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# Kinetic studies of mefloquine and of one of its metabolites, Ro 21-5104, in the dog and in man

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Mefloquine, rac. erythro-alpha-2-piperidyl-2,8-bis (trifluoromethyl)-4-quinoline methanol (= M), is a new quinoline methanol derivative developed by the Walter Reed Army Institute of Research, which received top priority from the WHO in its programme to control chloroquine-resistant malaria.

Several metabolites of the drug have been recently identified (Jauch, Griesser and Oesterhelt, 1980). One of them, 2,8-trifluoromethyl-quinoline-4-carboxylic acid, Ro 21-5104 (= MM), was found to be present in relatively high concentration in the plasma of animals and humans given mefloquine. Although the compound was found to be inactive against *Plasmodium berghei* in mice (R. Richle), it proved nearly as toxic orally as mefloquine in mice and rats (H. P. Bächtold). It therefore also required study. A TLC-method (D. E. Schwartz) was developed which permits simultaneous measurement of both the unchanged drug and its metabolite Ro 21-5104 in the plasma. In this study data on the pharmacokinetics of the two compounds as determined in the dog and in man are presented.

*Kinetic studies of mefloquine in man*

Plasma levels of mefloquine and of its metabolite were measured in human subjects given 1 g mefloquine base in the form of its hydrochloride orally. Fig. 1 gives the plasma level curve we observed in a Caucasian subject. Due to the extremely slow elimination of the drug, investigation of plasma had to be extended over a period of 3 to 4 months. A more detailed description of the absorption phase has therefore been drawn in the rectangle at the bottom of the graph. Absorption of M started rapidly within the first hour, plasma levels

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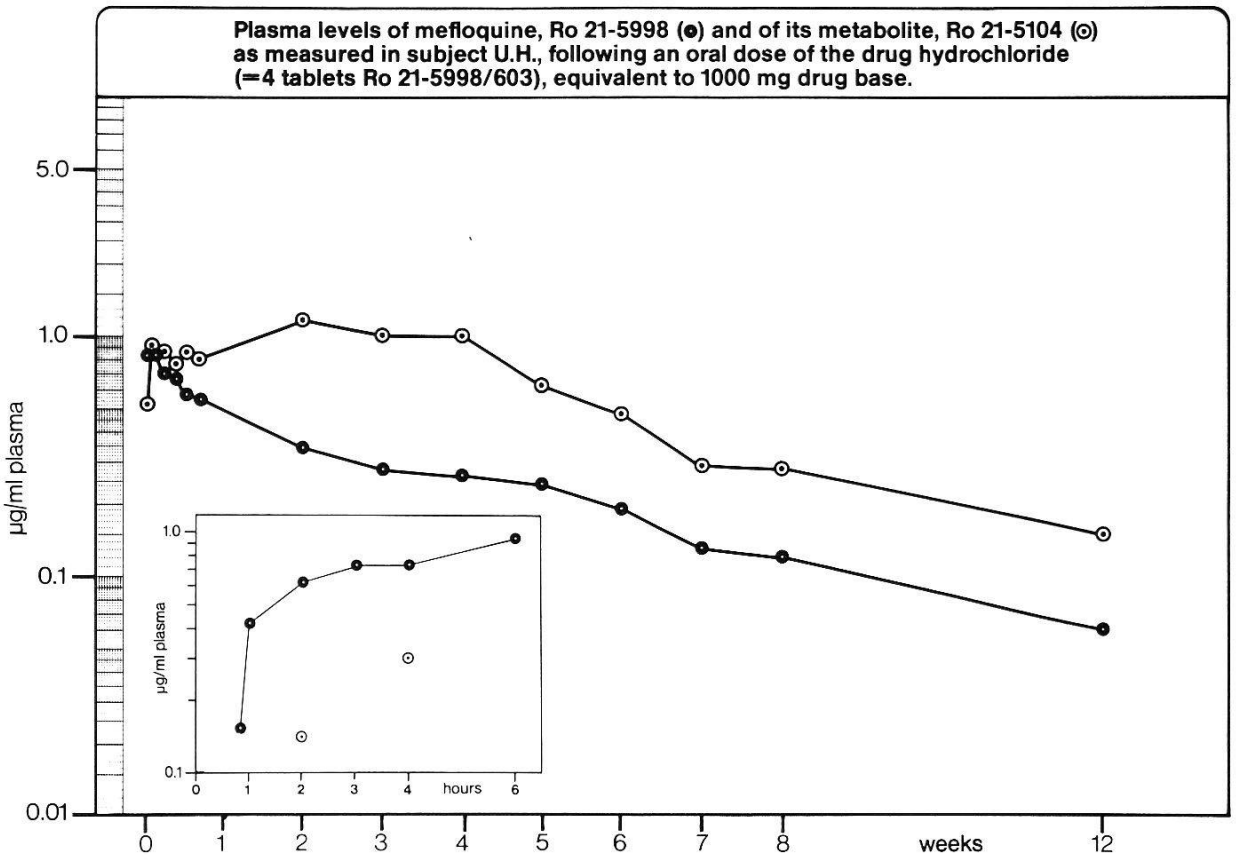


