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Influence of concurrent antiepileptic medication on the pharmacokinetics of lamotrigine as add-on therapy in epileptic children

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1 Lamotrigine is a new antiepileptic drug, chemically unrelated to currently used antiepileptic medication. Its pharmacokinetics can be influenced by concomitant antiepileptic medication.

2 This study was performed to assess the pharmacokinetic profile of lamotrigine in three groups of children treated with different types of comedication: drugs known to induce, to inhibit or to have no clinically significant influence on drug metabolism, respectively.

3 Thirty-one children aged 6 months to 5 years were included and received a 2 mg kg^{-1} single oral dose. Lamotrigine plasma profiles were different between the three comedication groups. The half-lives (mean $\pm$ s.d.) were: 7.7 ± 1.8 h, 21.9 ± 6.8 h, 44.7 ± 10.2 h in the 'inducer', 'other' and 'inhibitor' groups respectively.

4 Patients were then dosed to steady state, with the dosage adjusted on the basis of the single dose pharmacokinetics to achieve a minimum plasma concentration between 1.5 and 3 mg l^{-1}. The mean minimum plasma concentration for the three groups was 2.54 ± 1.28 mg l^{-1} at steady state.

5 Dosage of lamotrigine can be optimised with knowledge of the metabolic effects of antiepileptic comedication.

Keywords lamotrigine antiepileptic drugs epilepsy pharmacokinetics children

Introduction

Lamotrigine is a recently developed antiepileptic drug (AED), chemically unrelated to currently used antiepileptic medication. It is thought to exert its antiepileptic effects by blocking voltage-sensitive sodium channels and inhibiting the release of excitatory neurotransmitters, predominantly glutamate [1, 2]. The efficacy of lamotrigine as add-on therapy in adult patients with refractory partial epilepsy has previously been demonstrated [3–5] and improvements in seizure control in children have also been reported [6, 7].

The pharmacokinetics of lamotrigine have been studied in healthy adult volunteers and in adult patients with epilepsy receiving concurrent antiepileptic medication. Lamotrigine is rapidly and virtually completely absorbed after oral administration [8] reaching a maximum plasma concentration (C_{max}) after approximately 1 to 3 h [9, 10]. Both C_{max} and the area under the plasma concentration–time curve (AUC) correlate with lamotrigine dose, indicating linear kinetics in healthy subjects [9]. Elimination occurs mainly by hepatic metabolism, primarily glucuronidation [9].

Alterations in the elimination kinetics of lamotrigine have been observed in adults receiving other AEDs [11]. Coadministration of hepatic enzyme-inducing AEDs such as phenytoin, carbamazepine or phenobarbitone increase the elimination rate of lamotrigine [10, 12] compared with healthy subjects administered lamotrigine alone [9]. Conversely, concomitant administration of sodium valproate, which inhibits hepatic enzymes, decreases the elimination rate of lamotrigine [13]. The opposing effects of enzyme-inducing AEDs and sodium valproate on lamotrigine elimination appear

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to balance each other when these drugs are administered concurrently.

In paediatric patients, there is little information regarding the pharmacokinetics of lamotrigine, although preliminary studies suggest that the effects of concomitant AEDs on lamotrigine elimination are similar to those in adults [14, 15]. The purpose of the present study was to determine the kinetic parameters of lamotrigine after a single oral dose in children with epilepsy who were receiving concurrent treatment with other AEDs, in order to individually adjust the dose regimen. A previous study in adults has suggested that lamotrigine might be efficacious at minimum plasma concentrations ranging from 0.9 to 2.3 mg l^{-1} [12].

Methods

Patients

Thirty-one children (aged 6 months to 5.3 years) with refractory epilepsy and concurrently treated with other AEDs entered the study at the Saint-Vincent de Paul Hospital, Paris, France, between June 1990 and September 1993. Patients meeting the following criteria were included: age up to 5 years, a diagnosis of epilepsy uncomplicated by suspected pseudoseizures, a recognisable seizure type as classified by the International Classification of Seizures (1981) [16], a seizure frequency rate of at least 4 seizures per month during each of the previous 3 months, seizures resistant to first-line medication, concomitant AED treatment unmodified for at least 1 month or absence of response to conventional medication in patients no longer receiving AED treatment. The population was divided into three groups according to the AED comedication:

