J. Pharm. Pharmacol. 1997, 49: 1086–1090
Received March 13, 1997
Accepted July 16, 1997

Stereoselective Passage of Mefloquine Through the Blood–Brain Barrier in the Rat

S. BAUDRY, Y. T. PHAM, B. BAUNE*, S. VIDREQUIN, CH. CREVOISIER†, F. GIMENEZ AND R. FARINOTTI*

Faculté de Pharmacie, Département de Pharmacie Clinique, Chatenay-Malabry, France
**Hôpital Bichat Claude Bernard, Service Pharmacie Clinique et Biomatériaux, Paris, France and*
†Department of Clinical Pharmacology, F. Hoffmann–La Roche Ltd, Basel, Switzerland

Abstract

The pharmacokinetics of the enantiomers of mefloquine were studied in the rat after administration of a racemic mixture and of the separate enantiomers (+)-mefloquine and (−)-mefloquine.

When 50 mg kg^{-1} racemic mixture was administered orally for 22 days, plasma concentrations of the (+) enantiomer were 2–3 times higher than those of the (−) enantiomer whereas the opposite was true in every part of the brain (cerebellum, cortex, hippocampus, hypothalamus and striatum). Different concentrations of mefloquine were found in the different regions of the brain; the lowest concentrations of (±)-mefloquine (27·0 nmol g^{-1}) were in the cerebellum and the highest (110·0 nmol g^{-1}) in the hippocampus. The main metabolite, carboxymefloquine, was detected in plasma but not in the brain.

The results indicate that mefloquine crosses the blood–brain barrier stereoselectively.

Mefloquine is a quinoline methanol derivative used for prophylaxis and treatment of multidrug-resistant strains of *Plasmodium falciparum*. The drug is administered orally as a racemic mixture of the erythro isomers (+)- and (−)-mefloquine (Fig. 1). The two enantiomers of mefloquine were similarly active when tested against chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium falciparum*, (Basco et al 1992).

The main metabolite of mefloquine, in man and rat, is a quinoline carboxylic acid derivative without antimalarial activity (Basco et al 1991). Compared with the parent compound, this metabolite has lost its two asymmetric centres and so is not chiral (Fig. 1).

Because studies have shown that mefloquine pharmacokinetics are stereoselective (Gimenez et al 1994), it should be of interest to investigate which pharmacokinetic step is involved in the stereoselectivity. Reversible side-effects, such as nausea, dizziness and vertigo, often occur when mefloquine is used therapeutically (Stuiver et al 1989). Less frequently, but more seriously, an acute brain syndrome has been described with neuropsychiatric symptoms such as anxiety, depression, hallucination, acute psychosis and seizures (Rouveix et al 1989). The incidence of neuropsychiatric side-effects has been reported to be 1 in 13 000 with prophylactic use and 1 in 250 with therapeutic use (Weinke et al 1991). Sturchler et al (1990) pointed out that these side-effects occur more frequently with higher doses of (±)-mefloquine. Some authors have described serious neuropsychiatric disorders in patients with plasma concentrations of mefloquine within the therapeutic range (Weinke et al 1991) and others believe the main mefloquine metabolite to be responsible for the neurotoxicity (Björkman 1989). It is still not clear whether there is a relationship between the occurrence of CNS side-effects and the pharmacokinetic profile of mefloquine or its main metabolite.

Correspondence: F. Gimenez, Hôpital Pitié Salpêtrière, Pharmacie, 47 boulevard de l'hôpital, 75651 Paris Cedex 13, France.

Despite clinical reports of neuropsychiatric effects after administration of (±)-mefloquine, the mechanism of action is unknown and to the best of our knowledge its passage across the blood–brain barrier has never been studied.

