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Effect of metoclopramide on lamotrigine absorption in rabbits

M.S. Al-Humayyd*

Department of Medical Pharmacology, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia

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Abstract

This study was carried out to determine the effect of metoclopramide on the absorption of lamotrigine when the two drugs were given concurrently by the oral route in rabbits. The first group of animals was given lamotrigine (20 mg/kg, p.o.) alone and the second group was given the same dose of lamotrigine together with metoclopramide (3 mg/kg, p.o.) and plasma samples were collected at different time intervals following drug administration. The concentrations of lamotrigine in plasma were determined by using a high-performance liquid chromatographic (HPLC) method. Co-administration of lamotrigine with metoclopramide resulted in a significant increase ($P < 0.05$) in the mean maximum plasma concentration (C_{max}), mean area under the plasma concentration—time curve (AUC) and a significant decrease ($P < 0.05$) in the mean time to reach maximum concentration (T_{max}) as compared to those obtained for lamotrigine alone. No significant changes were observed in the elimination half-life ($t_{1/2}$) of lamotrigine when it was administered together with metoclopramide. These results suggest an increase in the total absorption of lamotrigine when it is administered concurrently with metoclopramide. Copyright © 1996 Elsevier Science B.V.

Keywords: Lamotrigine; Metoclopramide; Pharmacokinetic interaction; Rabbits

1. Introduction

Lamotrigine, (LTG, 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine) is an anti-epileptic drug which is chemically unrelated to the other major anti-epileptics in current use. It is effective as add-on therapy against partial and secondarily generalized tonic-clonic seizures (Goa et al., 1993). It is also effective for other types of epilepsy, such as absence, myoclonic, tonic-clonic, tonic and clonic seizures (Brodie, 1992). The anti-convulsant profile of lamotrigine in animals has been shown to be similar to that of phenytoin, but it is more potent and has a longer duration of action than the latter drug (Leach et al., 1986; Miller et al., 1986). Its precise mechanism of action is unknown, but it is believed to suppress

* Corresponding address. Fax: +966 01 4936033.

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seizures by blocking the voltage-dependent sodium channels, stabilizing neuronal membranes and thereby inhibiting the release of excitatory neurotransmitters such as glutamate and aspartate (Leach et al., 1986; Miller et al., 1986).

Lamotrigine does not seem to induce or inhibit cytochrome *P*-450 liver enzyme systems and thus has no significant effects on the metabolism of other drugs which are known substrates of these enzymes (Brodie, 1994). It is metabolized primarily by hepatic glucuronidation to the inactive 2N-glucuronide metabolite (Cohen et al., 1987; Brodie, 1994). Hence, any drug which is able to induce or inhibit this glucuronidation reaction may potentially interact with lamotrigine. For instance, phenytoin, carbamazepine and phenobarbitone, which are known to induce hepatic microsomal enzymes (Craig, 1994) have been shown to increase the metabolism and consequently reduce the elimination half-life of lamotrigine (Jawad et al., 1987). Conversely, sodium valproate, an inhibitor of liver microsomal enzymes (Brodie, 1992b), has been shown to increase the elimination half-life of lamotrigine (Binnie et al., 1986; Jawad et al., 1987; Yuen et al., 1992).

Lamotrigine is completely absorbed from the gastrointestinal tract (Yuen and Peck, 1988; Richens, 1992). Drugs which are known to accelerate gastric emptying may alter the rate of lamotrigine absorption from the gastrointestinal tract. Metoclopramide, a dopamine antagonist, is known to enhance the gastric emptying and has been shown to increase the oral bioavailability of other drugs when given concurrently with it. For example, it has been reported that metoclopramide increases the rate of absorption of acetaminophen (Nimmo et al., 1973); acetylsalicylic acid (Volans, 1975) and cyclosporine (Wadhwa et al., 1987). The present study was, therefore, designed to investigate the possible effects of metoclopramide on the gastrointestinal absorption of lamotrigine when they are administered concurrently to rabbits.

