The African Journal of Medicine and Medical Sciences

Editors: T.A. Junaid
O. Bademosi and D.D.O. Oyebola

Volume 16
1987

BLACKWELL SCIENTIFIC PUBLICATIONS
Oxford London Edinburgh Boston Palo Alto Melbourne

Afr. J. Med. med. Sci. (1987) **16**, 43–46.

The pharmacokinetics of proguanil in human subjects following a single oral dose

E. M. CHILUBA*, K. A. FLETCHER AND A. H. PRICE
Liverpool School of Tropical Medicine, Pembroke Place, Liverpool, U.K.

Abstract

The pharmacokinetics of orally administered 200-mg dose of proguanil in volunteers, one African and one Caucasian, is described. The drug was rapidly absorbed reaching a peak concentration in the blood within 3 h, and declining slowly thereafter to give a terminal phase elimination half life of 11.20 ± 4.10 h and a systemic clearance of 1.270 ± 0.020 l/h/kg. The small apparent volume of distribution shows that the drug is confined mainly to the blood and is not extensively bound to tissues; it undergoes cyclic oxidation in the liver to cycloguanil — the active metabolite repsonsible for antimalarial activity. Cycloguanil was detected in the plasma 3 h after proguanil ingestion and reached peak concentration between 5 h and 6 h. Excretion of proguanil was rapid, 60% of the single dose passing through the renal system within 24 h.

Résumé

La pharmacocinétique d'une dose de 200 mg de proguanil administrée oralement à des volontaires, un Africain et un Caucasien est décrite. Le médicament était rapidement absorbé pour atteindre une concentration maximale dans le sang en trois heures et diminuer ensuite lentement jusqu'à une phase d'élimination terminale (vie moyenne) de 11.20 ± 4.10 heures et une élimination du système de 1.270 ± 0.020 l/heure/kg. Le petit volume apparent de distribution montre que le médicament se limite surtout au sang et n'est pas lié d'une façon considérable aux tissus; il subit une oxydation cyclique dans le foie en cycloguanil — le métabolite actif responsable pour l'activité antipaludique. Le cycloguanil est détecté dans le plasma trois heures après l'ingestion du proguanil et atteint une concentration maximale entre 5 et 6 heures. L'excrétion du proguanil est rapide, 60% d'une dose unique passe par le système rénal en 24 heures.

*Present address and address for correspondence: Tropical Diseases Research Centre, PO Box 71769, Ndola, Zambia.

Introduction

The spread of chloroquine resistance in many parts of the world has stimulated a resurgence of interest in the use of proguanil for antimalarial chemoprophylaxis (Olsen, 1983; Rombo *et al.*, 1983; McLarty *et al.*, 1984). This is mainly due to its proven efficacy, safety, cheapness and freedom from side effects. Although it has been used extensively for mass prophylaxis against malaria infection, very little information has been documented about its absorption and disposition following a single oral dose.

The development of specific and sensitive assays using high performance liquid chromatography (HPLC), now permit accurate investigations of the kinetics of proguanil and of cycloguanil, its metabolite, in the plasma.

The method has been used to monitor this drug in army personnel on long term proguanil prophylaxis. Maegraith *et al.* (1946) documented a study of normal subjects and patients suffering from either *Plasmodium vivax* or *P. Falciparum* malaria, on the pharmacology of proguanil given as an anti-malarial drug, using the methods of Spinks and Tottey (1945) to estimate concentrations of the drug in the plasma and urine.

Although they obtained useful information about the absorption and elimination of proguanil by this method, they were unable to

measure cycloguanil — an active metabolite of proguanil.

This study, therefore, attempted to investigate the pharmacokinetics of both proguanil and cycloguanil in human plasma and urine following the ingestion of a single oral dose of proguanil. Such investigations are considered necessary to determine the levels of both proguanil and cycloguanil achieved during and after prophylaxis.

