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Pharmacokinetics of the individual enantiomers of vigabatrin (γ-vinyl GABA) in epileptic children

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1 The pharmacokinetics of the enantiomers of vigabatrin were investigated after oral administration of a single 50 mg kg^{-1} dose of the racemate to two groups of six epileptic children (I: 5 months–2 years, II: 4–14 years).

2 The mean (± s.d.) values of maximum plasma concentration and area under the plasma concentration-time curve of the R(−) enantiomer were significantly higher than those of S(+) vigabatrin in both groups : R(−) C_{max}: 21 ± 6.6 (I)–41.3 ± 13.9 (II) *vs* S(+) C_{max}: 13.9 ± 4.5 (I)–23.8 ± 12.2 (II) mg l^{-1}; R(−) AUC: 106 ± 28.5 (I)–147 ± 34 (II) *vs* S(+) AUC: 90.9 ± 27.9 (I)–117 ± 26 (II) mg l^{-1} h. In group I, the half-life of the R(−) isomer was significantly shorter than that of the S(+) isomer; in group II, the half-lives were comparable.

3 For the R(−) enantiomer the area under the curve, and the elimination half-life increased linearly with age.

4 During chronic administration (50 mg kg^{-1} vigabatrin racemate twice a day for 4 days), the morning trough plasma drug concentrations did not increase.

Keywords vigabatrin enantiomers chiral pharmacology pharmacokinetics epileptic children

Introduction

Vigabatrin (γ-vinyl GABA) is a selective enzyme activated irreversible inhibitor of GABA transaminase (Metcalf, 1979), the enzyme responsible for GABA inactivation. As such, vigabatrin increases GABA concentrations in CSF (Grove *et al.*, 1980, 1981) and is effective in the treatment of refractory epilepsy in adults (Browne *et al.*, 1987; Loiseau *et al.*, 1986; Rimmer & Richens, 1984). The drug is supplied as a racemate. However, only the S(+) enantiomer is active in experimental animals (Meldrum & Murugaiah, 1983). In healthy adults the pharmacokinetics of the two enantiomers are slightly different (Haegele & Schechter, 1986); the active S(+) enantiomer showing a lower maximum plasma concentration and area under the plasma concentration-time curve than the inactive R(−) enantiomer. However, the presence of the R(−) enantiomer of vigabatrin does not influence the pharmacokinetics of the active S(+) enantiomer, nor does chiral inversion occur *in vivo* (Haegele & Schechter, 1986). Most of the dose (60–80%) of vigabatrin is excreted unchanged in urine within

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24 h (Schechter, 1986). Therefore, interactions with other anticonvulsants which are cleared principally by hepatic metabolism are unlikely. The purpose of this study was to describe possible age related differences in the pharmacokinetics of vigabatrin during maturation and to determine the extent of enantiospecificity in the kinetics.

Methods

Patients

Two groups of six children with refractory epilepsy entered the study. Group I comprised six infants aged 12.1 ± 5.9 months (range 5–22 months) and weighing 8.9 ± 2.4 kg (range 5.4–12 kg). Group II comprised six children aged 8.7 ± 3.8 years old (range 4.6–14.2 years) and weighing 31 ± 15.4 kg (range 14.5–55 kg). All patients had uncontrolled seizures in spite of antiepileptic treatment with between 1 and 3 of the following drugs: carbamazepine, clobazam, phenytoin, phenobarbitone and valproate. The dosage of these drugs was kept constant throughout the pharmacokinetic study. The patients were given a single oral dose of vigabatrin, in addition to current therapy, administered as 50 mg kg^{-1} of the racemate (not exceeding 1.5 g in older children). After 24 h, the treatment was continued as 50 mg kg^{-1} twice a day.

Venous blood samples (500 μl) were collected before and at 0.5, 1, 2, 3, 6, 9, 12, 24 h after the first administration. Samples were drawn before and 1 h after the morning dose for 4 days during chronic treatment. Urines were collected for 20–23 h after the initial dose. Samples were frozen and stored at −20° C until assay.