Fig. 1.

rising then more slowly to reach maximum values of 0.9 to 1.0 $\mu$g/ml within 2 to 12 hours of administration. Thereafter M showed a somewhat fluctuating decline to which, however, an overall half-life of elimination can be attributed. The metabolite MM, the corresponding 4-quinoline carboxylic acid, appeared in blood 2 to 4 hours after the oral administration of mefloquine. Its concentration rose steadily to maximum values of 1.1 to 1.4 $\mu$g/ml within 1 or 2 weeks of administration, remained practically constant for about 2 to 3 weeks to decline thereafter at a rate similar to that of mefloquine.

*Comparative kinetic studies of mefloquine and its metabolite in the dog*

The pharmacokinetic properties of M and MM were further investigated and compared in dogs, using i.v. administration. Both drugs were administered at a dose of 10 to 20 mg/kg. The injection solution consisted, for M, of the drug lactate dissolved in Glycofurol 75 and diluted to 10 ml with 5% glucose, for MM, of the free acid dissolved in 10 ml isotonic phosphate buffer of pH 7.4. Solutions of both compounds were injected into the jugular vein at a constant rate by means of an infusion pump over a period of 10 minutes. The intravenous injection of 250 mg M produced initial plasma levels of approximately 3 to 4 $\mu$g M/ml. In contrast the intravenous injection of 204 mg MM resulted in initial plasma levels of approximately 100 $\mu$g MM/ml. In these experiments both

compounds showed virtually the same half-life of elimination, but the initial plasma levels of MM reached were about 30 times higher than those of M. The volumes of distribution of the two substances are therefore extremely different. On comparing the area under the curve ($AUC_0^{\infty}$) of MM formed after intravenous administration of 250 mg M with that measured after intravenous administration of 204 mg MM, a dose equivalent to 250 mg M, it was found that only 26% of M had been metabolically converted to MM.

In conclusion, the relatively high plasma levels of the mefloquine metabolite observed after oral administration of mefloquine are explained by its much smaller volume of distribution. In fact, following administration of mefloquine to dogs and also to man, the amount of the metabolite formed is relatively small; it will therefore contribute only to a minor extent towards the toxicity of the drug in these species.

*Pharmacokinetic profile of mefloquine in the dog and in man*

A thorough investigation of the pharmacokinetic profile of mefloquine, including bioavailability, volume of distribution and clearance, can only be made by using a parenteral form of application of the drug.

Since such studies could not be done in humans, they were carried out in dogs. Comparing the areas under the mefloquine curve following oral and i.v. administration to dogs, the bioavailability of the drug from tablets was found to range between 67 and 90% of the dose (mean 78%). Assuming that the absorption of mefloquine is also almost complete in man, first estimates of its volume of distribution and total clearance were attempted.

