Antimalarials prescribing patterns in Gezira State: precepts and practices

M.A. Yousif [1] and A.A. Adeel [2]

أنماط وصف مضادات البرداء (الملاريا) في ولاية الجزيرة: مبادئها وممارساتها

ميرغني عبد الرحمن يوسف وأحمد عوض عديل

خلاصة: أجريت دراسة وبائية دوائية طولانية حول أنماط وصف مضادات البرداء (الملاريا) في راد مدني بولاية الجزيرة في وسط السودان. وتم تحديد مؤشرات وصف مختلف الأدوية الجوهرية، كما تم قياسها وبحث ارتباطاتها. وتبيَّن أن الكلوروكين والكينين كانا أكثر ما يوصف من أدوية البرداء (الملاريا). ولكن جرعاتهما كانت في 44.7% من الحالات غير ملائمة وليست مطابقة للنظم العلاجية المعيارية. ولقد وجدنا أنه نتيجة للتغيرات التي تحدث في أنماط مقاومة الأدوية من دون رصد هذه التغيرات، فإن الغالبية العظمى من الأطباء الممارسين في السودان يميلون إلى تطبيق أنظمتهم الخاصة لمعالجة حالات البرداء (الملاريا) الوخيمة بدلاً من الالتزام بالنظم العلاجية المعيارية. وفي رأينا أن ظهور معدل مرتفع لمقاومة المعالجة الكيميائية للبرداء (الملاريا) إنما مردّه إلى هذه الممارسات. ونوصي بتطبيق تدخلات من شأنها ضمان الوصف الرشيد للأدوية، وندعو إلى صياغة سياسة وطنية فيما يتعلق بالأدوية المضادة للبرداء (الملاريا).

ABSTRACT A longitudinal pharmacoepidemiological study on prescribing patterns of antimalarials was conducted in Gezira State, Sudan. Different core drug prescribing indicators were identified, measured and correlated. Chloroquine and quinine were the most frequently prescribed antimalaria drugs but in 44.7% of cases, the dosage was inappropriate and did not conform to standard regimens. Due to variable and unmonitored patterns of drug resistance, most medical practitioners in Sudan tend to follow their own protocols to treat severe cases of malaria rather than conforming to standard regimens. We attribute the emergence of a high rate of resistance to malaria chemotherapy to such practices. We recommend interventions to ensure rational prescribing, and call for the formulation of a national antimalarial drugs policy.

La prescription des antipaludéens dans l'Etat de Gezira: préceptes et pratiques
RESUME Une étude pharmaco-épidémiologique longitudinale sur le mode de prescription des antipaludéens a été réalisée dans l'Etat de Gezira au Soudan. Plusieurs indicateurs de base pour la prescription de médicaments ont été identifiés, mesurés et mis en corrélation. La chloroquine et la quinine étaient les antipaludéens les plus fréquemment prescrits mais dans 44,7% des cas, la dose était inappropriée et ne se conformait pas aux schémas thérapeutiques standards. Du fait des caractéristiques de pharmacorésistance variables et non surveillées, la majorité des médecins au Soudan ont tendance à suivre leurs propres protocoles pour traiter les cas sévères de paludisme plutôt que de se conformer aux schémas thérapeutiques standards. Nous attribuons l'émergence d'un taux élevé de résistance à la chimiothérapie du paludisme à de telles pratiques. Nous recommandons des interventions pour garantir une prescription rationnelle, et demandons la formulation d'une politique nationale pour les antipaludéens.

[1] *Faculty of Pharmacy, University of Gezira, Wad Medani, Sudan.*
[2] *Blue Nile Research and Training Institute, Wad Medani, Sudan.*
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Introduction

Malaria due to *Plasmodium falciparum* is a major health problem in Sudan. It constitutes 30% of all attendance in health facilities and it is the main cause of hospital death [*1*]. One of the essential elements in control of the disease is appropriate management and chemotherapy to reduce morbidity and to prevent mortality. However, there are several factors that can affect the effectiveness of treatment related to local variables in our country. There are certain prescribing patterns that might have a direct influence on the effectiveness of the control of the disease by chemotherapy. Moreover, these patterns may encourage drug resistance. Because of variable and unmonitored patterns of drug resistance, the vast majority of medical practitioners in Sudan tend to follow their own protocols based on limited personal experience rather than to conform to the recommended regimen for treating malaria cases. Inadequate, excessive or incorrect prescribing are probably the commonest forms of irrational prescribing habits.