Analytical methods

The stereospecific assay of the enantiomers of vigabatrin used a gas chromatography mass spectrometry procedure modified slightly from that of Haegele *et al.* (1983). Briefly, the plasma sample (100 μl) was mixed with the internal standard (20 μl (RS)-γ-acetylenic GABA) and deproteinised with methanol (200 μl). After centrifugation the supernatant was evaporated to dryness under a stream of nitrogen at room temperature. The residue was esterified with propanol HCl (prepared by bubbling HCl gas for 1 h into 200 ml of propanol) at 110° C for 20 min. After cooling the solvent was evaporated under nitrogen at room temperature and the residue was redissolved in dichloromethane (100 μl) and trifluoracetic anhydride (100 μl) and left to react for 30 min at room temperature. The solvent was evaporated to dryness under nitrogen at ambient temperature and the residue was redissolved in hexane (100 μl). The separation of the derivatized enantiomers of R(−) and S(+) vigabatrin and the internal standard was performed using a 25 m × 0.22 mm Chirasil-L-Val capillary column (Chrompack). Detection was by chemical ionization using ammonia and measurements were made using selected ion monitoring (SIM) at m/z 268 (γ-vinyl GABA) and m/z 266 (γ-acetylenic GABA). The calibration curve was linear for concentrations from 5 to 50 mg l^{-1}. The reproducibility was 5.3% (n =10) and 4.1% (n = 10) for 5 mg l^{-1} R(−) and S(+) vigabatrin, respectively.

Data analysis

For each enantiomer the time to maximum plasma drug concentration (t_{max}) and the maximum concentration (C_{max}) were direct observations. The areas under the plasma drug concentration-time curves (AUC) were calculated by standard procedures (Gibaldi, 1977). The elimination half life ($t_{½}$) was calculated from the slope (λ_z), estimated by log linear regression, of the terminal phase of the plasma drug concentration-time curve. C_{max} and AUC values were normalised for a 50 mg kg^{-1} dose in older children. Dose-linear kinetics have been demonstrated for vigabatrin (data on file Merell-Dow).

A one way analysis of variance for paired values (for the two enantiomers) was used to compare the pharmacokinetic parameters in the two groups of patients. When interaction was significant an analysis of variance for paired values was used for comparison of enantiomers in the same group. The sign test was used to compare t_{max} values between enantiomers in the same children and the median test was used to compare t_{max} values between groups.

The renal clearance (CL_R) of each isomer was estimated from the ratio $Ae(t)$/AUC(t) where $Ae(t)$ is the amount of drug recovered in urine up to t h and AUC(t) is the area under the plasma drug concentration curve over the same time interval.

A two way analysis of variance for paired values (the times during chronic administration) was used to compare C_{min} and C(1 h) over 4 days for each enantiomer.

Relationships between the different kinetic parameters and age were examined by linear regression.

Values are presented as mean and s.d. except in the figures where s.e. mean is used.

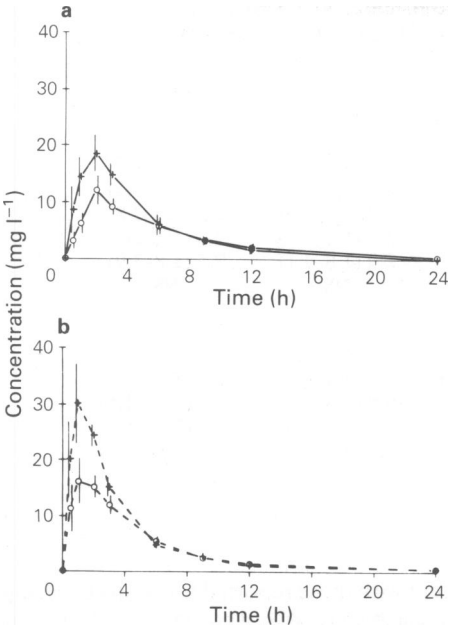

Figure 1 Mean (± s.e. mean) plasma concentrations (mg ml^{-1}) of the enantiomers of vigabatrin (+ R, ○ S) after oral administration of 50 mg kg^{-1} vigabatrin as the racemate to children

a : group I (1 month–2 years)
b : group II (2–15 years)

