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The effect of parenteral imipramine on the oral absorption of lamotrigine in rats

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Abstract

The interaction between imipramine and lamotrigine was investigated following the acute administration of lamotrigine (20 mg kg^{-1}, p.o.) alone or together with imipramine (25 mg kg^{-1}, i.p.) to rats. Similarly, the same doses of lamotrigine alone or when they were given together with imipramine (15 mg kg^{-1}, i.p.) were administered to rats chronically for 5 days. Plasma samples were collected at 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0 and 24.0 h after lamotrigine administration. An assay of lamotrigine in plasma was performed using a high-performance liquid chromatographic (HPLC) method. The concomitant administration of imipramine (25 mg kg^{-1}, i.p) with lamotrigine (20 mg kg^{-1}, p.o.) acutely, resulted in a significant ($P < 0.05$) decrease in the maximum plasma concentration (C_{max}), the mean area under the plasma concentration–time curve (AUC) and the half-life ($t_{1/2}$), and a significant decrease ($P < 0.001$) in the time to reach maximum concentration (t_{max}), as compared to those obtained for lamotrigine alone. Similarly, the chronic administration of imipramine together with lamotrigine lead to significant decreases in C_{max}, AUC and $t_{1/2}$ while the t_{max} remained unchanged. These results suggest that a significant decrease in the absorption of lamotrigine occurs when it is given acutely or chronically together with the antidepressant imipramine. © 1997 Elsevier Science B.V.

Keywords: Imipramine; Lamotrigine; Pharmacokinetic interaction; Rats

1. Introduction

Lamotrigine, 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine, is a new anti-epileptic drug which is structurally and pharmacologically unrelated to the known currently used anti-epileptic medications. It is effective as an add-on therapy in the management of partial and secondarily generalized seizures (Goa et al., 1993) and has been shown to be effective in other types of epilepsy including resistant partial seizures (Mikati et al., 1989; Brodie, 1992). Current evidence suggests

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that the mechanism of action of lamotrigine is through its ability to block the voltage-sensitive sodium channels, stabilizing neuronal membranes, and hence inhibiting the release of excitatory neurotransmitters, principally glutamate (Lamb et al., 1985; Leach et al., 1986; Yuen, 1994). The profile of the anticonvulsant activity of lamotrigine in animal studies resembles that of phenytoin and carbamazepine (Goa et al., 1993).

An understanding of the pharmacokinetic properties of lamotrigine and a determination of the factors that influence its pharmacokinetics are essential for optimal use of this agent in clinical practice. Following administration, the absorption of lamotrigine is almost complete and its bioavailability was reported as 97.6% (Yuen and Peck, 1988). The time required to reach peak plasma concentration (t_{max}) following the oral administration of lamotrigine is about 1–3 h and does not vary significantly with its dose (Cohen et al., 1987; Ramsay et al., 1991; Yau et al., 1991).

In humans, lamotrigine is metabolized primarily in the liver to form a glucuronide conjugate (Cohen et al., 1987; Posner et al., 1991). This was identified as the 2-*N*-glucuronide (Sinz and Remmel, 1991) and the remainder is retrieved in urine as the parent compound (Posner et al., 1989, 1991). In the rat, however, lamotrigine is excreted mainly as unchanged drug whereas in primates it is excreted predominantly as a glucuronide (Binnie, 1990).

The rate of gastric emptying has important effects on the rate of drug absorption. Many drugs that possess intrinsic pharmacological actions on gastrointestinal motility may influence drug absorption through effects on gastric emptying. It had previously been shown that the absorption of paracetamol (Heading et al., 1973), acetylsalicylic acid and acetaminophen (Kaka and Al-Khamis, 1986), cyclosporine (Wadhwa et al., 1987) and lamotrigine (Al-Humayyd, 1996) is related to the rate of gastric emptying. Drugs which are known to delay gastric emptying may alter the rate of absorption of lamotrigine from the gastrointestinal tract. For instance, it has been reported that propantheline, like atropine, had inhibitory effects on the motor activity of the stomach and small intestine and delayed the absorption of riboflavine (Levy et al., 1972) and paracetamol (Nimmo et al., 1973). Similarly, atropine delayed the absorption of orally administered lignocaine (Adjepon-Yamoah et al., 1973) and tricyclic antidepressants slowed down the absorption of phenylbutazone (Consolo et al., 1970). Since tricyclic antidepressants delay gastric emptying, the influence of imipramine (a tricyclic antidepressant) on the absorption of lamotrigine is described in the present report.

