taken, and on compliance and non-compliance.

Phase I. As mentioned above, this phase was carried out in five counties of Hunan Province. Patients in the control group were prescribed medication with oral instructions on their use; the antimalarial tablets (chloroquine and primaquine) were put into a paper envelope and given to the patients. Patients in the intervention group were prescribed medication with identical oral instructions; the antimalarial tablets were given in two separate blister packs, marked with appropriate daily dosages and containing detailed written instructions. The advice given by the doctor to both the control and the intervention groups was the same regarding malaria and treatment. However, each patient in the intervention group was asked to open the blister pack and read the instructions for treatment found inside. When they had finished reading the instructions, they were asked if they understood what they had just read. Patients in the control group were asked if they had understood the doctor's oral instructions. If the patient indicated a poor understanding, the instructions for treatment were repeated for both groups.

The sample size was determined using an expectation of 15% noncompliance in the control group and an expected 10% improvement in compliance (or 15% noncompliance) in the intervention group. With a desired confidence level of 95%, a power of 80%, and a ratio of 1:1 in the control and intervention groups, the sample size was determined to be 318 persons — 159 in the control group and 159 in the intervention group. The choice of 15% noncompliance and an expected improvement in a compliance of 10% was conservative as was also the sample size.

On day 9 (after the start of treatment), each patient was either visited at home by a doctor in the study team or patients returned to the Epidemic Station for follow-up. All patients were retested for the presence of malaria parasites. In addition, a questionnaire was administered regarding the patient's compliance, whether the medication had been taken according to the doctor's advice, the method of taking the medicine, the duration of treatment, and any causes of an incomplete course of treatment.

Phase II. This was a randomized study, which was carried out in seven counties of Hunan Province. Upon entering any one of the seven clinic sites, a patient was randomly assigned to one of the following treatment groups:

— Intervention group 1: Blister pack with phenobarbital-marked chloroquine plus blister pack with unmarked primaquine.

— Intervention group 2: Blister pack with unmarked chloroquine plus blister pack with phenobarbital-marked primaquine.

— Control group 3: Normal package with phenobarbital-marked chloroquine plus unmarked primaquine.

— Control group 4: Normal package with unmarked chloroquine plus phenobarbital-marked primaquine.

To obtain the marked drugs, chloroquine and primaquine tablets were each reground, marked with phenobarbital, and put into capsules by the Centre for Drug Research, Universiti Sains Malaysia. The capsules of chloroquine were white, as were the chloroquine tablets; the primaquine capsules were dark pink, while the tablets were red. All the phenobarbital was obtained from the same source — the laboratory of the Universiti Sains Malaysia.

The marked capsules and unmarked tablets for the intervention groups were blister packaged, and boxed with instructions on proper drug administration. These same drugs were also available in bulk for administration to the non-blister-pack groups. The marked chloroquine capsule contained the normal daily dose (150 mg chloroquine phosphate + 1 mg phenobarbital). The marked primaquine capsule contained the daily dose (39 mg primaquine phosphate + 2 mg phenobarbital). The unmarked chloroquine was the standard single dose tablet and the normal daily dose of unmarked primaquine was contained in 3 tablets.

Groups 1 and 3 were required to take a total of 10 capsules of marked chloroquine (4 capsules on day 1 followed by 3 capsules on each of days 2 and 3) and 24 tablets total of primaquine over 8 days (3 tablets daily for 8 days). Groups 2 and 4 were required to take 8 capsules of marked primaquine (1 capsule daily for 8 days) and 10 tablets of unmarked chloroquine (4 tablets on day 1 followed by 3 tablets on each of days 2 and 3). Groups 1 and 3 therefore received the same drug formulations, with group 1 receiving the blister pack; groups 2 and 4 received the same drug formulations, with group 2 receiving the blister pack.

Each patient was either visited at home by a doctor in the study team or returned to the county Epidemic Station for follow-up. This was done on the fourth day for the marked chloroquine intervention and control groups (groups 1 and 3), and on the ninth day for the marked primaquine intervention and control groups (groups 2 and 4). Patients were asked whether they had completed the course of treatment, and 4 ml blood was drawn from each patient. The blood was separated by centrifuge, and the plasma was stored in two test tubes at −25 °C. One sample was subsequently sent to the Centre for Drug Research, Universiti Sains Malaysia, Penang, Malaysia, and the other to the Department of Pathological Sciences/Chemical Pathology, School of Medicine, Leeds University, England, for phenobarbital detection. Plasma samples were analysed using the methodology given in the paper "Initial evaluation of low-dose phenobarbital as an indicator of compliance with antimalarial drug treatment" in this Supplement of the *Bulletin* (see p. 67–73).

A subgroup of 57 patients was followed up 1–100 days after the treatment to determine any recrudescence and to assess, through interview, their acceptance and compliance with drugs in the blister packs. They were asked whether they were satisfied with the new packaging or the paper envelopes, whether they had read the printed instructions in the box, and whether they had taken the medicine according to the given instructions.