2. Materials and methods

2.1. Materials

Lamotrigine was obtained from Glaxo-Wellcome, London, UK; acetonitrile (HPLC grade) from Merck, Darmstadt, Germany. Metoclopramide monohydrochloride was purchased from Sigma Chemical, St. Louis, Mo. USA.

Lamotrigine was suspended by the aid of one drop of Tween 80 and made up to the required volume (20 ml) in normal saline. Metoclopramide monohydrochloride was dissolved in normal saline.

2.2. Methods

2.2.1. Pharmacokinetic study

Male New Zealand white rabbits weighing 2–2.5 kg were bred in the animal house, College of Medicine, King Saud University. The animals were fasted overnight prior to the experiment but water was allowed ad libitum. Food and water were withheld during the first 6 h of the experiment.

Rabbits were given 1000 IU/kg of heparin intramuscularly prior to drug treatment. In one group of rabbits ($n = 8$) lamotrigine (20 mg/kg) was administered orally. The other group of rabbits ($n = 8$) received a combination of lamotrigine (20 mg/kg, p.o.) and metoclopramide (3 mg/kg, p.o.). Blood samples (0.3 ml) were collected in heparinized test-tubes through a cannula secured to the ear vein before treatment with drugs and thereafter at 0.25, 0.50, 1.0, 1.50, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0 and 24 h after oral administration of lamotrigine or lamotrigine together with metoclopramide. After each sample withdrawal, the cannula was flushed with an equal volume of heparinized saline. Plasma samples were stored at -20°C for subsequent determination of lamotrigine levels.

2.2.2. Determination of plasma lamotrigine concentrations

The plasma concentrations of lamotrigine were determined by using an HPLC method, with ultraviolet detection as has previously been de-

scribed by Fraser et al., 1995. The sensitivity limit of the assay is 0.10 μg/ml. Using this method there was no interference by metoclopramide with the detection of lamotrigine.

2.2.3. Analysis of data

The area under the plasma concentration-time curve (AUC) to the last sampling time was estimated by the linear trapezoidal method. Terminal half lives were calculated from the log-linear part of the slope. The differences between the two respective treatment groups were analyzed for significance using the Unpaired Student's *t*-test. *P* values equal to or less than 0.05 were considered significant.

3. Results

The mean plasma concentration-time profiles in rabbits following the administration of lamotrigine alone (20 mg/kg, p.o.) or in combination with metoclopramide (3 mg/kg, p.o.) is shown in Fig. 1. The pharmacokinetic parameters derived from these data are summarized in Table 1. The mean time taken to reach the maximum plasma concentration (T_{max}) was significantly reduced from 1.30 ± 0.20 h (lamotrigine alone), to 0.60 ± 0.12 h (lamotrigine together with metoclopramide) ($P < 0.05$, Table 1). A decay in the concentration of lamotrigine being evident within 2 h when given alone, and 1 h following its administration together with metclopramide (Fig. 1). Plasma lamotrigine concentrations were consistently higher during its co-administration with metoclopramide than when the drug was given alone.

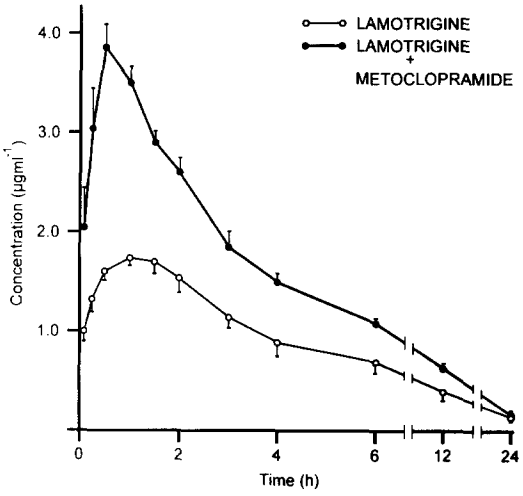

Fig. 1. Plasma lamotrigine concentration—time profiles for lamotrigine alone (○), or when given concurrently with metoclopramide (●). Each point represents the mean ± S.E.M. of eight observations.