– group 1 (inducers) : receiving AEDs inducing drug metabolism (carbamazepine: mean 26.2 [10–49] mg kg^{-1}, $n=9$; phenytoin: mean 11.7 [6.25–15.9] mg kg^{-1}, $n=4$);

– group 2 (others): receiving comedication not known to modify drug metabolism (clonazepam, ethosuximide, vigabatrin, progabide, clobazam); or no comedication at all;

– group 3 (inhibitor): receiving sodium valproate (mean 31.2 [16–46] mg kg^{-1}, $n=10$) either alone or associated with comedication not known to modify drug metabolism (vigabatrin, clobazam, clonazepam, ethosuximide).

Exclusion criteria were: serious organic or psychiatric disease (other than epilepsy), progressive neurological disease, a clinically significant abnormal laboratory test result, convulsive status epilepticus that occurred within the previous 6 months or more than once in the previous 2 years (for patients under 2 years a short disease duration prevented definition of a limit), use of an investigational drug in the previous 6 months, treatment with more than two AEDs or chronic use of medication other than AEDs.

Parents or guardians gave written informed consent for each child's participation, and the study was approved by the local ethics committee.

Study design and procedure

Patient eligibility for single dose administration of lamotrigine was assessed by a physical and neurological (including EEG) examination. In addition, haematological and biochemical assessment was conducted and the history of epilepsy (including EEG results) of each patient was recorded.

After this initial screening, patients were hospitalised for 48 h to determine the pharmacokinetic profile of lamotrigine following a single oral dose. Capsules containing lamotrigine 12.5 mg, 25 mg, 50 mg or 100 mg were administered in a combination of approximately 2 mg kg^{-1} body weight. For children unable to swallow capsules, the content was emptied and administered with food.

Blood samples (1 ml) were collected before and 1, 3, 6, 12, 24 and 48 h after administration with one additional sample at the end of the first month treatment just before the morning administration to measure the lamotrigine minimum plasma concentration.

Drug analysis

Plasma lamotrigine concentrations were measured by an internally standardized assay verified by the Wellcome Foundation Ltd, using liquid-liquid extraction followed by normal phase h.p.l.c. with ultra-violet detection [9]. The limit of quantification of the assay was 0.25 mg l^{-1} and the range was 0.25 to 5 mg l^{-1}.

Pharmacokinetic and statistical analysis

Data management, pharmacokinetic and statistical analysis were performed using the TRIOMPHE software. Individual kinetic parameters were determined using a model independent calculation [17]. Recommended dosing intervals were choosen according to the value of the half-life : twice a day for $t_{1/2} < 18$ h and once a day for half-life ≥ 18 h. The recommended dosage was calculated from a simulation using both the dose of the single dose kinetic study and the chosen dosing interval that provided a predicted lamotrigine minimum plasma concentration. The recommended dosage was then calculated by the rule of three using the lamotrigine minimum plasma concentration predicted from the simulation, the dose used in the simulation and the aimed lamotrigine minimum plasma concentration chosen as 2.25 mg l^{-1}, the middle point of the interval 1.5–3 mg l^{-1}. Half the dosage of lamotrigine was given for the first fighteen days, then the full dosage was administered. Comparisons of the calculated parameters in the different groups were performed using the non-parametric Kruskal Wallis test. The influence of age was assessed by linear regression.

Table 1 Patient characteristics according to the comedication group (Mean ± s.d.)

	n	*Age (years)*	*Weight (kg)*	*Single dose (mg kg^{-1}) (kinetic study)*
'Inducers'	11	2.2 ± 1.2	11.7 ± 3.8	1.97 ± 0.36
(group 1)	5M-6F	(0.6–4.0)	(6.7–18.6)	(1.49–2.44)
'Others'	10	2.5 ± 1.4	13.0 ± 4.3	2.10 ± 0.53
(group 2)	6M-4F	(0.5–4.5)	(7.0–20.5)	(1.34–3.13)
'Inhibitors'	10	3.0 ± 1.7	15.1 ± 5.3	2.05 ± 0.30
(group 3)	6M-4F	(0.6–5.3)	(7.5–24)	(1.67–2.55)
P		NS	NS	NS
Total	31 17M/14F	2.6 ± 1.4	13.3 ± 4.6	2.04 ± 0.40

M, Male, F, Female, *P*, Significance of the difference between the three groups for the corresponding parameters.

