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Effects of rifampicin and cimetidine on pharmacokinetics and pharmacodynamics of lamotrigine in healthy subjects

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Abstract *Objective*: To study the effects of rifampicin, a potent inducer of the microsomal P_{450} enzyme system and of specific isoforms of the uridine 5′-diphosphate(UDP)-glucuronyl-transferase enzyme system, and cimetidine, a known inhibitor of the hepatic microsomal cytochrome P_{450} enzyme system, on pharmacokinetics and pharmacodynamics of lamotrigine in healthy subjects.
Methods: Ten healthy male subjects received a single oral dose of 25 mg lamotrigine after a 5-day pretreatment with (1) cimetidine 800 mg divided into two equal doses, (2) rifampicin 600 mg, or (3) placebo. Serum and urine samples were analyzed using high-performance liquid chromatography. Changes in electroencephalographic (EEG) power were determined up to 48 h after lamotrigine administration.
Results: The values of the pharmacokinetic parameters of lamotrigine were: clearance over bioavailability (CL/F) 2.60 ± 0.40 l/h, renal clearance (CL_R) 0.10 ± 0.03 l/h, terminal half-life ($t_{1/2}$) 23.8 ± 2.1 h, mean peak serum concentration (C_{max}) 0.29 ± 0.02 μg/l, time to reach C_{max} (t_{max}) 1.6 ± 0.28 h, and total area under the serum concentration-time curve ($AUC_{0-\infty}$) 703.99 ± 82.31 μg/ml/min (mean ± SEM). The amount of lamotrigine excreted as glucuronide was 8.90 ± 0.77 mg. Rifampicin significantly increased CL/F (5.13 ± 1.05 l/h) and the amount of lamotrigine excreted as glucuronide (12.12 ± 0.94 mg), whereas both $t_{1/2}$ (14.1 ± 1.7 h) and $AUC_{0-\infty}$ (396.24 ± 60.18 μg/ml/min) were decreased ($P < 0.05$). Cimetidine failed to affect pharmacokinetics of lamotrigine. Lamotrigine did not change EEG power.
Conclusion: Rifampicin altered pharmacokinetics of lamotrigine due to induction of the hepatic enzymes responsible for glucuronidation, while coadministration of cimetidine to ongoing lamotrigine therapy has negligible effects on lamotrigine pharmacokinetics. Lamotrigine administered as a single dose of 25 mg has no effect on EEG power in healthy subjects.

Key words Lamotrigine · Pharmacokinetics · Electroencephalogram

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Introduction

Lamotrigine (3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine) is an antiepileptic drug registered for treatment of partial seizures and/or generalized tonic–clonic seizures [1, 2, 3]. The pharmacokinetics of lamotrigine can be adequately described by a one-compartment open model with first-order absorption and elimination. Lamotrigine is well absorbed when given orally with an elimination half-life ($t_{1/2}$) of 30 h (range 21–53 h) in healthy volunteers [4, 5, 6, 7]. Elimination is predominantly through the formation of a *N*-2 glucuronide acid conjugate by the action of uridine 5′-diphosphate (UDP)-glucuronyl-transferases and renal excretion [4, 6]. Two other metabolites are present in smaller concentrations [7]. There are no known active metabolites of lamotrigine.

Coadministration of drugs known to induce or inhibit drug-metabolizing enzymes could affect the pharmacokinetics of lamotrigine. Previous studies in epileptic patients have shown that lamotrigine pharmacokinetics are altered by concomitant antiepileptic drugs. The coadministration of antiepileptic drugs that induce hepatic enzymes, such as phenytoin, carbamazepine, or phenobarbital, reduce the half-life of lamotrigine by nearly 50% [6, 8, 9, 10]. These antiepileptic drugs have been reported to activate the cytochrome P_{450} and UDP-glucuronyl-transferase enzyme systems [11]. Methsuximide and oxcarbazepine also decrease the lamotrigine serum concentration [12]. The concomitant administration of valproic acid, on the other hand, prolonged the half-life

of lamotrigine to approximately 70 h [13, 14]. Valproic acid, like lamotrigine, is extensively metabolized by glucuronidation. Valproic acid acts as an inhibitor of several hepatic enzymes, including cytochrome P_{450}, epoxide hydrolase, and UDP-glucuronyl-transferase [15].