Table 1 gives the pharmacokinetic parameters calculated for three Caucasian subjects from plasma data using a two-compartment model. The very large volume of distribution (Vd) of 27 to 50 liters/kg indicates that the major portion of the drug is located in peripheral tissue compartments. This is remarkable because the drug is tightly bound to human plasma proteins (99.1%). This extensive binding to proteins may well be responsible, at least in part, for the rather small total plasma clearance ($Q_{tot.}$) of less than 0.5 $ml \cdot min^{-1} \cdot kg^{-1}$ observed.

The same table gives pharmacokinetic parameters of mefloquine as determined in two Swiss beagle dogs. It will be seen that while the half-life of the drug in dogs is about 30 times shorter and its volume of distribution about 5 times smaller, its total body clearance is 10 times greater than in man.

In collaboration with two centres, one in Paris and one in Libreville, Gabon, we also investigated the elimination half-life of mefloquine in eight Africans, three living in Paris and five in Libreville. The mean values found in these two groups suggest that in Africans, particularly those living in Africa, the half-life of mefloquine would be shorter than in Caucasians (Table 2). However, the plasma samples of Africans living in Libreville were less in number than those of the other groups and were collected at different, perhaps not optimal

Table 1. Pharmacokinetic parameters

| Species | | Humans (Caucasian) | | | Dogs (Swiss beagles) | |
|---|---|---|---|---|---|---|
| | | U. H. | H. N. | A. F. | Emir | Asterix |
| Weight (age/size)<br>kg (years/cm) | | 81 (42/183) | 84 (44/184) | 81 (49/180) | 14.0 | 12.3 |
| Administration | | oral | | | intravenous | |
| $t_{½\,(a)}$<br>Absorption half-life | (h) | 1.0 | 1.8 | 0.5 | | |
| $t_{½\,(\beta)}$<br>Terminal elimination half-life | (days) | 27 | 22 | 33** | 0.82 | 1.08 |
| $X_0 = \frac{\text{Dose}}{\text{Body weight}}$ | $(\text{mg}\cdot\text{kg}^{-1})$ | 12.35 | 11.90 | 12.35 | 7.14 | 20.32 |
| $V_d = \frac{X_0}{\beta \cdot AUC_0\int^{\infty}(\text{pl})}$ | $(\text{l}\cdot\text{kg}^{-1})$ | 40.3* | 27.3* | 50.5* | 6.1 | 9.1 |
| $Q_{tot} = \frac{X_0}{AUC_0\int^{\infty}(\text{pl})}$ | $(\text{ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1})$ | 0.41* | 0.34* | 0.42* | 3.58 | 4.16 |

* Calculated assuming complete oral absorption of the drug

** The log linear phase in this subject was not well defined due to the scattering of data.

Table 2. Terminal half-life of elimination of unchanged mefloquine from human plasma – mean values and standard deviations. Administration: one oral dose of mefloquine. HCl equiv. to 1000 mg mefloquine base

| Ethnical groups (number of subjects) | Place of study | Diet | $t_{1/2\,(\beta)} \pm SD$ (days) |
|---|---|---|---|
| Caucasian (3) | Grenzach (Germany) | european | $27.5 \pm 5.4$ |
| African (3) | Paris (France) | european | $20.8 \pm 2.7$ |
| African** (5) | Libreville (Gabon) | local african*** | $12.3 \pm 2.2$ |

* Terminal half-lives were determined in the log-linear phase of the plasma concentration curve. Similar values were obtained by non-linear regression, using all data points.

** Plasma samples taken from each individual subject of this group were less in number and were collected at different intervals (see text).

*** Diet rich in carbohydrates, low in proteins, as compared to european.

intervals, so that the figures are not strictly comparable. Further studies will be necessary to elucidate the possible role of genetic, climatic and/or dietary factors.

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