The aim of our study was to investigate, on the one hand, the importance of passage of mefloquine and mefloquine meta-

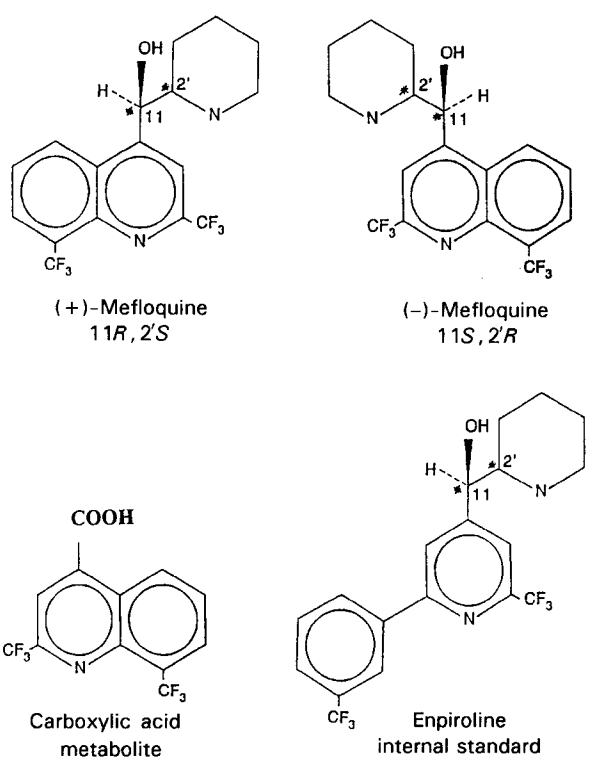

FIG. 1. Chemical structures of the enantiomers of mefloquine, its carboxylic metabolite and the internal standard enpiroline. * Indicates the positions of asymmetric carbon atoms.

bolite through the blood–brain barrier and, on the other hand, the stereoselectivity of this passage in the rat. Initially we studied the partition of mefloquine enantiomers in plasma and brain; their specific partition was then investigated in different cerebral regions.

Materials and Methods

Drugs and chemicals

Mefloquine and carboxymefloquine were kindly supplied by F. Hoffmann-La Roche (Basel, Switzerland). Racemic enpiroline (internal standard, Fig. 1) was a gift from the Walter Reed Army Research Institute (Washington, USA). Mefloquine enantiomers were obtained by fractional crystallization (Carroll & Blackwell 1974). Solvents were HPLC grade and were purchased from Carlo-Erba (Saint Quentin Fallavier, France).

Animals and drug administration

Male Wistar rats (IFFA CREDO), 150–180g, were kept under standardized conditions with free access to food and water. Rats were randomly assigned to one of their cages and received mefloquine orally. Administration began one week after arrival at the laboratory.

Brain–plasma partition. Fifty rats received (±)-mefloquine orally, in repeated doses (50 mg kg^{-1}) for 22 days to investigate blood–brain barrier passage of (±)-mefloquine, (+)-mefloquine, (−)-mefloquine and the main mefloquine metabolite. Rats were again randomly assigned to one out of ten cages and five rats were killed with a guillotine 0, 12, 24, 48, 72, 96, 192, 240, 336 and 408 h after the last dose. Blood was collected in heparinized polypropylene tubes. Brains were washed with sodium chloride, then crushed in liquid nitrogen with a Spex 6700 (Bioblock Scientific). Plasma and brain samples were stored at −80°C until analysis.

Distribution of mefloquine enantiomers in specific cerebral regions. Twenty four rats were randomly assigned to one of three cages and received mefloquine orally, in repeated doses, for 22 days.

The first group (n = 8) was treated with 50 mg kg^{-1} (±)-mefloquine; the second group (n = 8) received 25 mg kg^{-1} (+)-mefloquine; the last group (n = 8) received 25 mg kg^{-1} (−)-mefloquine. Rats were killed with a guillotine 24 h after the last administration. Blood was collected in heparinized polypropylene tubes. Brains were isolated and divided into two hemispheres as described elsewhere (Glowinski & Iversen 1966). The cerebellum, hypothalamus, hippocampus, striatum and cortex were removed from one hemisphere. The other hemisphere was used as reference for mefloquine quantification. Brain regions were washed with sodium chloride, stored at −80°C and then crushed in liquid nitrogen with a Spex 6700.