Materials and methods

Chemicals

Paludrine tablets (each tablet equivalent to 100 mg proguanil hydrochloride) were obtained from Imperial Chemical Industries Ltd, (ICI), Macclesfield, Cheshire, U.K.

Cycloguanil standard (4, 6 - diamino - 1(4 - chlorophenyl) - 1,2 - dihydro - 2,2 - dimethyl-s-triazine) was supplied by Dr R. E. Howells and metoprine, the internal standard, (2,4 - diamino - 5 - (3,4-dichlorophenyl - 6 - methyl-pyrimidine) was kindly donated by Dr C. R. Jones.

Chromatography

All assays were carried out on a high performance liquid chromatography system consisting of an LKB 2150 HPLC pump (LKB Instruments Ltd, Croydon, Surrey, U.K.), Kratos Spectroflow 757 variable wavelength u.v. absorbance detector (Kratos Analytical Instruments, Urmston, Manchester, U.K.) and a Rheodyne injector valve fitted with 50-μl loop. A Kipp and Zonen BD8 flat bed recorder (Talbot Instruments, Alderley Edge, Cheshire, U.K.) was used to record the detector response. High performance liquid chromatography columns were supplied by Phase Separation Ltd, Queensferry, Clwyd, U.K. and were of stainless steel (250 mm long with an internal diameter of 4.5 mm, packed with spherisorb S5CN), and used in a reverse-phase mode. Full features of the method employed have been described elsewhere (Kelly & Chiluba, 1986).

Volunteer study

Two healthy male volunteers, one Caucasian and one African, who were taking no other drugs, each received an oral dose of two tablets of a standard preparation equivalent to 200 mg proguanil.

The drug was administered in the morning after overnight fasting. Fasting was continued for 3 h when a light lunch was permitted. Blood samples were withdrawn by venepuncture into heparinized containers before the dose and at 2, 4, 6, 8, 24, 32 and 48 h after dosing. The samples were centrifuged immediately (at 3000 r.p.m.) and the plasma removed and stored at −20°C until analysis. Urine samples were collected over a 24-h period, and stored at −20°C until analysis.

Assay methods

Proguanil and cycloguanil were simultaneously measured using metoprine as the internal standard. Samples were chromatographed on a nitrile column and eluted with a mobile phase of acetonitrile, methanol and water (9:2:89) containing 0.05 M ammonium formate (pH 4.0) as an ion-pairing agent. Detection for both cycloguanil and proguanil was achieved at 252 nm.

Pharmacokinetic analysis

The peak plasma concentration (C_{pk}) and the times at which they were reached (t_{pk}) were obtained graphically. The area under the plasma concentration/time curve from $t = 0$ to 48 h (AUC_{0-48}) was calculated using the trapezoidal rule (Gibaldi & Perrier, 1975). The terminal phase elimination half-life ($t_{½}$) was obtained by linear regression analysis (SR-52, Texas Instruments, Texas, U.S.A.) of the post-absorption and distribution phase of the plasma concentration/time data. Systemic clearance (Cl), elimination rate constant (K_{el}) and apparent volume of distribution (V_d) were determined by model-independent pharmacokinetic formulae (Rowland & Tozer, 1980).

Results

Table 1 shows the pharmacokinetic parameters derived for cycloguanil and proguanil in plasma of two volunteers following a 200 mg single oral dose of proguanil base.

Table 1. Pharmacokinetic parameters of cycloguanil and proguanil in two subjects

Pharmacokinetic parameter	Subject 1*		Subject 2†	
	Cycloguanil	Proguanil	Cycloguanil	Proguanil
Peak concentration, C_{pk} (ng/ml)	122.5	172.5	52.5	195.0
Time to peak concentration, t_{pk} (h)	6.0	2.0	5.0	3.0
Elimination rate constant, K_{el} (per h)	0.089	0.049	0.073	0.084
Elimination half-life, $t_{1/2}$ (h)	7.78	14.10	8.7	8.3
Systemic clearance, Cl (l/h/kg)	—	1.256	—	1.285
Area under the curve, AUC_{0-48} (μg/l/h)	1857.5	1830.0	892.8	2509.4
Apparent volume of distribution, V_d (l/kg)	—	25.64	—	15.30

*Subject 1 (Caucasian, body weight 82 kg).
†Subject 2 (African, body weight 64 kg).
Bioavailability (F) of 100% was assumed in the calculation of these parameters.