A total of 320 patients were to be recruited. However, the trial was stopped earlier than planned because an analysis when 272 vivax malaria patients had been recruited into the study in the seven sites revealed that the numbers required to show significance between the two groups had been reached. A total of 138 patients were assigned to the intervention group (62 received blister packs with phenobarbital-marked chloroquine and 76 received blister packs with phenobarbital-marked primaquine); 134 patients were assigned to the control group (70 received paper envelopes with phenobarbital-marked chloroquine and 64 received paper envelopes with phenobarbital-marked primaquine).

Table 1: **Compliance, by county, in the intervention and control groups**

County	Intervention group		Control group	
	No. of cases	No. who complied	No. of cases	No. who complied
Shaoyang	38	33 (87)[a]	39	31 (80)
Dongkou	39	39 (100)	41	35 (85)
Longhui	13	13 (100)	16	15 (94)
Daoxian	39	39 (100)	38	31 (82)
Lanshan	32	32 (100)	29	24 (82)
Total	161	156 (97)	163	136 (83)

[a] Figures in parentheses are percentages.

Table 2: **Reasons given for non-compliance by patients in the intervention and control groups**

Reason	No. in intervention group	No. in control group
Doctor's advice unclear	1	0
Misunderstood the doctor	1	3
Forgot to take medication	1	2
Just stopped taking medication	2	6
Medication was lost	0	8
Medication dissolved/crumbled	0	8
Total	5	27

Statistics. Wilcoxon–Mann–Whitney tests on phenobarbital level-to-dose ratios were performed using the Astute Programme for Microsoft Excel COOLL Software, University of Leeds.

Results

Phase I. The 300 male and 24 female patients for evaluation were aged 16–63 years (mean, 31 years); three-quarters of the group were aged <38 years. Using patients' reports as a measure of compliance, Table 1 shows the extent of compliance in five counties in the control and experimental groups: 97% of patients in the intervention group and 83% in the control group completed the proper treatment regimen. This result is statistically significant $P < 0.01$ using the Kruskal–Wallis one-way analysis of variance for data not normally distributed. If the number of lost or spoilt medication is removed from the analysis, the result is not statistically significant ($P = 0.13$). From data (not presented here) compliance was not related to patient's age, occupation or education, or gastrointestinal distress — defined as nausea, vomiting, abdominal pain or diarrhoea. The reasons for not completing the treatment are given in Table 2.

Following the treatment regimen, patients in both the control and intervention groups were retested for malaria by blood smear. All were negative and asymptomatic. From data (not presented here) for those who reported that they had failed to complete the course, the majority took at least their full dose of chloroquine which would cure their symptoms and parasitaemia. Although the course of primaquine in the non-compliant group was incomplete, all except one took at least 5 days of primaquine which made the chances of relapse remote.

Phase II. A total of 272 vivax malaria patients were enrolled in the study, ranging in age from 11 years to 67 years, the majority being aged 20–40 years; most patients were male. Of these, 138 were assigned to the intervention group (62 received blister packs with marked chloroquine, and 76 received blister packs with marked primaquine); 134 patients were assigned to the control group (70 receiving marked chloroquine and 64 marked primaquine).

The overall treatment compliance for patients who received blister packs (combined chloroquine and primaquine) was 97.1% (134/138). The compli-

Table 3: **Comparison of compliance rates between 3-day (chloroquine) and 8-day (primaquine) treatments**

Treatment	Intervention group (blister pack)		Control group (paper envelope)	
	No. of cases	No. who complied	No. of cases	No. who complied
Marked chloroquine	31	29 (93.5)[a]	35	30 (85.7)
Unmarked chloroquine	38	38 (100)	32	29 (90.6)
3-day compliance	69	67 (97.1)	67	59 (88.1)
Marked primaquine	38	36 (94.7)	32	23 (71.9)
Unmarked primaquine	31	31 (100)	35	26 (74.3)
8-day compliance	69	67 (97.1)	67	49 (73.1)
Treatment compliance	138	134 (97.1)	134	108 (80.5)

[a] Figures in parentheses are percentages.

Table 4: **Phenobarbital LDRs (level-to-dose ratios) in intervention (blister packs) and control (old packaging) groups for chloroquine and primaquine**

	Chloroquine		Primaquine	
	Blister packs (n = 36)	Old packaging (n = 23)	Blister packs (n = 31)	Old packaging (n = 34)
Minimum	1.2	1.99	2.29	3.74
25th percentile	3.26	2.92	5.27	6.52
Median	3.86	3.46	7.25	7.12
75th percentile	4.86	4.8	9.88	9.19
Maximum	18.85	30.9	19.99	30.24
w	375	453	569.5	484.5
U	1119	651	980.5	1164.5
Corrected for ties:				
z	−0.6061	−0.6062	−0.5582	−0.604
P	0.5444	0.5444	0.5767	0.5444

ance for patients whose medication was in paper envelopes (combined chloroquine and primaquine) was 80.5% (108/134). The difference is statistically significant ($P < 0.001$).