Therefore, we hypothesized that coadministration of rifampicin, a known inducer of the microsomal P_{450} enzyme system and of specific isoforms of the UDP-glucuronyl-transferase enzyme system [16, 17], could affect the elimination rate of lamotrigine. In contrast, cimetidine, an imidazole derivative, has been shown to inhibit the hepatic microsomal cytochrome P_{450} enzyme system [18]. The influence of cimetidine on glucuronidation pathways is controversial. A number of studies have shown a lack effect of cimetidine on glucuronidation, sulfation, and acetylation [19, 20, 21], while in vivo and in vitro investigations have demonstrated a cimetidine-induced inhibition of the glucuronidation pathways [22, 23]. Therefore, the present study was undertaken to assess this potential pharmacokinetic interaction by evaluation of the lamotrigine serum concentration versus time profiles after coadministration with rifampicin or cimetidine and its effects on the electroencephalographic power spectrum in healthy subjects.

Materials and methods

Subjects

In a randomized, placebo-controlled, open labeled, crossover study, ten healthy, non-obese, nonsmoking male subjects (mean age ± SD, 25 ± 4 years; weight range 63–100 kg, height range 170–189 cm) were investigated. The subjects were randomized using a simple randomization procedure after screening tests were completed. All subjects were in good health as determined by complete physical examination, 12-lead electrocardiogram (ECG), and routine biochemical and hematological tests. Each subject was given a detailed description, both verbally and in writing, of the purpose of the study, the discomfort and likely risks involved, and the procedures to be followed. Each subject gave written informed consent before taking part in the study, which was approved by the ethics committee of the Faculty of Medicine of the Technical University, Dresden. The study was conducted in agreement with the Declaration of Helsinki (Somerset West Amendment, 1996). No concomitant drug therapy, including over-the-counter drugs, was allowed 2 weeks before and during the trial periods. The subjects refrained from oral intake for 10 h before testing. The subjects were also asked not to consume alcoholic or caffeine-containing beverages 10 h prior to and throughout the three trial periods. They were also asked to sleep for at least 8 h prior to the individual study days.

Study design

The study consisted of three periods (lamotrigine + cimetidine, lamotrigine + rifampicin, and lamotrigine + placebo). All experiments were begun between 0600 hours and 0700 hours. Subjects were studied in a quiet room at the University Hospital kept at a constant temperature of 22 ± 2 °C. Lamotrigine administration was preceded by a 5-day course of (1) cimetidine (Altramet 400) 400 mg orally at 0700 hours and 1900 hours, (2) rifampicin (Rifa 600) 600 mg orally at 1900 hours, or (3) placebo (mannit). On the study day (day 6), subjects received single oral doses of 25 mg lamotrigine. If the study period included cimetidine treatment, cimetidine was taken 1 h prior to lamotrigine administration and continued in the dosage regimen described above until the end of this trial period. A drug-free interval of at least 10 days was kept between trial periods. Individual capsules containing 25 mg lamotrigine (Lamictal, GlaxoWellcome GmbH, Hamburg, Germany) or placebo were prepared by the hospital pharmacy. Cimetidine (Astra Medica AWD, Frankfurt, Germany) and rifampicin (Grünenthal, Aachen, Germany) were used from commercial sources. A standard breakfast was served 5 h after drug administration followed by a standard dinner 5 h later.

Blood and urine sampling

Blood samples of 7.5 ml were collected from an indwelling 18-gauge cannula (Vasofix Braunüle, B. Braun Melsungen AG, Melsungen, Germany) inserted into the antecubital vein before and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, and 48 h after lamotrigine administration. Serum was separated by centrifugation and stored at −25 °C until analysis. Subjects were instructed to empty the bladder just prior to lamotrigine administration and a voided urine sample was collected. Total urine (0–48 h) was collected in 4-h increments during the first 12 h of each trial period; total urine was collected in 12-h increments after the first 12 h. Total volumes were measured; aliquots of 10 ml were separated and stored at −25 °C until analysis.