Discussion

The single dose studies in the human volunteers in this exercise have shown that proguanil is rapidly absorbed from the gastrointestinal tract reaching peak concentration of 183.75 ± 15.9 ng/ml within 3 h. Thereafter, the drug levels declined fairly slowly with a terminal phase elimination half-life of 11.20 ± 4.10 h and a systemic clearance of 1.270 ± 0.020 l/h/kg (Figs 1 and 2). The apparent volume of distribution is within the order of 15.30–25.64 l/kg, which indicates that proguanil is not heavily bound to organs or tissues as also observed by Maegraith *et al.* (1946).

Renal clearance of either the parent compound or its metabolite cycloguanil represents the major route of elimination, as more than 60% of the dose was recovered from the urine of both subjects within 24 h (Fig. 3).

Proguanil undergoes cyclic oxidation by the hepatic microsomal oxidases of the cytochrome P-450 system to form its active metabolite, cycloguanil (Briggs & Briggs, 1974). Peak levels of this metabolite of 87.5 ± 49.5 ng/ml were reached between 5 h and 6 h post-dose.

In view of the paucity of information on the pharmacokinetics of proguanil, it is difficulty to relate these findings to other studies. However, although using somewhat unspecific and less sensitive methods, Maegraith *et al.* (1946) reported the rapid absorption of proguanil reaching peak concentrations between 2 h and 3 h and observed that 40% of the dose is excreted renally.

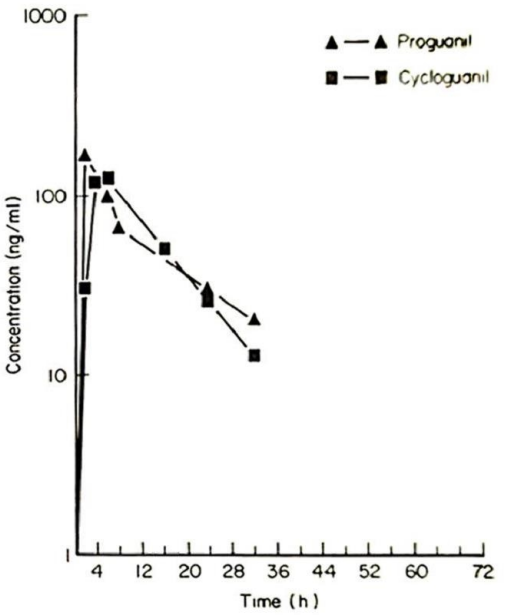

Fig. 1. Plasma concentrations of cycloguanil and proguanil as a function of time after a single oral dose of 200 mg paludrine to a Caucasian volunteer.

The oxidative cyclization of proguanil to cycloguanil by the liver is thought to be influenced by many factors, including the ingestion of certain types of contraceptives (Kelly, 1983). It appears from these kinetic studies that

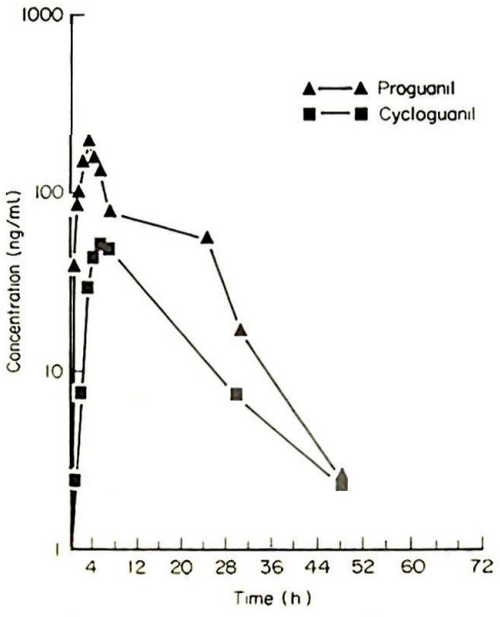

Fig. 2. Plasma concentration of cycloguanil and proguanil as a function of time after a single oral dose of 200 mg paludrine to an African volunteer.