Sample preparation

Plasma extraction. Enpiroline (125 μL of a 4 mg L^{-1} solution in methanol), HCl 1·0 N (50 μL), acetonitrile (1 mL) and a small amount of sodium chloride were added to 250 μL plasma. Samples were mixed for 1 min and centrifuged (3000 rev min^{-1}, 15 min, +4°C). The supernatant (800 μL) was evaporated at 30°C under a stream of air.

Brain tissue extraction. Enpiroline, acetonitrile (1 mL) and crushed brain (20 mg) were mixed for 1 min and centrifuged (3000 rev min^{-1}, 15 min, +4°C). The supernatant (900 μL) was evaporated at 30°C under a stream of air.

Liquid chromatography

Changes with time of the concentrations of the enantiomers of mefloquine in plasma and in the brain were measured using a sequential achiral–chiral system. (±)-Mefloquine and mefloquine metabolite were quantified on an achiral column and the mefloquine–enantiomer ratio was then determined on a chiral stationary phase.

Achiral assays of (±)-mefloquine and mefloquine metabolite

Achiral chromatography. (±)-Mefloquine and mefloquine metabolite were quantified on an achiral Hypersil ODS2 (250 × 4·5 mm) C_{18} column (Touzart & Matignon, Vitry-sur-Seine, France); water–acetonitrile–orthophosphoric acid, 45 : 54 : 1 (v/v), containing 0·2% triethylamine was used as mobile phase at a flow rate of 1·5 mL min^{-1}. The detector was set at 230 nm. Plasma and tissue extracts were re-constituted with methanol (50 μL) and 40 μL was injected on to the achiral column. During the run, the mobile phase fraction containing (±)-mefloquine was collected for determination of the enantiomer ratio.

Enantiomeric mefloquine assay. The mobile phase collected from achiral chromatography and containing both enantiomers of mefloquine was made alkaline with ammonia (13 N; 100 μL) and *t*-butyl methyl ether (1 mL) was added. The mixture was mixed for 1 min and centrifuged (3000 rev min^{-1}, 15 min, +4°C). Supernatant (900μL) was evaporated at 30°C under a stream of air, the residue was re-constituted with ethanol (50 μL) and 40 μL was injected on to a 250 × 4·6 mm *S*-naphthylurea chiral column (SFCC Shandon, Cergy-Pontoise, France); hexane–2-propanol–methanol, 65:5:30 (v/v), containing 0·003% triethylamine was used as mobile phase at a flow rate of 1·5 mL min^{-1}. The UV detector was set at 285 nm.

Data analysis

Concentrations of (+)- and (−)-mefloquine were compared by use of Student's *t*-test for unpaired samples, with a level of significance set at $P = 0.05$. Pharmacokinetic analysis was performed using Siphar 4·0 software. The elimination half-life values were calculated from the slope of the terminal log-linear portion of the plasma concentration–time plot.

Results

Brain–plasma partition

The concentrations of (±)-mefloquine, (+)-mefloquine, (−)-mefloquine and mefloquine metabolite after administration of the racemic mixture are presented in Table 1. Maximum concentrations, C_{max}, of each compound were observed in the plasma and in the brain 12 h after the last dose. In plasma the concentrations of (+)-mefloquine were 2–3 times higher than those of (−)-mefloquine for 4 days after administration of the last dose. The elimination half-life of (+)-mefloquine in plasma was longer than that of (−)-mefloquine (153 compared with 95 h). In brain, in contrast with plasma, we measured

significant ($P < 0.001$) differences between the mean brain concentrations of the two stereoisomers, that of (−)-mefloquine being larger. A similar trend was observed in brain/-plasma ratios. Elimination half lives of (+)- and (−)-mefloquine were similar.

Mefloquine metabolite could be quantified in the plasma but not in the brain.

Distribution of mefloquine enantiomers in specific cerebral regions

The concentrations of racemic mefloquine and its enantiomers in different regions of the brain after administration of the racemic mixture and the separated enantiomers are presented in Table 2. Mefloquine accumulates mainly in hippocampus. In all parts of the cerebral regions, concentrations of (−)-mefloquine were higher than those of (+)-mefloquine.