A comparison of 3-day and 8-day treatments showed that the blister-pack group had 97.1% (67/69) compliance with 3 days of chloroquine and 97.1% (67/69) compliance with 8 days of primaquine. For the control group, 88.1% (59/67) completed the 3-day treatment, and 73.1% (49/67) completed the 8-day treatment (Table 3). The difference between the two groups for both the 3-day and 8-day regimens is statistically significant ($P < 0.05$).

The rate of noncompliance and reasons given for noncompliance are similar in both studies. The compliance (blister pack vs paper package) in 1994 was 96.9% and 83.4% and in 1996, 97.1% and 80.5%. respectively. The reasons included drugs got lost or dissolved, or the patient simply forgot.

Among 57 patients who received a second follow-up visit 1–100 days after the treatment, 28 were from the blister pack group and 29 from the control group. One patient from the control group had a relapse; he had not completed his treatment and recrudesced 88 days after the initial diagnosis. Of 55 patients who responded, 48 (87.3%) preferred the blister pack because they were more hygienic, convenient to carry, and more difficult to lose. Of 26 patients who had used the new packaging, 22 (88.7%) had read the instructions, 21 (80.8%) understood the instructions, and 14 (53.9%) took the medication exactly according to the instructions.

The overall phenobarbital level-to-dose ratios (LDRs) for the intervention and control groups are given in Table 4. The differences between the two groups are not significant.

Discussion

The cure rate of *P. vivax* malaria with 8 days of chloroquine and primaquine treatment is 99.2% (*1*). This therapy is widely practised in China, and considered safe and effective (*2*). However, because of the

bulk packaging of chloroquine and primaquine, their distribution is inconvenient for both doctors and patients. The result is inefficiency due to misunderstanding the necessity for completing the treatment, and possibly increased recrudescence rates (*3*).

Compliance with antimalarial treatment appears to be affected by the type of packaging and instructions given on dosage and treatment. This observation does not necessarily support the conclusion that the blister pack is the best method of distribution, because poor compliance could be due to poor packaging. Paper has limited properties for protecting water-soluble medication, and 16 out of 27 patients in the control group in phase I were noncompliant as a result of losing the medication or tablet disintegration. None of the patients in the intervention groups were noncompliant for these reasons. Indeed, if lost or disintegrating tablets are discounted because they are beyond the control of the patient, there is no statistical difference in compliance between the two groups although there was a difference between the aggregate number of patients in the intervention and control groups who were compliant. From the patients' perspective, the blister pack was treated with more care, and this may be reflected in a higher compliance rate.

The rate of completing the treatment among blister-pack recipients was significantly higher than the paper package control group. This holds true for both a 3-day and 8-day regimen. As some of the reasons given for noncompliance were related to the poor paper packaging leading to crumbling and loss of medication, the blister pack resolves these deficiencies.

The above results using phenobarbital as a marker of compliance are inconclusive. The LDRs in all groups were considerably higher than expected, possibly because these patients had consumed other medications containing low doses of phenobarbital. Comparison of the chloroquine and primaquine LDRs, excluding patients with the high values, was also not significant, as was a comparison of the control population's LDRs with the levels obtained in the Thai reference study (*4*, see pp. 59–66 in this Supplement). To assess the value of using phenobarbital as a marker of compliance, data from this study should be compared with data from a reference group of good compliers, who would have consumed the phenobarbital under observation.

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Résumé

Effet du conditionnement des médicaments sur l'observance du traitement du paludisme à *Plasmodium vivax* en Chine

Une étude réalisée en 1994 a montré que le conditionnement des antipaludiques sous plaquette thermoformée ("blister") améliore sensiblement l'observance du traitement par rapport à la dispensation traditionnelle dans une enveloppe en papier. La présente étude évalue l'observance du traitement et compare la différence liée au conditionnement entre le traitement de 3 jours et le traitement de 8 jours par la primaquine dans le paludisme à vivax. Le taux effectif d'observance a été déterminé par marquage des médicaments avec du phénobarbital, dont a mesuré le taux sanguin à l'issue du traitement. Les résultats montrent que le conditionnement sous plaquette thermoformée augmente de façon significative l'observance ($p < 0,001$) par rapport aux moyens traditionnels de dispensation; aucune différence d'observance n'a été trouvée entre le traitement de 3 jours et celui de 8 jours lorsque les médicaments étaient présentés sous plaquette thermoformée. Avec la présentation habituelle, le taux d'observance était significativement plus faible pour le traitement de 8 jours que pour celui de 3 jours ($p < 0,05$).

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