Drug analysis

A high-performance liquid chromatography (HPLC) method with a solid-phase extraction was used to determine lamotrigine in serum and urine samples as previously described [24]. In brief, a liquid chromatographic system consisted of an autosampler (Varian 9100, Walnut Creek, USA), a HPLC pump (LC 6A, Shimadzu, Kyoto, Japan) transferring the sample onto two SPE cartridges (LiChroCART 25-4 packed with LiChrospher RP-18 ADS; Merck, Germany), and a 10-port valve (E C10W, Valco, Schenkon, Switzerland). The mobile phase consisted of acetonitrile and phosphate buffer (0.05 mol/l, pH 4; 20:80, v/v) with a solvent flow rate of 1 ml/min. The ultraviolet detector was operated at a wavelength of 280 nm. Separation was accomplished using a 125 × 4-mm RP 18 chromatographic column (5 μm; Merck, Germany). The retention time of lamotrigine was 3.1 min. The coefficient of variation (C.V.) of this assay was less than 10% with a limit of quantification of 50 ng/ml. Cimetidine and rifampicin did not interfere with the assay.

Pharmacodynamics

Heart rate and systolic and diastolic blood pressures were monitored at baseline and throughout the study periods using an automated blood pressure monitor (Dinamap Monitor, Critikon Inc., Tampa, Fla.).

Electroencephalographic recording

An electroencephalogram (EEG) was recorded from 17 surface electrodes attached to the scalp by an electrode cap (ElectroCap Co., Eaton, Ohio) according to the international 10:20 standard system [25] with C_Z as a physical reference. All EEG recordings were made while the subjects were in a supine position with an upward angle of 30° from the horizontal with eyes closed. Subjects were lying down for at least 10 min before registrations were recorded for EEG. A 15-min EEG examination was performed to determine baseline (predrug) prior to the initial dose of cimetidine, rifampicin, and placebo. EEG was also recorded before and subsequently 2, 5, 24, and 48 h after administration of lamotrigine for time periods of 15 min, as previously described [26]. For all registrations, only impedance levels less than 5000 Ω were regarded as acceptable.

Electroencephalographic analysis

Artifacts or noisy signals were identified on the raw EEG tracing and were deleted from the final data. Epochs of 4-s duration were frequency analyzed, and power spectra (0.25 Hz resolution) were computed using fast Fourier transformation. Mean power spectra relating to consecutive intervals of 1 min were calculated [27]. EEG raw data were filtered using a custom-designed program (LabView for Windows, Version 3.1, National Instruments, Austin, Tex.). The EEG raw data of the Cateem system consists of consecutive records of 1-min frequency means, the frequencies reach from 1.25 Hz to 35 Hz with steps of 0.25 Hz. These data have been rearranged, and mean values were calculated using the following algorithm with respect to frequency bands: 1.25–3.25 Hz (delta), 3.50–7.25 Hz (theta), 7.50–11.25 Hz (alpha), and 11.50–30.00 Hz (beta). This procedure follows the guidelines of the German EEG Society [28]. Total power (μV^2) representing the area under the entire power versus frequency histogram was used as EEG effect measure.

Data analysis

Lamotrigine serum concentration–time data were analyzed for each subject using noncompartmental methods. Basic pharmacokinetic parameters such as clearance over bioavailability (CL/F), renal clearance (CL_R), and terminal half-life ($t_{1/2}$) were calculated according to standard procedures [29]. The apparent terminal elimination rate constant, k, was determined using linear regression of the terminal phase of the log serum concentration–time curve and $t_{1/2}$ was calculated as $\ln 2/k$. The area under the serum concentration–time curve (AUC) was obtained using the non-linear trapezoidal rule up to maximum serum concentration (C_{max}) and the log-linear trapezoidal rule after C_{max}. The total area under the serum concentration–time curve ($AUC_{0-\infty}$) was determined by adding the AUC from zero to the last blood level point to the remaining area calculated by dividing the last blood level, which is the fit concentration at that time, by the elimination rate constant. The mean residence time (MRT) was calculated using the area under the first moment versus time curve (AUMC) and AUC. For C_{max} and time to reach C_{max} (t_{max}) observed values were taken.

Statistical analysis

All data were statistically analyzed using a personal computer with the Sigma Stat software package (Jandel Corp., San Rafael, Calif.). One-way analysis of variance (ANOVA) was used to determine differences between the pharmacokinetic parameters of lamotrigine calculated from the three trial periods. Pharmacodynamic baseline values from the three respective trial periods were screened for homogeneity using the one-way ANOVA; if the normality test failed, the Kruskal-Wallis ANOVA on ranks was performed. The software package Sigma Stat uses the Kolmogorov-Smirnov test to test for a normally distributed population. One-way ANOVA was used to determine the EEG effects of cimetidine and rifampicin compared with placebo. In order to determine the EEG effects of lamotrigine, the total power of the four EEG frequency bands were tested for differences compared with baseline using ANOVA with repeated measurements to test treatment, time, subject, and the interactions. Pairwise comparisons were done using the Student-Newman Keuls test. A value of $P < 0.05$ was considered to be significant. Results are expressed as mean ± SEM unless otherwise stated.