2. Materials and methods

2.1. Materials

Imipramine hydrochloride was purchased from Sigma (St. Louis, MO, USA). Lamotrigine was obtained from Glaxo-Wellcome (London, UK), and acetonitrile (high-performance liquid chromatography (HPLC) grade) from Merck (Darmstadt, Germany).

Imipramine was dissolved in normal saline (0.9%) while lamotrigine was suspended with the aid of two drops of Tween 80 and made up to the required volume (20 ml) in normal saline.

2.2. Methods

2.2.1. Experimental procedure

Male Wistar rats of approximately the same age, weighing 300–350 g, were obtained from the Animal House, College of Medicine, King Saud University, Riyadh, Saudi Arabia. The animals were housed under standard laboratory conditions with free access to food and water ad libitum.

The animals were assigned to four separate drug treatment groups, each comprising nine rats. In acute experiments, the first group of rats was given lamotrigine (20 mg kg^{-1}; p.o.) while the second group had received imipramine (25 mg kg^{-1}; i.p.) together with lamotrigine (20 mg kg^{-1}; p.o.). For the chronic experiments, the third group of rats was given oral lamotrigine (20 mg kg^{-1}) daily for 5 days whereas the fourth group of animals received imipramine (15 mg kg^{-1}; i.p.) together with oral lamotrigine mg kg^{-1}) daily for 5 days.

Rats were then anaesthetized with ether and the right femoral artery was surgically exposed and was cannulated using a fine flexible polyethylene tube. The other end of the tube was then drawn under the skin to an incision in the back region and was connected to a syringe containing heparinized saline. Rats were given 1000 IU kg^{-1} heparin through the cannula prior to drug treatment. The cannula was periodically flushed with heparinized saline and remained functional for 24 h.

After recovery from anaesthesia, rats in groups 1 and 3 were orally challenged with lamotrigine (20 mg kg^{-1}) alone, while those in groups 2 and 4 were given a combination of lamotrigine (20 mg kg^{-1}, p.o.) and imipramine (25 mg kg^{-1}, i.p., for acute studies or 15 mg kg^{-1}, i.p., for the chronic studies). Each animal was housed individually in specially made wooden cages ($22 \times 10 \times 7$ cm) with a metal grid top and kept in a temperature-controlled room (21 ± 1°C). Blood samples (0.3 ml) were withdrawn via the cannula and collected into heparinized Eppendrorff tubes at 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0 and 24 h. The cannula was flushed with an equal volume of heparinized saline after each sample withdrawal.

2.2.2. Determination of plasma lamotrigine concentrations

The concentrations of lamotrigine in plasma were determined by using a HPLC method, with ultraviolet detection as previously described by Fraser et al. (1995). The sensitivity of the assay of this method was 0.10 $\mu g\ ml^{-1}$. Imipramine did not interfere with the detection of lamotrigine when this method was used.

2.2.3. Analysis of data

The plasma concentration–time profile of lamotrigine was constructed for each animal. The individual C_{max} values and the times at which these were reached (t_{max}) values were obtained from the resulting curves. The area under the plasma concentration–time curve (AUC) was calculated by the linear trapezoidal method. Terminal half-lives ($t_{1/2}$) were calculated from the log–linear part of the slope. The differences between any 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

3.1. Acute experiments

The mean plasma concentration–time curves of oral lamotrigine alone or when it was given together with imipramine (i.p.) following single doses are shown in Fig. 1. The absorption process was completed with a mean t_{max} of 7.20 ± 0.04 and 2.80 ± 0.91 h for lamotrigine alone and lamotrigine plus imipramine, respectively. Imipramine induced a downward shift in the time–concentration curve of lamotrigine, a concentration decay being evident 4 h following the antidepressant administration.