We compared (+)-mefloquine concentrations inside the brain after administration either of the racemic mixture or of the (+) enantiomer. The data show that higher (+)-mefloquine concentrations are observed when the racemic mixture is administered ($P < 0.001$, Student's t-test). This phenomenon was not observed for (−)-mefloquine.

Plasma levels of mefloquine metabolite could be quantified when rats were treated with (−)-mefloquine whereas mefloquine metabolite was just detectable when rats were given (+)-mefloquine (Table 2). Mefloquine metabolite was not detectable in the brain.

Discussion

Our study has shown stereoselectivity in the pharmacokinetics of mefloquine in the rat. After oral administration of 50 mg kg^{-1} racemic mefloquine for 22 days plasma concentrations of (+)-mefloquine were at least twice as high as those of (−)-mefloquine, and mefloquine metabolite was detectable up to 240 h after the last dose. Conversely, in the brain, concentrations of (−)-mefloquine were higher than those of (+)-mefloquine, and mefloquine metabolite was not detectable. The dose of 50 mg kg^{-1} was chosen because it results in plasma concentrations in rats similar to those observed in man after therapeutic doses.

These results suggest that mefloquine, but not mefloquine metabolite, crosses the blood–brain barrier and that passage seems to be stereoselective in favour of (−)-mefloquine. It is interesting to note that in plasma stereoselectivity in man is the opposite of that in the rat. After administration of the racemic mixture, higher concentrations of the (−) enantiomer are observed in man (Gimenez et al 1994) whereas higher concentrations of the antipode are quantified in rat.

This stereoselectivity might be explained by one or more stereoselective pharmacokinetic processes, for example absorption, excretion, metabolism and distribution.

Concerning absorption, if drugs are absorbed by a passive process the absorption is not stereoselective; certain chiral drugs can, however, be absorbed stereoselectively if the absorption process is active (Jamali et al 1989). The mechanism is unknown for mefloquine.

Table 1. Concentrations (± s.d.; n = 5) of (±)-mefloquine, (+)-mefloquine, (−)-mefloquine and mefloquine metabolite in the plasma (μmol L^{-1}) and the brain (μmol g^{-1}) after the last oral administration of 50 mg kg^{-1} racemic mefloquine in rats (administration for 22 days).

(h)	0 h	12 h	24 h	48 h	72 h
Plasma					
(±)-Mefloquine	7·22 ± 1·36	8·36 ± 2·4	7·8 ± 2·26	5·28 ± 0·7	3·6 ± 0·89
(+)-Mefloquine	4·81 ± 0·98	6·66 ± 1·82	5·74 ± 1·76	3·96 ± 0·54	2·77 ± 0·55
(−)-Mefloquine	2·41 ± 0·42	2·28 ± 0·50	2·08 ± 0·51	1·32 ± 0·26	0·83 ± 0·40
Mefloquine metabolite	7·5 ± 4·9	7·8 ± 4·1	7·2 ± 4·5	5·6 ± 2·1	3· 1 ± 1·0
Brain					
(±)-Mefloquine	0·09 ± 0·012	0·113 ± 0·02	0·093 ± 0·012	0·067 ± 0·021	0·061 ± 0·011
(+)-Mefloquine	0·029 ± 0·008	0·043 ± 0·006	0·038 ± 0·007	0·026 ± 0·006	0·024 ± 0·005
(±)-Mefloquine	0·061 ± 0·009	0·07 ± 0·014	0·055 ± 0·006	0·041 ± 0·013	0·037 ± 0·006
Brain/plasma ratios (nmol g^{-1})/(nmol mL^{-1})					
(+)-Mefloquine	6·0 ± 3	6·5 ± 1	6·6 ± 1	6·5 ± 2	8·6 ± 2
(−)-Mefloquine	26 ± 4	31 ± 3	27 ± 6	31 ± 7	44 ± 13