Results

Drug safety

All ten subjects completed the study. Mild to moderate headache was observed in three subjects 24–48 h after ingestion of lamotrigine. These side effects occurred during the study period if lamotrigine administration was preceded by a 5-day course of placebo. Heart rate and systolic and diastolic blood pressures did not significantly change during the three trial periods.

Pharmacokinetics of lamotrigine

Figure 1 shows the time profile of lamotrigine serum concentrations (mean ± SEM) after pretreatment with either cimetidine, rifampicin, or placebo. The serum profiles of lamotrigine are similar for placebo and cimetidine pretreatment. In five subjects, a second C_{max} occurred between 2.5 h and 4 h after lamotrigine administration. Pharmacokinetic parameters of lamotrigine are listed in Table 1. Rifampicin significantly

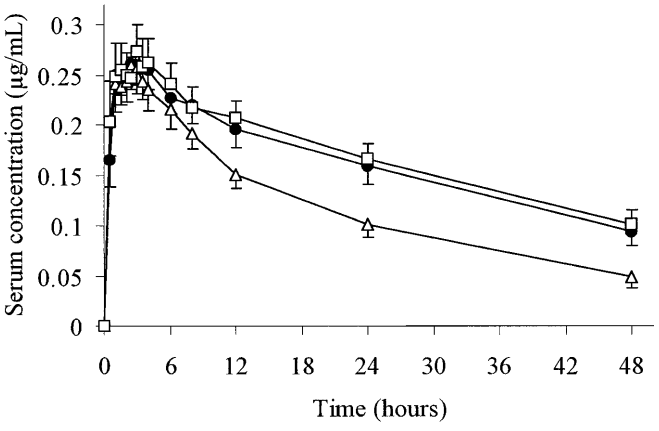

Fig. 1 Serum concentration versus time profile (mean ± SEM) of lamotrigine after administration of a single oral dose of 25 mg after a 5-day pretreatment with placebo (*filled circles*), cimetidine (*open squares*), or rifampicin (*open triangles*)

Table 1 Effect of a 5-day course of cimetidine or rifampicin on pharmacokinetics of lamotrigine determined after administration of a single oral dose of 25 mg lamotrigine (mean ± SEM; $n = 10$). CL/F clearance over bioavailability; CL_R renal clearance; $t_{1/2}$ terminal half-life; MRT mean residence time; $AUC_{0-48\ h}$ area under the lamotrigine serum concentration–time curve; $AUC_{0-\infty}$ total area under the lamotrigine serum concentration–time curve; C_{max} maximum lamotrigine serum concentration; t_{max} time to reach C_{max}

	Lamotrigine + placebo	Lamotrigine + cimetidine	Lamotrigine + rifampicin
CL/F (l/h)	2.60 ± 0.40	2.48 ± 0.35	5.13 ± 1.05*
CL_R (l/h)	0.10 ± 0.03	0.14 ± 0.03	0.16 ± 0.04
$t_{1/2}$ (h)	23.8 ± 2.1	24.2 ± 1.9	14.1 ± 1.7*
MRT (h)	18.4 ± 1.3	19.5 ± 0.4	15.2 ± 1.31*
$AUC_{0-48\ h}$ (µg/ml/min)	477.04 ± 44.83	486.50 ± 50.19	328.30 ± 43.42*
$AUC_{0-\infty}$ (µg/ml/min)	703.99 ± 82.31	718.45 ± 93.40	396.24 ± 60.18*
C_{max} (µg/ml)	0.29 ± 0.02	0.29 ± 0.03	0.29 ± 0.03
t_{max} (h)	1.6 ± 0.28	1.1 ± 0.26	1.1 ± 0.2

*$P < 0.05$ compared with lamotrigine + placebo and lamotrigine + cimetidine using one-way analysis of variance (ANOVA)

Table 2 Urinary recovery of lamotrigine glucuronide (mean ± SEM, $n = 10$)