Results

Comparison between age groups

As shown in Table 1, AUC values for each isomer were significantly lower in infants (Group I) than in children (Group II). There was no difference in elimination half-life between children and infants.

Values of AUC and $t_{½}$ of the R(−) enantiomer increased linearly with age ($r = 0.74$, $P < 0.01$ and $r = 0.82$, $P < 0.01$, respectively). The kinetic parameters of the S(+) enantiomer did not vary significantly with age.

Comparison between enantiomers

The mean C_{max} value of the S(+) enantiomer was significantly lower than that of the R(−) enantiomer in both age groups.

The mean R(−)/S(+) ratios of C_{max} were 1.6 and 1.8 in groups I and II, respectively. However the plasma concentrations of both enantiomers were similar between 6 and 24 h after administration (Figure 1a, b).

Table 1 Mean pharmacokinetic parameters of the R(−) and S(+) enantiomers of vigabatrin after a single oral dose of vigabatrin as the racemate (50 mg kg^{-1}) in two groups of epileptic children

	Group I		*Difference between enantiomers*	*Group II*		*Difference between enantiomers*	*Difference between age groups*	
	S	*R*		*S*	*R*		*S*	*R*
t_{max} (h)	2.85 ± 1.61	2.35 ± 1.87	NS	1.36 ± 0.96	1.28 ± 0.58	NS	*	NS
C_{max} (mg l^{-1})	13.8 ± 4.4	20.6 ± 5.7	–	19.4 ± 6.9	34.7 ± 12.1	–	–	–
C_{max}^{c} (mg l^{-1})	13.9 ± 4.5	21.0 ± 6.6	*	23.8 ± 12.2	41.3 ± 13.9	*	NS	*
$t_{½}$ (h)	5.65 ± 1.52	2.87 ± 1.03	*	5.47 ± 1.93	5.68 ± 2.86	NS	NS	*
AUC (mg l^{-1} h)	90.7 ± 31.3	104.0 ± 26.1	–	98.3 ± 23.5	123.0 ± 26.1	–	–	–
AUC^{c} (mg l^{-1} h)	90.9 ± 27.9	106.0 ± 28.5	*	117.0 ± 26.0	147.0 ± 34.0	*	*	*

[c] calculated for a dose of 50 mg kg^{-1}
* significant at $P < 0.05$
NS = not significant

The mean AUC of the S(+) enantiomer was significantly lower than that of the R(−) enantiomer in both age groups.

In group I the half-life of the S(+) enantiomer was significantly longer than that of the R(−) enantiomer.

Table 2 Plasma concentrations (mg l^{-1}) of the enantiomers of vigabatrin during 4 days of continuous treatment (50 mg kg^{-1} twice a day) before the morning dose (minimum) and 1 h after dosing (1 h value)

