Pharmacokinetics of the S(+) and R(–) enantiomers of vigabatrin during chronic dosing in a patient with renal failure

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Aims To study the pharmacokinetics of vigabatrin in a patient affected with tuberous sclerosis who developed major agitation and aggression, while receiving vigabatrin orally (1.5 g every 12 h) and in whom impaired renal function was diagnosed.

Methods The patient received vigabatrin (0.5 g day^{−1}). A pharmacokinetic study of the S(+) and R(–) enantiomers of vigabatrin was performed before and during dialysis. Plasma concentrations were measured at 0, 1, 2, 3, 4, 6, 12, 18 and 24 h by a specific GCMS assay.

Results Before dialysis, the maximum and minimum plasma concentrations of vigabatrin at steady-state were lower for the S(+) than for the R(–) enantiomer, while the apparent oral clearance was higher for the S(+) than for the R(–) enantiomer (2.97 vs 0.48 l h^{−1}). In addition, the haemodialysis clearance was similar for the two enantiomers (4.96 vs 5.15 l h^{−1}).

Conclusions Vigabatrin is an irreversible inhibitor of GABA-transaminase, effective in the treatment of drug-resistant epilepsy and reported to be eliminated unchanged by renal excretion. Although vigabatrin is known to have stereoselective kinetics, the difference in plasma dry concentrations and pharmacokinetics of the S(+) and R(–) enantiomers that we observed during long term administration at high doses in a patient with impaired renal function, has not been reported before. The question remains of the potential toxicity of the high levels of the R(–) enantiomer.

Keywords: vigabatrin, enantiomers, renal failure

Introduction

Vigabatrin (γ-vinyl GABA) is a selective, enzyme-activated, irreversible inhibitor of GABA-transaminase, the enzyme catalysing the catabolism of the neurotransmitter GABA [1, 2]. Vigabatrin produces a dose-related increase in CSF GABA [3]. It reduces the frequency of partial seizures by at least 50% in about half of adult and paediatric patients with drug-resistant epilepsy [4–7].

Vigabatrin is a racemic mixture of two enantiomers S(+) and R(–), the S(+) enantiomer being the active compound. The drug is reported not to be protein bound and to be eliminated unchanged by renal excretion [8, 9]. The pharmacokinetics of the two enantiomers are very similar [10, 11].

Here, we describe a 15 year old epileptic patient, who was treated with vigabatrin for more than 6 months at the standard dose of 3 g day^{−1} and was admitted to hospital with end-stage renal failure. A pharmacokinetic study of the drug was performed before the decision to dialyse and during a dialysis session. The pharmacological data demonstrated major differences in the disposition of the two enantiomers.

Methods

Patient

The patient, born in 1980, was affected with tuberous sclerosis, diagnosed at the age of 3 months when she developed partial seizures, with secondary generalized tonic-clonic seizures. From 1980 to 1993, she received various anti-epileptic drugs, including carbamazepine alone or in combination with phenobarbitone, with phenytoin or clobazam, without complete remission of seizures. She also presented with behavioural disturbances with social disability. In 1993, vigabatrin (3 g day^{−1}) was added to carbamazepine (600 mg day^{−1}). The frequency of seizures decreased to 2 to 3 per week. Sixteen months later, the patient complained of fatigue and presented with nausea and vomiting and she developed important additional behavioural changes, while routine laboratory tests revealed that serum creatinine was 770 µmol l^{−1}. At admission, her weight was 64 kg, clinical examination revealed major agitation and aggression, alternating with phases of confusion and drowsiness. Laboratory tests included haemoglobin, 5.4 g dl^{−1}, serum creatinine 848 µmol l^{−1} and creatinine clearance was 10 ml min^{−1} (1.73 m²^{−1}). The patient received a blood transfusion and erythropoietin. Renal echography revealed multiple microcysts and end-stage renal failure was attributed to tuberous

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sclerosis. At that time, she was receiving vigabatrin (1.5 g every 12 h), carbamazepine (200 mg every 12 h) and pipamperone (40 mg every 12 h). Plasma concentrations of carbamazepine and carbamazepine epoxide were 6.9 and 1.9 mg l⁻¹ respectively, while plasma concentrations of the S(+) and R(-) enantiomers of vigabatrin were 69 and 217 mg l⁻¹. The neurologic manifestations were attributed to vigabatrin and the dose was decreased to 1g every 12 h then to 0.5 g daily. Renal dialysis was performed, on the basis of three sessions per week. The patient continued to receive vigabatrin (0.5 g day⁻¹) and carbamazepine (200 mg every 12 h). Neurologic symptoms resolved following dosage reduction and dialysis. She is now treated with vigabatrin 0.75 g day⁻¹.

Drug analysis

Blood samples (1 ml) were collected in heparinized tubes, centrifuged and kept frozen (-20°C) until analysis. The enantiomers of vigabatrin were measured using a specific gas chromatography mass spectrometry procedure [10]. The coefficients of variation were less than 13.8% at all concentrations from 0.5 to 50 µg ml⁻¹ for both enantiomers.

Pharmacokinetics in end-stage renal failure Blood samples were collected before drug administration and at 1, 2, 3, 4, 6, 12, 18 and 24 h after administration. Pharmacokinetic analysis was performed with use of compartment independent methods. The oral apparent clearance was determined using the following relationship:

$$CL/F = (\text{Dose (E)} / \tau) / (AUC / \tau)$$

in which *F* is the bioavailability factor, *E* is the dose of each enantiomer (i.e. half the oral administered dose), τ is the interval between two administrations, AUC is the area under the plasma concentration time curve between two administrations at steady-state.