Table 1
Plasma pharmacokinetic parameters of lamotrigine (20 mg/kg, p.o.) administered alone or together with metoclopramide (3 mg/kg, p.o.) in rabbits

Parameter	Lamotrigine	Lamotrigine + Metoclopramide
C_{max} (μg ml^{-1})	1.80 ± 0.10	4.0 ± 0.30[a]
t_{max} (h)	1.30 ± 0.20	0.60 ± 0.12[a]
AUC_{0-24} (μg ml^{-1})	13.40 ± 1.63	22.90 ± 0.90[a]
$t_{1/2}$ (h)	6.40 ± 0.62	5.31 ± 0.30

Each value is the mean ± S.E.M. of eight observations.
[a]Statistically significant from the values obtained for lamotrigine alone ($P < 0.05$; unpaired *t*-test).

Table 1 shows that treatment of rabbits with metoclopramide significantly increased the mean area under the curve (AUC) for lamotrigine from 13.40 ± 1.63 μg ml^{-1} (lamotrigine alone) to 22.90 ± 0.90 μg ml^{-1} (lamotrigine together with metoclopramide). Similarly, the maximum plasma concentration (C_{max}) of lamotrigine in the animals that had received lamotrigine and metoclopramide was also significantly higher than that obtained in animals that were given lamotrigine alone ($P < 0.05$, Table 1). Although metoclopramide reduced the elimination half-life ($t_{1/2}$) for lamotrigine from 6.40 ± 0.62 (lamotrigine alone) to 5.31 ± 0.30 (lamotrigine with metoclopramide) (Table 1), this value was not statistically significant.

4. Discussion

The results of the present study show that the concurrent administration of metoclopramide

with lamotrigine markedly increases the rate of absorption of the latter as reflected by the significant decreases in the mean time to reach maximum concentration (T_{max}). This is also accompanied by significant increases in the area under the curve (AUC) and maximum plasma concentration (C_{max}) of lamotrigine. However, no significant changes were observed in the elimination half-life ($t_{1/2}$) of lamotrigine when it was co-administered with metoclopramide.

The time taken for an orally administered drug to reach the small intestine is an essential factor in determining the rate and extent of its absorption. Indeed, the oral bioavailability of numerous drugs has been shown to be markedly affected by the rate of gastric emptying (Heading et al., 1973; Nimmo et al., 1973). Drug-induced changes in the rate of gastric emptying may have a therapeutic significance if rapid absorption is required or if toxicity is associated with high drug plasma concentrations. Pharmacodynamic studies in humans and animals have established that metoclopramide, after oral and parenteral administration, rapidly increases gastric motility and relaxes the pyloric sphincter and thus reduces the gastric emptying time (Jacoby and Brodie, 1967; Johnson, 1971; Harrington et al., 1983). It is expected, therefore, that metoclopramide, by accelerating gastric emptying, would influence the rate of absorption of other drugs given concurrently with it. Indeed, it has been shown that the concomitant administration of metoclopramide with acetylsalicylic acid (ASA) increases its rate of absorption in patients who are suffering from migraine (Volans, 1975). In addition, metoclopramide has been reported to increase the rate of absorption of paracetamol (Nimmo et al., 1973), tetracycline (Gothoni et al., 1972), levodopa (Mearrick et al., 1974), ethanol (Gibbons and Lant, 1975) and cyclosporine (Wadhwa et al., 1987).

Our finding that metoclopramide increases the rate of absorption of lamotrigine is in agreement with what had previously been reported when other drugs were co-administered with metoclopramide. Hence, the present results may be explained by an enhanced gastric emptying of lamotrigine when it was given together with metoclopramide.

In conclusion, the concurrent administration of metoclopramide and lamotrigine to rabbits produced a significant increase in the rate and extent of absorption of the latter. Although our findings may not be extrapolated to humans, it is possible that the same results may be obtained when lamotrigine is administered simultaneously with other drugs that are known to accelerate gastric emptying.

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