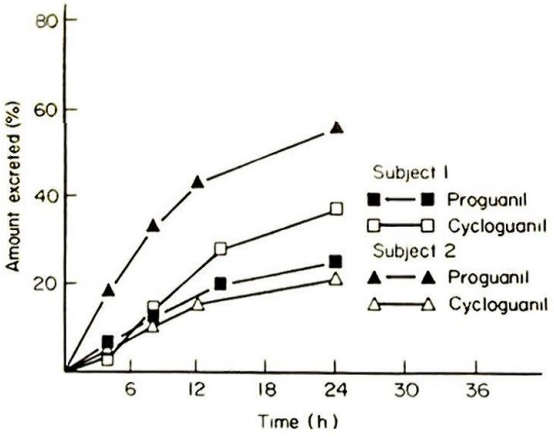

Fig. 3. Cumulative urinary output of cycloguanil and proguanil in two volunteers following a single oral dose of 200 mg paludrine.

subject 2 (African) was 'unable' to convert proguanil to cycloguanil efficiently. This is of clinical importance, as it is the cycloguanil and not the proguanil that is required in desirable concentration to protect against malarial infection, and clearly warrants for further investigations.

Acknowledgments

This study was supported by the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. We wish to thank Dr R. E. Howells, Department of Parasitology, Liverpool School of Tropical Medicine, for supplying cycloguanil standard chemical and Dr C. R. Jones, Wellcome Research Laboratories, Beckenham, Kent for supplying metoprine.

References

Briggs, M. & Briggs, M. (1974) *The Chemistry and Metabolism of Drugs and Toxins*. Heinemann Medical, London.

Gibaldi, M. & Perrier, D. (1975). *Drugs and Pharmaceutical Sciences, Vol. 1. Pharmacokinetics*. Marcel Dekker, New York.

Kelly, J.A. (1983) *Analysis of antimalarial drug levels*. MSc Thesis, University of Liverpool.

Kelly, J.A. & Chiluba, E.M. (1986) Simultaneous determination of proguanil and cycloguanil by ion-pairing agent. HPLC application. *J. Chromatogr.* (in press).

Maegraith, B.G., Tottey, M.M., Adams, A.R.D., Andrew, W.H.H. & King, J.D. (1946) The absorption and excretion of paludrine in the human subject. *Ann. Trop. Med. Parasitol.* **40**, 493–506.

McLarty, D.G. *et al.* (1984) Chemoprophylaxis of malaria in non-immune residents of Dar-es-salaam, Tanzania. *Lancet* **ii**, 656–659.

Olsen, V.V. (1983) Why not proguanil in malaria prophylaxis? *Lancet* **i**, 649.

Rowland, M. & Tozer, T.N. (1980) *Clinical Pharmacokinetics; Concepts and Applications*. Lea & Febiger, Philadelphia.

Rombo, L., Hedman, P., Kihamia, C.M., Ramji, B.D., Bjorkman, A. & Bengtsson, E. (1983) Proguanil for malaria prophylaxis. *Lancet* **i**, 997.

Spinks, A. & Tottey, M.M. (1945) Studies on synthetic antimalarial drugs. VIII. Colorimetric determination of 2-p-chlorophenyl-guanidino-4-β-diethylamino-6-methylpyrimidine (3349). *Ann. Trop. Med. Parasitol.* **39**, 190–192.

(*Received* 30 *June* 1986; *accepted* 11 *July* 1986)