	Group I (n = 5)		*Group II* (n = 6)	
	S (+)	*R (−)*	*S (+)*	*R (−)*
Minimum	*Mean (range)*	*Mean (range)*	*Mean (range)*	*Mean (range)*
Day 1	3.8 (1.9–7.2)	2.9 (1.2–5.3)	2.6 (1.9–3.9)	3.0 (1.6–6.5)
Day 2	2.7 (1.1–5.7)	2.6 (1.5–3.6)	2.4 (1.7–2.9)	2.3 (1.5–3.8)
Day 3	2.0 (0–3.8)	1.5 (0–2.8)	2.5 (1.5–3.5)	2.3 (1–3.2)
Day 4	2.1 (1.5–2.4)	1.5 (1.2–1.9)	2.9 (1.8–4.1)	2.5 (1.8–3.9)
Inter-day variation	NS	NS	NS	NS
1 h value				
Day 1	13.6 (1.2–29.2)	20.7 (0.6–37.5)	11.8 (5–24)	21.0 (3.5–55.1)
Day 2	13.2 (2–35.7)	20.3 (1.6–55.4)	16.8 (2.8–35)	28.0 (4.3–51.5)
Day 3	10.3 (2.1–22.6)	16.1 (1.5–35)	17.4 (3.7–40)	24.6 (7.3–48)
Day 4	11.5 (3.7–14.4)	20.9 (8.1–29.1)	16.0 (3.8–42.6)	24.0 (6.1–71.7)
Inter-day variation	NS	NS	NS	NS

Urinary excretion

Only consecutive complete urine collections were pooled for the measurement of R(−) and S(+) excretion. Thus, it was only possible to calculate the amount excreted in five children, two from group I and three from group II. The percentage of the dose recovered as R(−) and S(+) isomers varied between 21.2–47.8 and 20.2–37.2, respectively. The ratio of recovery of R(−) to S(+) was greater than unity (range: 1.04–1.52). The renal clearance calculated in these five patients varied from 0.059–0.187 and 0.031–0.120 l h^{-1} kg^{-1} for the R(−) and S(+) enantiomers, respectively.

Repetitive dosing

During chronic administration, the morning minimum drug concentration (C_{min}) was measured for 4 consecutive days. C_{min} did not increase significantly over the 4 day period for either enantiomer or either group (five patients in group I, six patients in group II) (Table 2). The concentrations of vigabatrin 1 h after the morning dose did not increase significantly over this 4 day period. The mean ratio of R(−) to S(+) enantiomer concentrations 1 h after drug administration was greater than unity (1.42–1.95) for both groups.

Discussion

Our results in children with regard to enantiospecific pharmacokinetics of vigabatrin are consistent with those reported for adults by Haegele & Schechter (1986), who stated that maximum plasma concentrations of R(−) enantiomer always exceeded those of the active S(+) enantiomer. Furthermore in adults the AUC of the R(−) isomer (84.3 ± 11.6 mg l^{-1} h) was higher than of the S(+) form (64.7 ± 7.5 mg l^{-1} h). When corrected for a 50 mg kg^{-1} dose these values are higher than those that we have found in children (R(−): 211 ± 29; S(+): 161 ± 18.7 mg l^{-1} h).

Urinary recovery of both enantiomers within 20–23 h appears to be lower than the 24 h recovery in adults (R(−): 58 ± 5%; S(+): 44 ± 5%) (Haegele & Schechter, 1986). Although values of renal clearances were calculated in five of our patients only, it appears that the values are similar to those observed in adults (Haegele *et al.*, 1986) (R(−): 0.077 ± 0.076; S(+): 0.070 ± 0.018 l h^{-1} kg^{-1}. Schechter (1986) has shown that renal excretion of unchanged drug is the predominant route of elimination in adults and no metabolites of vigabatrin have been identified. Therefore, since renal clearance in children was similar to that in adults a lower AUC in children might be explained by a lower bioavailability.

On chronic administration we have shown that neither enantiomer of vigabatrin accumulates and that the R(−)/S(+) ratio 1 h after administration remained stable and higher than unity. This last observation is consistent with the higher bioavailability of the inactive R(−) enantiomer reported by Haegele & Schechter (1986).

In conclusion, the absence of significant differences in the kinetic parameters of vigabatrin

for the biologically active enantiomer S(+) between the two groups does not support the use of a different dosage regimen according to age between 1 month and 15 years of age. However, clinical data in children are too sparse to confirm this conclusion and since no concentration-effect relationship has yet been established, the dosage should be determined by clinical response rather than by plasma drug concentration.

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