In our study we investigated the influence of prescribing habits on malaria in Gezira State, central Sudan. The study was conducted in Wad Medani, a town located on the west bank of the Blue Nile River and surrounded by the two main continuously irrigated crop-producing agricultural schemes in the region, Gezira and Rahad.

General practitioners are the main providers of health care in the different urban parts of Sudan. However, medical assistants working in rural areas, who are also entrepreneurs, dispensing pharmacists and other nonprofessional dealers are also engaged in prescribing and selling antimalarial drugs. The empirical results demonstrate that the revenue and net profits of such dealers are directly related to the quantity of drugs used. Abe [*2*] and Greenhalgh [*3*] examined the prescribing and dispensing of medicines to patients by the public and private medical sectors and by private pharmacies in five Indian cities. Their studies showed that over-prescription by doctors in the private sector was common and that many of the drugs used and prescribed were dubious and dangerous. They concluded that an essential drugs list is useless unless accompanied by intensive efforts to improve the prescribing of doctors and dispensing of pharmacists. Isenalumhe and Oviawi showed that on average, there is a tendency to prescribe more expensive and unnecessary drugs [*4*]. In an Indian study, Kapil described the doctor–patient roles as a client relationship [*5*].

Patients and methods

The study included some of the patients who seek treatment in Wad Medani Teaching Hospital, especially those who collected their prescribed drugs from the counter of the public retail pharmacy, which is adjacent and attached to the exit of the outpatient clinics of the different specialties. The patients included residents of the town who were referred from different health centres in Wad Medani, as well as those living in the surrounding villages and towns scattered within the agricultural schemes; these villages and towns lack such medical specialty services.

The first period of collection was between September and October of the same year, which is the end of the normal rainy season. This period is considered a high season for malaria infection in Gezira State. Another collection period took place during the coldest period of the year for this region—in January and February. This period was considered by the researchers to be

the low season or the season of least occurrence of malaria infection in Gezira State.

Every fifth incoming patient, after payment and collection of his/her prescribed medicine, was briefed on the objectives of the research. Those who agreed to participate in the study were then requested to hand in their prescriptions to the interviewer and to complete a pretested questionnaire, which was composed of two parts. The first part included information on the patient, his/her age, sex, education and the prescriber's specialty. The second part included a record of the prescribed and dispensed drugs, the drug names, the unit dosage formulation, the administered dose, the route of administration, the drugs actually dispensed and the reason for incomplete dispensing.

Data on malaria chemotherapy were tabulated and analysed using *SPSS* to determine different indicators for core drug use (Table 1).

The core drug use indicators recommended by the World Health Organization (WHO) [6] are as follows:

Prescribing indicators

- Percentage of prescriptions containing antimalarials
- Percentage of antimalarials/antibiotics combinations
- Percentage of antimalarial combinations
- Percentage of antimalarial drugs plus analgesics
- Percentage of different unit dosage forms
- Percentage of different routes of administration
- Percentage of prescribers' specialty

Patient care indicators

- Percentage of drugs actually dispensed
- Percentage of drugs adequately prescribed.

Results

Of the 400 prescriptions investigated, male respondents were predominant, 210 (52.5%). Of the prescriptions collected during both periods of study, antimalarials had a high prescribing rate 167 (41.8%) (Table 1). Chloroquine had the highest prescribing rates, 53 (54.1%) and 45 (45.9%) in the high and low seasons comprised 58.7% of the total prescribed antimalarials and 24.5% of the total prescriptions in the two seasons. Quinine was the second most prescribed antimalarial agent

Table 1 **Prescriptions containing antimalarials by malaria season**

Prescription	High season		Low season		Total (n = 400)	
	No.	%	No.	%	No.	%
Chloroquine	53	54.1	45	45.9	98	24.5
No antimalarial	155	66.5	78	33.5	233	58.2
Quinine	18	41.9	25	58.1	43	10.8
Sulfodoxine/pyrimethamine	4	25.0	12	75.0	16	4.0
Other antimalarials	4	40.0	6	60.0	10	2.5

and constituted 43 (10.8%) of the total prescriptions and 25.7% of the total prescribed antimalarials, of which 18 (41.9%) and 25 (58.1%) were in the high and low seasons respectively. In comparison, the other antimalarial drugs had much lower prescribing rates in both periods of the study (Table 1).