Results

Patient demographics

Mean age, weight and lamotrigine dose were comparable for each treatment group (Table 1).

Pharmacokinetics

The lamotrigine plasma concentration curves in each treatment group are displayed in Figure 1: they are dependent on the type of concurrent AED medication. The individual kinetic parameters are presented in Table 2.

Mean maximum plasma concentration (C_{max}) differed according to the treatment group and were significantly higher in the group receiving inhibitors (1.33 ± 0.43 mg l^{-1}) than in the group receiving inducers (0.82 ± 0.19 mg l^{-1}). The area under the curve (AUC (0, 48 h)) was significantly different in the three groups increasing from 9.0 ± 2.3 mg l^{-1} h to 25.4 ± 6.3 mg l^{-1} h and to 41.4 ± 142 mg l^{-1} h in the 'inducers', 'others' and 'inhibitors' groups, respectively.

Mean elimination half-life was significantly different in the three groups, the shortest in the 'inducers' group (7.7 ± 1.8 h), the longest in the 'inhibitors' group (44.7 ± 10.2 h) and intermediate (21.9 ± 6.8 h) in the 'others' group.

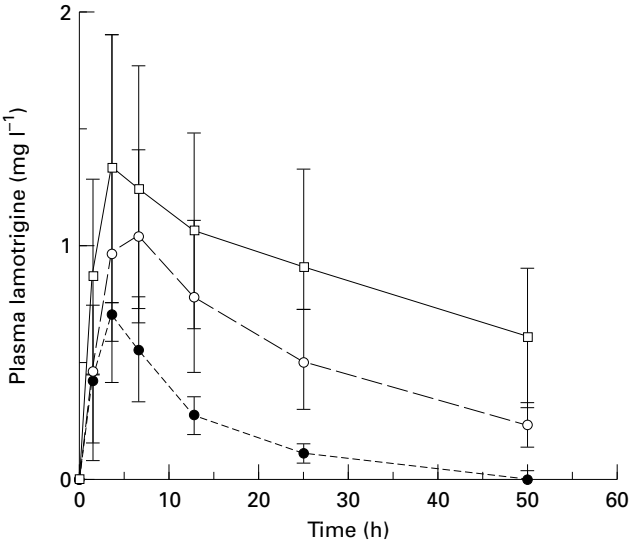

Figure 1 Mean ± s.d. lamotrigine plasma concentration-time profiles in epileptic children after a single 2 mg kg^{-1} oral dose according to the antiepileptic comedication group: 'inducers' $n = 11$ (●), 'others' $n = 10$ (○), 'inhibitors' $n = 10$ (□).

Dose adjustment

The recommended dosage and dosing interval varied according to the comedication. The dosing interval was 12 h and 24 h in all the patients of the 'inducers' and 'inhibitors' groups respectively. It was 12 h in 20% and 24 h in 80% of the patients of the 'others' group. The average dosage was 20.3 ± 6.3 mg kg^{-1} day^{-1} (range: 12.3–36.1) in the 'inducers' group significantly higher than in the 'inhibitor group'. The dosages were 5.5 ± 3.3 mg kg^{-1} day^{-1} (range 3.0–14.3) in the 'other' group and 1.9 ± 0.8 mg kg^{-1} day^{-1} (range 1.0–3.3) in the 'inhibitors' group. The minimum plasma concentration measured in 18 children at steady state i.e. after 1 month treatment was 2.54 ± 1.28 mg l^{-1}, and within the proposed range in 50% of these children. Individual values are given in Table 3.

Influence of maturation

No significant correlation could be found between the different pharmacokinetic parameters and age within the age range studied.

Although only one-third of the patients in each group were under 2 years of age, the available mean kinetic parameters (Table 4) do not suggest that the kinetics are substantially different from the 2.5 year olds.

