(Goldenberg & Meurer 1984; Hwang et al 1985b; Swingle & Reiter 1986). This suggests that the biosynthesis of prostaglandins or leukotrienes is not involved in PAF-induced conjuctival inflammation in the rat.

In summary, the local injection of low doses of PAF into the rat conjunctiva elicits a marked inflammatory response. This phenomenon is not dependent upon eicosanoids, as reflected in the ineffectiveness of orally administered indomethacin and BW 755C. In contrast, the PAF receptor antagonist L-652,731 significantly decreased the oedematous response to PAF after oral, topical and subconjunctival administration. The usefulness of PAF receptor antagonists on other forms of conjunctival inflammation remains to be determined.

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Distribution and urinary excretion of the desethylmetabolites of chloroquine in the rat

L. A. SALAKO*, FUNMILAYO O. AJAYI, *Department of Pharmacology & Therapeutics, University of Ibadan, Ibadan, Nigeria*

The tissue distribution of desethylchloroquine and bisdesethylchloroquine has been studied in rats after single intraperitoneal administration of the drugs at a dose of 10 mg kg^{-1}. Concentrations of the chloroquine metabolites in the liver, heart, lungs, kidney and spleen were 34 to 250 times higher than their plasma concentrations 24 h after the drugs had been injected. Urinary excretion of the drugs was studied in rats after single intravenous administration of 2·5, 5 or 10 mg kg^{-1} doses. The total estimated urinary excretion of desethylchloroquine and bisdesethylchloroquine was 25 and 64% respectively of the administered dose, with the maximum urinary excretion occurring on the first day. The results show that the desethylmetabolites of chloroquine are concentrated in the tissues in the same manner as the parent compound.

The major metabolites of chloroquine are desethylchloroquine which forms about 25% of total plasma quinolines and bisdesethylchloroquine (BDCQ) which forms about 6% (McChesney et al 1967). Both desethylchloroquine (Aderounmu & Fleckenstein 1983) and bisdesethylchloroquine (Ajayi et al 1987) have antimalarial activity which is at least as great as that of the parent compound against chloroquine-sensitive *Plasmodium falciparum*. Desethylchloroquine is concentrated in red blood cells to at least the same extent as chloroquine itself (Gustafsson et al 1983). The pharmacodynamics and pharmacokinetics of the metabolites might therefore be important in the overall antimalarial activity of chloroquine and possibly also in the development of resistance to it and also in the adverse reaction and toxicity profile seen during treatment. We have therefore examined the tissue distribution and urinary excretion of desethyl- and bisdesethylchloroquine using the rat as a model.

Materials and methods

Male and female Swiss albino rats, 210–240 g, were used. Rats were divided into 4 groups of three, one

* Correspondence.

Table 1. Plasma, red cell and tissue concentrations of chloroquine, desethylchloroquine and bisdesethylchloroquine 24 h after intraperitoneal injection of 10 mg kg^{-1} dose of each drug in the rat. The tissue/plasma concentration ratios are also shown.

	Chloroquine		Desethylchloroquine		Bisdesethylchloroquine	
	Concn ($\mu g\ g^{-1}$ or $\mu g\ mL^{-1}$)	Tissue/ plasma	Concn ($\mu g\ g^{-1}$ or $\mu g\ mL^{-1}$)	Tissue/ plasma	Concn ($\mu g\ g^{-1}$ or $\mu g\ mL^{-1}$)	Tissue/ plasma
Plasma	0·067	—	0·05	—	0·05	—
Red cells	0·19	3·1	0·17	3·5	0·22	4·5
Heart	1·86	27·9	1·20	24·0	2·56	51·2
Liver	2·29	34·3	4·01	80·2	8·41	168·3
Kidney	4·76	71·2	3·90	78·0	8·17	163·6
Spleen	13·31	198·7	5·61	112·4	17·32	346·6
Lungs	16·64	248·4	9·29	185·9	21·79	435·9

group served as control while the remaining groups were treated with chloroquine, desethylchloroquine or bisdesethylchloroquine as a single dose of 10 mg kg^{-1} intraperitoneally in approximately 0·5 mL 0·9% NaCl (saline). The control rats received 0·5 mL saline. Twenty-four hours later the rats were lightly anaesthetized and 5 mL blood obtained by cardiac puncture. The blood was immediately centrifuged and the plasma and red blood cells were stored separately at −20 °C. The animals were killed immediately after the cardiopuncture and the lungs, liver, heart, kidney and spleen removed. Portions of these tissues were blotted dry, weighed and stored at −20 °C.

Twenty-seven rats were allowed to acclimatize to their metabolic cages for 24 h before being used for the urinary excretion study. The drug and its two metabolites were each injected into the caudal vein of 9 rats at 2·5, 5·0 and 10·0 mg kg^{-1} so that each dose was given to three animals. Urine samples collected during the acclimatization period were stored at −20 °C and used for plotting the standard curves. Urine was collected daily for 10 days. The volumes were recorded and 10 mL aliquots stored in screw-capped glass specimen bottles kept at −20 °C.

Chloroquine and its metabolites were analysed in blood, urine and tissue using a modification of the fluorometric method described by Adelusi & Salako (1980, 1982a, b). Samples were analysed in duplicates and standard curves were produced for each day's analyses.

The quantity of drug eliminated in the urine during the 10-day observation period was determined from the area under the urine concentration-time curve (AUC_t) using the trapezoidal rule.

Results and discussion

Table 1 summarizes the concentration of the metabolites in various tissues. Like the parent drug, both metabolites are highly concentrated in the liver, heart, kidney, spleen and lungs with the tissue/plasma concentration ratio varying between 24 and 436. All three compounds were also about equally concentrated in red blood cells with the RBC/plasma concentration ratios (3·5 for desethyl; 4·5 for bisdesethyl) being similar to the value of 3·1 obtained for chloroquine.

First day urinary excretion and the estimated total urinary recovery of chloroquine, desethylchloroquine and bisdesethylchloroquine after their administration was (%) 9·0, 6·0 15·0 1st day and 26·4, 25·2, 63·7 after 10 days, respectively. The percentage of the dose excreted was not dose-dependent and so the three doses were pooled. Maximum urinary excretion occurred on the first day but the drugs were excreted throughout the collection period.

These results show that the two desethyl-metabolites are distributed in rat tissues in a manner similar to the parent drug. Both McChesney et al (1967) and Fletcher et al (1975) found desethylchloroquine in the livers of chloroquine-treated monkeys. BDCQ was not recorded. The present work therefore confirms the earlier studies and provides new data for the tissue distribution of bisdesethylchloroquine. It also shows this metabolite to be excreted in the urine at least twice as rapidly as chloroquine or desethylchloroquine. Its high rate of excretion is not surprising since it is the more polar compound, but it is of interest since it may be an important means of eliminating chloroquine from the body.

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