With regard to the antimalarial formulae prescribed, the injectable formulation was the commonest, 72 (44.7%), tablet formulation came second in line of preference, 59 (36.6%) while the syrups were the least recommended unit dosage form, 11 (6.8%). For 12.6% of the prescribed antimalarial drugs in the low season and 10.8% in the high season, doctors were inclined to start with the injectable formulations and complete the treatment with an oral medication.

Only 73 (18.3%) of the prescriptions collected in the two periods contained antimalarial and antibiotic combinations. The adjuvant administration of sulfamethoxazole/trimethoprim combination with antimalarial drugs were the commonest, 34 (46.6%), followed by combinations of antimalarial drugs with: tetracycline 6 (8.2%), beta-lactam antibiotics 5 (6.8%) and other miscellaneous antibiotics 22 (30.1%).

In both the high and low seasons, prescription of antimalarials in combination was very rare, 8 (2.0%). Of all the prescriptions, only 31 (7.8%) contained a combination of antimalarial and analgesic preparations. Paracetamol was the most commonly combined analgesic, 23 (74.2%); other combinations were acetylsalicylic acid (16.1%) (Aspirin®) and dipyrone (9.7%) (Novalgin®).

Of the 93 oral preparations prescribed to treat malaria infections, chloroquine was the most frequently prescribed drug, 44 (47.3%), followed by quinine oral formulation, 21 (22.6%), sulfadoxine/pyrimethamine, 17 (18.3%) and then other miscellaneous oral formulations, 9 (9.7%).

Of the total prescriptions, 63 (15.8%) were for intramuscular antimalarial drugs. Again chloroquine was the most frequently prescribed, 57 (90.5%), followed by quinine, 6 (9.5%). Of the total prescriptions, quinine was the only intravenously administered antimalarial prescribed in the study, 26 (6.5%).

Most of the respondents, 244 (61.0%), were seen by general practitioners, followed by 136 (34.0%) who were seen by different specialists; the rest of the respondents, 20 (5.0%), were diagnosed and treated by medical assistants.

Table 2 Prescriptions containing antimalarials by prescriber

Prescriber	Chloroquine		Sulfadoxine/ pyrimethamine		Quinine		Miscellaneous		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Specialists	26	55.3	3	6.4	15	31.9	3	6.4	47	100
General practitioners	68	63.6	12	11.2	25	23.4	2	1.9	107	100
Medical assistants	4	80.0	1	20.0	–	–	–	–	5	100
Total	98	61.6	16	10.1	40	25.2	5	3.1	159	100

Specialists versus general practitioners: $\chi^2_3 = 4.11$, $P = 0.25$.

According to the criteria for the dose adequacy and stability measures [*17*], only 84 (55.3%) out of the given antimalarial doses adequately conformed to the standard dose regimen.

Nearly all the antimalarials prescribed were available at the time of the study in the pharmacy outlet where the data collection took place.

When the prescriptions containing antimalarials were correlated with the prescribers' job (Table 2), the results showed that 26 (55.3%) of the 47 prescriptions written by specialists contained chloroquine and 15 (31.9%) contained quinine. For the 107 prescriptions written by general practitioners, 68 (63.6%) contained chloroquine and 25 (23.4%), contained quinine. Few prescriptions were for antimalarial drugs other than the two above-mentioned examples.

Of the analgesics prescribed in combination with antimalarials, 23 (74.2%) were for paracetamol, of which 17 (73.9%) were combined with chloroquine, 2 (8.7%) with quinine and 4 (17.4%) with other antimalarials. Acetylsalicylic acid was combined in 5 (16.1%) and dipyrone in 3 (9.7%) of the total antimalarial analgesic combinations.

Chloroquine formulations constituted 30 (51.7%) of the prescribed tablet unit dosage forms, followed by sulfadoxine/pyrimethamine, 13 (22.4%), quinine, 10 (17.2%), and miscellaneous antimalarial tablet formulations, 5 (8.6%). Chloroquine injectable formulation was the most frequently prescribed antimalarial injectable formula, 51 (70.8%), followed by quinine, 19 (26.4%), and sulfadoxine/pyrimethamine, 2 (2.8%). Chloroquine was the only antimalarial in syrup form at the time of the study and constituted 7 (4.2%) of the total antimalarial prescriptions.

In 19 (11.4%) of the total antimalarial prescriptions, the treatment was started by administering an injectable preparation and completed by oral tablet forms. Of these, 7 (36.8%) were for quinine, 5 (26.3%) for chloroquine, 4 (21.1%) for chloroquine plus sulfadoxine/pyrimethamine, and 1 (5.3%) was for quinine plus sulfadoxine/pyrimethamine.