Table 2 Individual kinetic parameters according to comedication group

Patient number	*Age (years)*	t_{max} *(h)*	$C_{max}{}^{+}$ *(mg l^{-1})*	*AUC(0, 48 h)*$^{+}$ *(mg l^{-1} h)*	$t_{1/2}$ *(h)*
Group 1: inducers (n = 11)					
29	0.58	6.00	1.08	12.6	7.5
20	0.83	3.05	0.67	6.0	5.7
25	0.92	2.83	0.67	8.5	11.4
4	1.05	0.98	1.03	13.5	10.0
8	2	2.83	0.77	7.7	8.9
3	2.25	3.00	0.74	9.3	8.2
9	2.58	2.95	0.65	8.2	7.3
21	3	2.90	1.07	9.6	5.8
24	3.58	3.00	0.77	7.7	6.7
12	3.67	5.92	0.57	6.5	6.9
22	4	2.92	0.99	9.2	6.4
Mean		2.95†	0.82	9.0	7.7
s.d.			0.19	2.3	1.8
Kruskal		$P < 0.05$	$P < 0.05$	$P < 0.05$	$P < 0.05$
Wallis test		*	**	***	***
Group 2: others (n = 10)					
28	0.5	1.17	1.55	30.4	36.5
31	0.75	6.00	0.93	20.9	20.3
32	1.33	6.03	0.94	25.2	22.9
16	1.67	6.00	1.05	31.8	26.2
14	2.67	6.08	0.83	26.6	27.1
1	3.33	2.92	1.65	23.9	12.9
27	3.33	6.00	1.01	22.6	15.2
23	3.5	3.10	0.77	11.5	20.3
2	3.75	6.00	1.11	28.3	19.6
13	4.5	6.05	1.25	33.3	18.0
Mean		6.0†	1.11	25.4	21.9
s.d.			0.29	6.3	6.8
Kruskal		$P < 0.05$		$P < 0.05$	$P < 0.05$
Wallis test		*		***	***
Group 3: inhibitors (n = 10)					
33	0.58	6.18	0.78	26.2	28.8
17	1.17	2.97	1.19	38.5	48.0
30	1.25	3.00	1.41	48.6	58.9
19	2.0	1.00	1.00	26.5	35.8
26	2.5	0.97	1.32	31.7	49.8
6	4.0	3.00	1.91	57.1	43.5
18	4.0	3.00	0.78	26.6	47.8
11	4.58	6.00	1.49	51.6	52.4
7	4.92	3.07	1.36	40.9	29.5
10	5.25	2.92	2.06	66.7	52.5
Mean		3.00†	1.33	41.4	44.7
s.d.			0.43	14.2	10.2
Kruskal			$P < 0.05$	$P < 0.05$	$P < 0.05$
Wallis test			**	***	***

+ Corrected for a 2 mg kg^{-1} administration. * Difference between group 1 and 2. ** Difference between group 1 and 3. *** Group different from the other two. † Median

Discussion

This study shows that lamotrigine pharmacokinetics in children are dependent on the effect of concomitant antiepileptic medication that influences hepatic drug metabolizing enzyme activity. Thus, compared with concomitant drugs with no known effect on hepatic enzymes, AUC and elimination half-life were doubled in children treated with sodium valproate and more than halved in those receiving enzyme inducing agents. This is similar to observations previously made in adult patients with epilepsy [10, 12, 13]. Since lamotrigine is

Table 3 Individual values of lamotrigine concentration at steady state

	Comedication		*Lamotrigine*		
Patient	*Drug*	*Dosage* ($mg\ kg^{-1}\ day^{-1}$)	*Dosage* ($mg\ kg^{-1}\ day^{-1}$)	*Minimum plasma concentration* ($mg\ l^{-1}$) *predicted*	*measured*
1	ETH	31	6.25	2.3	2.1
3	CBZ	25	18.2	2.4	3.9
6	VAL	29	1.47	2.6	2.6
7	VAL	46	2.88	2.7	1.2
8	CBZ	21	20.7	2.05	0.3
	DPH	12.5			
9	CBZ	21	19.5	2.4	3.2
11	DPK	34	1.14	2.3	2.4
13	CLON	0.10	4.3	2.3	1.8
14	CLOB	0.80	4.0	2.5	2.3
16	CLON	0.09	3.0	2.1	2.4
20	CBZ	23	37.5	2.4	3.7
22	CBZ	10	19.2	2.0	2.3
23	GAB	32	14.3	2.25	1.5
25	CBZ	34	14.9	2.3	4.8
26	VAL	16	2.0	2.3	4.5
27	NONE	—	4.40	1.8	4.2
28	GVG	101	3.60	2.5	0.7
31	GVG	135	6.60	2.4	1.9