(h)	96 h	192 h	240 h	336 h	408 h	Half-life
Plasma						
(±)-Mefloquine	5·32 ± 1·46	4·24 ± 1·29	3·64 ± 0·88	2·1 ± 0·74	ND*	157
(+)-Mefloquine	3·94 ± 1·16	3·68 ± 0·96	3·26 ± 0·84	2·05 ± 0·68	ND	153
(−)-Mefloquine	1·38 ± 0·41	0·61 ± 0·41	0·43 ± 0·38	0·005 ± 0·07	ND	95
Mefloquine metabolite	2·4 ± 0·4	1·1 ± 0·5	1·1 ± 0·7	NQ†	ND	76
Brain						
(±)-Mefloquine	0·043 ± 0·21	0·027 ± 0·01	0·028 ± 0·016	0·009 ± 0·002	ND	94
(+)-Mefloquine	0·02 ± 0·01	0·013 ± 0·005	0·013 ± 0·007	ND	ND	98
(±)-Mefloquine	0·023 ± 0·009	0·014 ± 0·005	0·015 ± 0·007	ND	ND	94
Brain/plasma ratios (nmol g^{-1})/(nmol mL^{-1})						
(+)-Mefloquine	5·1 ± 2	3·5 ± 1	3·9 ± 2			
(−)-Mefloquine	16 ± 5	22 ± 6	34 ± 18			

* Not detectable. †Not quantifiable.

Table 2. Concentrations (± s.d., n = 8) of (±)-mefloquine, (+)-mefloquine, (−)-mefloquine and mefloquine metabolite in the regions of the brain and in the plasma 24 h after the last oral administration of 50 mg kg^{-1} (±)-mefloquine, 25 mg kg^{-1} (+)-mefloquine or 25 mg kg^{-1} (−)-mefloquine every day for 22 days.

Region	Brain	Cortex	Cerebellum	Hippocampus	Striatum	Hypothalamus	Plasma (μmol L^{-1})
Organ weight (mg)	1410 ± 80	582 ± 88	254 ± 25	137 ± 18	64 ± 17	28 ± 4·5	
Administration of (±)-mefloquine							
(±)-Mefloquine nmol g^{-1}	90 ± 10	81 ± 13	27 ± 8	110 ± 14	85 ± 13	50 ± 14	6·2 ± 1·2
nmol $organ^{-1}$	128 ± 10	49 ± 18	7 ± 2	17 ± 5	5·3 ± 2	1 ± 0·7	
(+)-Mefloquine nmol g^{-1}	33 ± 6	21 ± 10	11 ± 2	48 ± 11	36 ± 12	15 ± 10	4·1 ± 0·9
nmol $organ^{-1}$	46 ± 8	14 ± 4	3 ± 1	7 ± 1	2 ± 1	0·5 ± 0·4	
(−)-Mefloquine nmol g^{-1}	57 ± 9	52 ± 14	15 ± 5	62 ± 14	48 ± 9	34 ± 11	2·1 ± 0·4
nmol $organ^{-1}$	81 ± 10	31 ± 12	4 ± 1	9 ± 1	3 ± 1	1 ± 0·5	
Mefloquine metabolite	ND*	ND	ND	ND	ND	ND	3·7 ± 1·2
Administration of (+)-mefloquine							
(+)-Mefloquine nmol g^{-1}	15 ± 4	25 ± 6	20 ± 4	41 ± 8	29 ± 7·5	9 ± 3	3·7 ± 0·4
nmol $organ^{-1}$	20 ± 6	10 ± 2	4 ± 2	5 ± 3	2 ± 1	0·3 ± 0·1	
(−)-Mefloquine	ND	ND	ND	ND	ND	ND	ND
Mefloquine metabolite	ND	ND	ND	ND	ND	ND	NQ†
Administration of (−)-mefloquine							
(−)-Mefloquine nmol g^{-1}	63 ± 9	74 ± 11	38 ± 11	88 ± 16	85 ± 14	24·4 ± 8·4	2·5 ± 0·5
nmol $organ^{-1}$	90 ± 15	53 ± 6	12 ± 4	11 ± 2	5 ± 2	0·6 ± 0·3	
(+)-Mefloquine	ND	ND	ND	ND	ND	ND	ND
Mefloquine metabolite	ND	ND	ND	ND	ND	ND	2·3 ± 0·8

*Not detectable. †Not quantifiable.