With regard to the relationship between the unit dosage form of the drug given and the adequacy of the dosage, 18 (60.0%) of the prescribed chloroquine doses in tablet form were excessive, mostly in a quantity of more than 10 tablets for the treatment of the malaria episodes. Quinine tablets dosage was appropriate in 9 (42.9%) of the prescriptions and sulfadoxine/pyrimethamine dosage was appropriate in 11 (91.7%). Regarding quinine intravenous infusions, 20 (87.0%) did not conform to the recommended method of administration. Inadequate dosage mostly occurred as a result of partial administration of the drug over the recommended period of time. Only 2 (24.5%) of the chloroquine parenteral doses prescribed were excessive.

Analysis of the relationship between the adequacy of the dose and the type of antimalarial drug prescribed showed that chloroquine was adequately prescribed in 53 (54.1%) prescriptions, while an adequate dose of quinine was given in only 11 (27.5%); these constituted 63.1% and 13.1% of the total prescribed antimalarials respectively. Also, 26 (38.2%) of the prescribed doses of quinine did not meet the standard adequate dose limits.

Of the antimalarials prescribed in tablet unit dosage forms, 44 (74.6%) were prescribed by general practitioners, 13 (22.0%) by specialists and 2 (3.4%) by medical assistants. Syrups were exclusively prescribed by general practitioners, 10 (100%), while 38 (52.8%) of the parenteral antimalarials were prescribed by general practitioners, 31 (43.0%) by specialist and

3 (4.2%) by medical assistants. For treatments that started by parenteral administration and were completed by oral tablets, 13 (68.4%) of the prescribers were general practitioners and 5 (26.3%) were specialists. With regard to intramuscular administration of antimalarials, 35 (61.4%) of the prescriptions for intramuscular chloroquine were given by general practitioners, while 20 (35.1%) were given by specialists. On the other hand, 15 (57.7%) of the prescriptions for intravenous quinine were given by specialists. With regard to the other oral drugs, 24 (77.4%) were given by general practitioners, while the other 7 (22.6%) were prescribed by specialists.

For prescriptions containing only a single drug, 50 (56.8%) were prescribed by general practitioners, 30 (34.1%) by specialists and only 6 (6.8%) by medical assistants. For prescriptions containing two drugs, 90 (65.2%) were prescribed by general practitioners, 42 (30.4%) by specialists and 6 (4.3%) by medical assistants. For prescriptions containing three, four and five drugs, 80 (60.6%), 22 (56.4%) and 2 (66.7%) respectively were exclusively prescribed by general practitioners.

Discussion

In both studies, in the high and low seasons of malaria occurrence, the slight increase of male respondents noted is in agreement with Garnham [*7*], who attributed such an increase to the more frequent travelling of men compared with women.

The proportion of antimalarial drugs prescribed in our study (41.8%) was slightly higher than the national figure of 30% [*1*]. This increase may be attributed to the increased incidence of malaria infection in Gezira State because of the large and continuously irrigated agricultural areas of Gezira and Rahad, which provide optimal conditions for mosquito breeding throughout the year. The effect of irrigated schemes on malaria outbreaks was shown by Meyus et al. [*8*] and Marimbu et al. [*9*], who linked the malaria epidemic in Burundi to the expansion of an irrigation system in the rice fields. This explains the surprisingly high rate of prescriptions for antimalarial drugs during the supposed low season of malaria infection in the area.

The high number of chloroquine prescriptions in our study is similar to other studies carried out in different parts of the world. For example, Warrel observed that, despite the extensive spread of *P. falciparum* strains resistant to chloroquine, chloroquine is still by far the most widely used antimalarial drug in the world [*10*]. Chloroquine is the most commonly used drug to treat fever as it is readily available and comparatively cheap [*11*]. Quinine was the second most commonly prescribed antimalarial. The increased number of quinine prescriptions during the low season indicates the high rate of complicated malaria during this season. This may be due to the failure of chloroquine therapy, since most of the referred patients were treated first with chloroquine either by self-medication or by allied medical workers. Other antimalarials, namely mefloquine hydrochloride, amodiaquine and primaquine phosphate, were rarely prescribed. There were no prescriptions for the other recently launched antimalarials such as halofantrine hydrochloride or artemisinin. Thus the current prescribing patterns may encourage resistance to chloroquine and quinine, the most frequently prescribed drugs.