CBZ, Carbamazepine. CLON, Clonazepam. CLOB, Clobazam. DPH, Diphenylhydantoin. ETH, Ethosuximide. GAB, Gabrene. GVG, Vigabatrin. VAL, Valproate.

extensively metabolized by the liver, it is not suprising that drugs which induce hepatic enzymes enhance its metabolism and excretion. As glucuronidation is the major metabolic pathway of lamotrigine, the inhibition of lamotrigine metabolism by valproic acid is probably a consequence of competition at hepatic glucuronidation sites [9–18].

There appears to be no clear pattern of effect of concomitant AED administration on the rate of absorption of lamotrigine. There was a significant increase in C_{max} in the 'inhibitor' group. There was a considerable interindividual variation in t_{max} values which ranged from 1 to over 6 h. In adults t_{max} was less variable and ranged from 1 to 3 h [9, 10]. This may be due to infrequent sampling over the initial phase of the plasma concentration–time curve.

This pharmacokinetic interaction of concomitant AED therapy with lamotrigine has important clinical implications particularly with regard to dosage. The present data have clearly shown that children receiving concurrent enzyme-inducing AEDs require a higher lamotrigine dosage. Conversely those receiving sodium valproate require a lower dosage. The type of AE comedication should therefore be taken into account when choosing a dosage regimen. Based on single dose pharmacokinetics, patients were dosed to steady state to achieve a minimum lamotrigine plasma concentration in the range of the aimed therapeutic concentration (1.5–3 mg l^{-1}). This range was achieved in most of the children (six out of eight) in the group on comedications of no known influence on drug metabolism, compared with two out of four in the 'inhibitor' group and to one out of six in the 'inducers' group, suggesting that these enzymatic interactions may widely vary during treatment. This hypothesis should, however, be taken cautiously, due to small number of patients included in each treatment group and the absence of a statistically significant difference. Whenever clinical efficacy is doubtful it would be advisable to monitor lamotrigine minimum plasma concentration to verify that the dosage is appropriate.

Within our patient group no influence of age was seen. The narrow age range (0.5–5 years) of the children investigated may preclude such an influence. However the half-life seems to be shorter in children (7.7 ± 1.8 h) than in adults (15 h) [11–13] treated with inducers, while half-life in the two other comedication groups is of the same order of magnitude in both adults and children ('others' group: 29 h [12]; 'inhibitor' group: 59 h in adults) [12, 13]. This suggests greater susceptibility to induction in children or a more rapid metabolism and excretion of lamotrigine in children compared with adults. More data would be necessary to determine the clinical relevance of the influence of age on lamotrigine pharmacokinetics.

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Table 4 Mean (s.d.) kinetic parameters according to age and comedication group

	Group 1: inducers					*Group 2: others*					*Group 3: inhibitors*				
	n	t_{max}* (*h*)	C_{max}† (*mg l^{-1}*)	*AUC(0, 48h)*† (*mg l^{-1} h*)	$t_{1/2}$ (*h*)	n	t_{max}* (*h*)	C_{max}† (*mg l^{-1}*)	*AUC(0, 48h)*† (*mg l^{-1} h*)	$t_{1/2}$ (*h*)	n	t_{max}* (*h*)	C_{max}† (*mg l^{-1}*)	*AUC(0, 48h)*† (*mg l^{-1} h*)	$t_{1/2}$ (*h*)
≤2 years	5	2.83	0.84	9.66	11.0	4	6.00	1.12	27.1	38.1	4	2.99	1.10	35.0	68.2
			(0.20)	(3.25)	(3.45)			(0.29)	(5.0)	(10.2)			(0.27)	(10.7)	(34.5)
2–5 years	6	2.98	0.80	8.42		6	6.00	1.10	24.4	29.7	6	3.00		45.8	89.9
			(0.19)	(1.19)	(1.27)			(0.32)	(7.3)	(10.0)			(0.46)	(15.4)	(35.6)

* Median value. † Corrected for a 2 mg kg^{-1} administration

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