	Lamotrigine + placebo	Lamotrigine + cimetidine	Lamotrigine + rifampicin
Total amount recovered (lamotrigine and glucuronide) (mg)	9.72 ± 0.79	9.45 ± 0.76	12.88 ± 0.97*
Percentage of dose	39.7 ± 3.3	37.9 ± 3.0	50.6 ± 4.3*
Amount excreted as glucuronide (mg)	8.90 ± 0.77	8.40 ± 0.74	12.12 ± 0.94**

*$P = 0.019$ compared with lamotrigine + placebo and lamotrigine + cimetidine using one-way analysis of variance (ANOVA)
**$P = 0.013$ compared with lamotrigine + placebo and lamotrigine + cimetidine using one-way ANOVA

decreased both the lamotrigine $AUC_{0-48\ h}$ and the lamotrigine $AUC_{0-\infty}$ relative to placebo and cimetidine pretreatment ($P < 0.05$). The MRT and the $t_{1/2}$ of lamotrigine were significantly lower during the rifampicin pretreatment than placebo and cimetidine pretreatment ($P < 0.05$), while a significant increase in CL/F was observed after rifampicin pretreatment compared with placebo and cimetidine pretreatment ($P < 0.05$). CL_R, C_{max}, and t_{max} were unchanged. Cimetidine pretreatment had no effect on the pharmacokinetic parameters of lamotrigine compared with placebo. The percentage of the lamotrigine dose recovered in the urine in 48 h was approximately 40% after pretreatment with placebo and was unchanged during the cimetidine pretreatment. The lamotrigine total urinary excretion and the amount excreted as glucuronide was significantly higher during the rifampicin pretreatment than during both placebo and cimetidine pretreatment ($P < 0.05$; Table 2).

EEG effects

No differences were found in the baseline values of EEG between the trial periods. Lamotrigine did not significantly affect EEG delta, theta, alpha, and beta power (Table 3). Although lamotrigine decreased EEG delta power by 28 ± 4% (mean ± SEM) compared with baseline, this effect did not reach statistical significance. Statistical power analysis indicated that the number of subjects required to show a difference of 40% in EEG effect with 80% power and α equal to 0.05 was 113, assuming a coefficient of variation of 30%. Neither cimetidine, rifampicin, nor placebo influenced EEG (Table 3).

Discussion

This study was performed to determine whether rifampicin and cimetidine could alter the elimination rate of a single dose of lamotrigine compared with placebo. Rifampicin was able to reduce the AUC of lamotrigine representing a measure of the total body load of drug, and to increase both the CL/F of lamotrigine and the amount of lamotrigine in urine excreted as glucuronide. Additionally, coadministration of rifampicin was associated with a 30% shortening of the lamotrigine half-life. Cimetidine failed to show any influence on pharmacokinetics of lamotrigine.

In the present study, when lamotrigine was administered alone, the $t_{1/2}$ of lamotrigine was approximately 24 h and the mean CL/F was 2.60 l/h in healthy subjects, comparable with that previously shown [4, 5, 30,

Table 3 Electroencephalographic parameters determined after administration of a single oral dose of 25 mg lamotrigine (mean ± SEM; $n = 10$)

Absolute power (μv^2)	Baseline	Before lamotrigine	2 h after lamotrigine	5 h after lamotrigine	24 h after lamotrigine	48 h after lamotrigine
Placebo + lamotrigine						
Delta (1.25–3.25 Hz)	1.593 ± 0.318	1.404 ± 0.396	1.277 ± 0.194	1.341 ± 0.201	1.551 ± 0.314	1.792 ± 0.614
Theta (3.50–7.25 Hz)	0.504 ± 0.112	0.525 ± 0.132	0.531 ± 0.117	0.541 ± 0.108	0.456 ± 0.079	0.550 ± 0.122
Alpha (7.50—11.25 Hz)	0.681 ± 0.205	0.741 ± 0.201	0.576 ± 0.143	0.699 ± 0.204	0.774 ± 0.208	0.941 ± 0.267
Beta (11.50—30.00 Hz)	0.074 ± 0.013	0.075 ± 0.017	0.071 ± 0.010	0.078 ± 0.017	0.063 ± 0.009	0.071 ± 0.013
Cimetidine + lamotrigine						
Delta (1.25–3.25 Hz)	1.551 ± 0.328	1.131 ± 0.256	1.097 ± 0.183	1.142 ± 0.154	1.492 ± 0.320	1.432 ± 0.298
Theta (3.50–7.25 Hz)	0.369 ± 0.043	0.365 ± 0.063	0.379 ± 0.051	0.407 ± 0.055	0.391 ± 0.041	0.366 ± 0.052
Alpha (7.50—11.25 Hz)	0.797 ± 0.238	0.823 ± 0.256	0.632 ± 0.204	0.662 ± 0.215	0.865 ± 0.267	0.869 ± 0.283
Beta (11.50—30.00 Hz)	0.072 ± 0.015	0.071 ± 0.013	0.063 ± 0.009	0.071 ± 0.011	0.063 ± 0.015	0.065 ± 0.011
Rifampicin + lamotrigine						
Delta (1.25–3.25 Hz)	1.575 ± 0.500	1.185 ± 0.200	1.043 ± 0.162	1.219 ± 0.185	1.237 ± 0.147	1.382 ± 0.274
Theta (3.50–7.25 Hz)	0.388 ± 0.094	0.364 ± 0.053	0.375 ± 0.053	0.451 ± 0.056	0.356 ± 0.029	0.364 ± 0.057
Alpha (7.50—11.25 Hz)	0.827 ± 0.251	0.938 ± 0.293	0.521 ± 0.144	0.751 ± 0.215	0.633 ± 0.224	0.977 ± 0.243
Beta (11.50—30.00 Hz)	0.078 ± 0.019	0.076 ± 0.017	0.072 ± 0.014	0.079 ± 0.013	0.069 ± 0.013	0.081 ± 0.018