Haemodialysis plasma clearance Haemodialysis clearance (CL_{HD}) was calculated using the following relationship:

$$CL_{HD} = [(Q_P \times C_A) - (Q_P - Q_U) \times C_V] / C_A$$

where *C_A* and *C_V* are the concentrations in the arterial and venous segments of the blood flow loop, *Q_P* is the average plasma flow rate (equal to: blood flow rate × (1 - haematocrit)) and *Q_U* is the ultrafiltrate flow rate.

Results

The pharmacokinetic parameters of the S(+) and R(-) enantiomers of vigabatrin were determined at steady-state, after 22 days of treatment with an oral dose of 0.5 g day⁻¹ (Table 1 and Figure 1). The *C_{min}* values were 2.2 and 17.4 mg l⁻¹ for the S(+) and R(-) enantiomers respectively. The *C_{max}* value of the S(+) enantiomer was lower than that of the R(-) enantiomer (5.9 vs 27.8 mg l⁻¹) and the difference (*C_{max}* value - *C_{min}* value) was 3.7 and 10.4 mg l⁻¹ for the S(+) and R(-) enantiomers respectively. In addition, the apparent oral clearance was much higher for the S(+) than for the R(-) enantiomer. Because

Table 1 Pharmacokinetic parameters of the S(+) and R(-) enantiomers of vigabatrin in a patient with end-stage renal failure, before and during dialysis.

	S(+)	R(-)	S(+)/R(-) ratio
<i>Not dialyzed</i>			
<i>C_{max}</i> (mg l ⁻¹)	5.9	27.8	0.21
<i>C_{min}</i> (mg l ⁻¹)	2.2	17.4	
<i>C_{max}</i> - <i>C_{min}</i> (mg l ⁻¹)	3.7	10.4	/
<i>t_{max}</i> (h)	2	2	/
AUC 24 h (mg l ⁻¹ h)	84	523	0.16
CL/F (l h ⁻¹)	2.97	0.48	6.19
<i>Dialyzed</i>			
Amount recovered over 4 h in the dialysate (mg)	102	351	0.29
CL _{HD} (l h ⁻¹)	4.96	5.15	0.96

Figure 1 Pharmacokinetic profile of the S(+) (◆) and R(-) (■) enantiomers of vigabatrin, in a patient with end-stage renal failure, receiving 0.5 g day⁻¹ after chronic overdose.

the duration of sampling was limited to 24 h, the terminal half-life could only be estimated for the S(+) enantiomer and it was 16 h. It is certainly much longer for the R(-) enantiomer.

The patient underwent haemodialysis sessions of 4 h duration. The haemodialysis clearance was measured while the patient was receiving 0.5 g every 24 h (7.8 mg kg⁻¹ day⁻¹) and is presented in Table 1. The amount of R(-) enantiomer recovered in the dialysate over 4 h was 351 mg, while it was 102 mg for the S(+) enantiomer. The haemodialysis clearance was similar for the two enantiomers: 4.96 l h⁻¹ for the S(+) and 5.15 l h⁻¹ for the R(-) enantiomer.

Discussion

Vigabatrin, a structural analogue of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), is a racemic mixture of two enantiomers S(+) and R(-). The S(+) enantiomer is pharmacologically active while the R(-) enantiomer is inactive.

Vigabatrin is normally well tolerated and the incidence of side-effects appears low. Among them, the most frequent in children are agitation and hyperkinesia, estimated to occur in 15 to 25% of epileptic patients [5]. It usually appears

during the first months of treatment but often disappears by reducing the dose. It mainly involves patients with mental retardation and preexisting hyperkinesia [12–15]. As previously stated, our patient developed irritability, agitation and anxiety progressing to extreme aggression. The overall incidence of such disorder is approximately 1.5%. She had all the predisposing factors to hyperkinesia on vigabatrin, i.e. lesions of the central nervous system, mental retardation and high doses of the drug [12].

The patient was treated chronically with standard doses of vigabatrin while developing progressive renal failure and major neurotoxicity. She had high plasma concentrations of the active S(+) enantiomer but in addition the R(–) enantiomer accumulated to levels higher than that of the S(+) enantiomer.

The disposition of vigabatrin has been studied in most cases after administration of a single oral dose of the racemate. The drug is reported to be well absorbed, not bound to plasma proteins, and mainly eliminated unchanged in urine [8, 9]. Its elimination half-life is approximately 7 h. A multiple dose study, limited to 4.5 days did not demonstrate changes in the pharmacokinetics of racemic vigabatrin [8].

Data on the pharmacokinetics of the individual S(+) and R(–) enantiomers are only limited. Their disposition studied in healthy volunteers [11], in pediatric epileptic patients [10] and neonates [16] is reported to be very similar. However, during single dose studies, in adults and children with normal renal function, the peak plasma concentrations of the R(–) enantiomer were consistently two times higher while the recovery of unchanged drug in urine was lower for the S(+) than for the R(–) enantiomer [11]. The major differences that we observed in the disposition of the two enantiomers were unexpected but in agreement with stereoselective kinetics, probably of renal elimination. However, an effect on hepatic metabolism or absorption cannot be ruled out.

There is no difference in the pharmacokinetics of vigabatrin between normal volunteers and epileptic patients under add-on therapy for at least 4 weeks [7]. The pharmacokinetics of the drug is altered in patients with reduced renal function and dosage reduction is necessary to avoid drug accumulation leading to toxicity [17, 18]. During chronic overdosage associated with renal failure, the difference in the pharmacokinetics of the two enantiomers is unexplained and the potential therapeutic and toxic consequences of the high R(–) enantiomer concentrations remain to be investigated [19].

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