Of the different formulae prescribed, there was a preference for injectable preparations. Most patients believe in the fast action of injections, particularly as in health facilities injections are given mostly to severely sick patients. The popularity of in-

jections is also related to cultural reinterpretation [*12*].

Chloroquine was the most commonly prescribed oral antimalarial (47%), compared with quinine and other antimalarials. This may be because of the continuous availability of chloroquine tablets in both public and private pharmacies, the affordable price, or an established pattern by which most doctors and allied medical workers treat uncomplicated malaria initially by giving chloroquine, followed by oral quinine for nonresponding cases.

In 44.7% of the prescriptions, the dosage was inappropriate and did not conform to the official and standard regimens. Generally, larger quantities of antimalarials per course were prescribed. In prescriptions containing chloroquine tablets, some doctors used their own protocols to treat persistently repeated infections by giving more than the recommended 10 tablets; they prescribed 12, 14 and sometimes 16 tablets per course. It is assumed that the concentration of chloroquine in erythrocytes with no parasites is negligible, but its concentration in cells with parasites reflects its uptake by the plasmodia. The greatly reduced concentration in the resistant plasmodia as compared with sensitive plasmodia is evident [*13–15*]. This illustrates that giving an increased dose of chloroquine will add nothing to the therapeutic efficacy and may increase the possible side-effects. The availability of a registered brand of chloroquine in a 12-tablet blister pack may encourage this overdosage.

Almost all the intravenous quinine was wrongly prescribed. It is becoming a routine practice in Wad Medani Central Hospital to incorporate 1.2 g quinine (two ampoules) in a full pint (500 mL) of intravenous fluid at once. Then half of this mixture is infused for 4 hours, and the rest is retained for further use after 8–12 hours. There is no official or recommended reference for this type of administration, which may expose the drug to different physical, chemical and microbiological hazards—mainly the remarkable effect of exposure to light, temperature, chemical interactions and microbial cross-contamination—all of which may affect the activity and safety of the drug. Further pharmacokinetic, physical and chemical stability studies should be conducted to investigate the effect of this routinely used method of administration on the stability and safety of quinine.

General practitioners were the main prescribers of antimalarials. This illustrates the potential role of general practitioners in determining prescribing patterns. Thus attention should be focused on this group of doctors in any future intervention aimed to apply, modify or update a national drugs policy. The large number of prescriptions for quinine written by general practitioners during the study were issued for outpatients, and thus most of the quinine dispensed in this group was administered at the patients' homes without close medical supervision. One of the main misuses of antimalarial therapy (quinine in particular), which is now becoming a common and routine practice in our community, is the intravenous administration of drugs at home. Almost all those who administered the quinine in our study were either nurses or unqualified individuals. Quinine administration, especially intravenously, needs a well equipped place, a qualified person to administer the drug and close medical supervision. Quinine intravenous administration requires full supportive care because most measures aimed at enhancing the elimination of quinine after administration of large doses are ineffective, as quinine is extensively metabolized in the liver with only a small portion being excreted unchanged in the urine [*17*].

In our study, the specialists prescribed quinine formulations more frequently. This may be due to the severity the malaria infection or to the type of malaria they were treating since most of the referred cases are complicated types of infection.

The dose inaccuracy of the general practitioners and medical assistants was mainly due to increased quantities of chloroquine tablets prescribed. The high frequency of prescribing oral antimalarial tablets by this group for large numbers of patients may be due to the type of the malaria treated, which is mostly the non-complicated type. Since most of the patients referred to specialists have complicated malaria infections which have already been treated by oral drugs, either by general practitioners, medical assistants or by self-medication, specialists in our study rarely prescribed oral therapy and tended to prescribe intravenous quinine.

Recommendations

The high rate of antimalarial prescribing by general practitioners indicates the potential involvement and role of this group of prescribers in primary health care, and efforts should be made to update the knowledge of general practitioners of the treatment of infestation diseases.

The intensive prescribing of the few drugs available for malaria treatment may result in the development of resistance to these drugs. Increased effort should be made to measure and improve the use of different antimalarial drugs in Sudan. Such data could be used in the design of a national antimalarial drug policy, which ensured appropriate prescribing and increased public understanding of the value and need of strict compliance with the prescribing instructions.

Because of the problems of drug resistance, the few available antimalarials and the limited financial ability of those who need these drugs, it is vital to make optimal use of the less available antimalarials and to ensure rational prescribing, dispensing and use of antimalarials.

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