31]. The second lamotrigine peak concentration observed in one-half of the subjects may suggest enterohepatic recycling [31]. Lamotrigine is extensively metabolized primarily by the action of the UDP-glucuronyl-transferases [6]. Glucuronidation as a mechanism of elimination has advantages because it has a great capacity [32]. However, it can be induced by other drugs.

Rifampicin is one of the most potent enzyme inducers known to humans. It induces several cytochrome P_{450} isoforms and specific isoforms of the UDP-glucuronyl-transferase enzyme system [16, 17]. Therefore, the ability of rifampicin to induce the elimination of lamotrigine observed in the present study may result from induction of the hepatic enzymes responsible for glucuronidation. This has also been demonstrated for lamotrigine in studies in epileptic patients receiving enzyme-inducing comedication such as phenytoin, carbamazepine, or phenobarbital [6, 8, 9, 10]. Similar to the results of the present study, the half-life of lamotrigine was approximately 14 h in patients taking enzyme inducers. In addition, a 5-day course of rifampicin pretreatment produced a significant increase in both the CL/F of lamotrigine and the amount excreted as glucuronide. After rifampicin, the mean total AUC of lamotrigine reached only approximately 56% of the corresponding value in the placebo phase. The effect of rifampicin on lamotrigine pharmacokinetics was consistent in each subject. The magnitude of this interaction could be of clinical importance because it could result in negligible trough lamotrigine concentrations in epileptic patients.

No changes in EEG power were observed after administration of a single dose of lamotrigine in healthy subjects probably due to the low dose of lamotrigine or the small number of subjects included in this study. In contrast, van Wieringen et al. reported a reduced EEG power, an increase in alpha/theta and $alpha_1/alpha_2$ ratios, and reduced alpha/beta and $beta_1/beta_2$ ratios after administration of single doses of 120 mg and 240 mg lamotrigine to healthy subjects [33]. However, the characteristics of the effects of antiepileptic drugs on EEG do not provide a basis for the functional classification of these drugs nor for prediction of clinical efficacy, but could give some insight into the possible secondary psychotropic effects of antiepileptic drugs. Furthermore, EEG findings in healthy subjects cannot be easily extrapolated to epileptic patients. It has been shown that EEG background activity can be compromised due to deteriorated brain function in this patient population [33].

Our study did not show either an inhibition of lamotrigine metabolism or a pharmacodynamic interaction due to coadministration of therapeutic doses of cimetidine. The failure of cimetidine to alter the pharmacokinetics of lamotrigine in the present study suggests that cimetidine has no effect on the action of UDP-glucuronyl-transferases.

In conclusion, pretreatment with rifampicin increased lamotrigine clearance and reduced lamotrigine half-life due to induction of the hepatic enzymes responsible for glucuronidation. These findings strongly suggest that concomitant therapy with rifampicin will reduce trough lamotrigine concentrations in epileptic patients and could impair its antiepileptic properties. Coadministration of cimetidine to ongoing lamotrigine therapy has negligible effects on lamotrigine pharmacokinetics and should be safe in epileptic patients.

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