When drug excretion is active it can also be stereoselective. Mu et al (1975) showed that faecal excretion was the major route of elimination of mefloquine in rats even though glomerular filtration is low because of extensive binding of mefloquine to plasma and tissue proteins. Rozman et al (1978) corroborated the observation for mice despite some differences between the two rodent species. However, the excretion mechanism has not been fully elucidated for mefloquine and its stereoselectivity has yet to be studied.

More generally, the stereoselectivity of drug pharmacokinetics arises from differences between the metabolism of the two enantiomers. It has been demonstrated that (−)-mefloquine is transformed more rapidly than (+)-mefloquine by rat hepatic homogenates (Koch & Blaschke 1990), suggesting stereospecific metabolism of mefloquine in favour of the (−) enantiomer. This could explain why, in our study, mefloquine metabolite was quantified in plasma after administration of the (−) enantiomer but not after administration of the antipode.

The differences between the distribution of the two enantiomers depends on the affinity of the molecule for plasma or tissue proteins.

The blood–brain barrier, formed by brain capillaries whose endothelial cells have tight intercellular junctions, is located between the blood and the extracellular space of the brain. It acts as a selectively permeable membrane, preventing large or charged molecules from passing out of the bloodstream and into the brain. Transcellular passage of drugs from the bloodstream to the brain occurs selectively, in a manner dependent on the ability of the molecules to penetrate cell membranes (Van Bree et al 1992). The major factors involved in this process are drug lipophilicity and ionization, molecular size and binding to plasma protein. Therefore, small and lipophilic molecules with low protein binding are likely to penetrate into the central nervous system. Mefloquine is quite a large lipophilic molecule which is very tightly bound (98–99%) to plasma protein (Mu et al 1975).

The passage across the blood–brain barrier could be explained by its lipophilicity and could also be because of the existence of carrier or receptor systems (Rapoport et al 1979; Van Bree et al 1992). The blood–brain barrier is known to be the site of a high level of enzyme activity directed towards the inactivation of exogenous compounds. These enzymes could play an important part in a stereoselective enzyme-dependent metabolism of the drug (Andus et al 1992; Grieg 1992).

The selectivity of mefloquine brain distribution might thus be the consequence of four mechanisms, associated or not: active passage through the blood–brain barrier; passive passage through the blood–brain barrier with higher availability of (−)-mefloquine in the plasma compartment (stereospecific protein binding); possible metabolism in the brain; and stereospecific efflux.

Because the elimination half-lives of (+)- and of (−)-mefloquine in the brain were similar (Table 1), mefloquine efflux is not selective and should not be involved in the stereoselectivity observed.

Caillon et al (1992) suggested that the main metabolite did not cross the blood–brain barrier. This is consistent with our study and our inability to detect the main mefloquine metabolite in the brain. Because of its carboxyl group, mefloquine metabolite is more polar than mefloquine and is probably ionized at physiological pH. These two factors probably explain the limited uptake of mefloquine metabolite by the brain.

Neurotoxicity of a drug might result from a specific pharmacological action on the central nervous system. This might also be a result of a process of accumulation in the case of a prolonged exposure or after administration of high doses of the drug.

The absence of mefloquine metabolite in the brain of rats seems to indicate that the metabolite is probably not involved in mefloquine neurotoxicity. Mefloquine accumulates in the brain, especially in the hippocampus. This specific structure is

known to have a low sensitivity threshold and accumulation in this part of the brain could partly explain the ability of mefloquine to provoke seizures. A similar phenomenon has been described with quinolones (Kouichi et al 1989).

In conclusion, the results of the study suggest that mefloquine but not mefloquine metabolite crosses the blood–brain barrier and that this passage is stereoselective in favour of (−)-mefloquine. To investigate this phenomenon further it would be interesting to determine the amount of mefloquine required to induce seizures in the rat and to study whether there is any relationship between the occurrence of seizures and the concentrations of the drug in the cerebrospinal fluid.

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