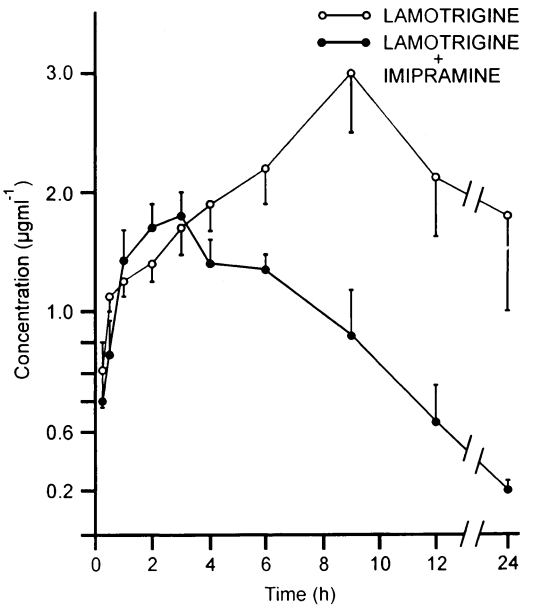

Fig. 1. Plasma lamotrigine concentration–time profiles for acute oral administration of lamotrigine alone (○——○), or when it is given concurrently with parenteral imipramine (●——●). Each point represents the mean ± S.E.M. of nine observations.

Table 1
Plasma pharmacokinetic parameters following the acute administration of lamotrigine (20 mg kg^{-1}, p.o.) alone or together with imipramine (25 mg kg^{-1}, i.p.) in rats

Parameter	Lamotrigine	Lamotrigine + imipramine
C_{max} ($\mu g\ ml^{-1}$)	2.54 ± 0.27	1.86 ± 0.17*
t_{max} (h)	7.20 ± 0.04	2.80 ± 0.91**
AUC_{0-24} ($\mu g\ ml^{-1}\ h^{-1}$)	29.89 ± 2.10	19.18 ± 2.57*
$t_{1/2}$ (h)	12.21 ± 1.10	8.41 ± 1.43*

Each value is the mean ± S.E.M of nine observations.
* $P<0.05$; ** $P<0.001$, as compared to the values obtained for lamotrigine alone (unpaired t-test).

Table 2
Plasma pharmacokinetic parameters following the chronic administration of lamotrigine (20 mg kg^{-1}, p.o.) alone or together with imipramine (15 mg kg^{-1}, i.p.) in rats

Parameter	Lamotrigine alone	Lamotrigine + imipramine
C_{max} ($\mu g\ ml^{-1}$)	6.81 ± 0.25	2.71 ± 0.34*
t_{max} (h)	0.65 ± 0.22	0.90 ± 0.30
AUC_{0-24} ($\mu g\ ml^{-1}\ h^{-1}$)	87.72 ± 2.43	31.30 ± 1.66*
$t_{1/2}$ (h)	19.80 ± 2.80	14.64 ± 1.40*

Each value is the mean ± S.E.M. of nine observations.
* Statistically significant as compared to the values obtained for lamotrigine alone ($P<0.05$; unpaired t-test).

Table 1 summarizes the various pharmacokinetic parameters. Treatment of rats with imipramine significantly ($P < 0.05$) decreased the mean AUC for lamotrigine from 29.89 ± 2.10 $\mu g\ ml^{-1}$ h (lamotrigine alone) to 19.18 ± 2.57 $\mu g\ ml^{-1}$ h (lamotrigine together with imipramine). Similarly, the maximum plasma concentration (C_{max}) for lamotrigine was significantly decreased ($P < 0.05$) from 2.54 ± 0.27 (lamotrigine alone) to 1.86 ± 0.17 (lamotrigine plus imipramine). The time taken to reach maximum plasma concentration (t_{max}) was significantly decreased ($P < 0.001$). The elimination half-life ($t_{1/2}$) for lamotrigine when given together with imipramine was also significantly reduced ($P < 0.05$) as compared to that for lamotrigine alone.

3.2. Chronic experiments

The computed parameters for lamotrigine after its oral administration alone or in combination with parenteral imipramine for 5 days are shown in Table 2, and the mean plasma concentrations are depicted in Fig. 2. Imipramine significantly decreased ($P < 0.05$) the C_{max}, AUC and $t_{1/2}$ of lamotrigine when it was administered together with imipramine, as compared to those values obtained for lamotrigine alone. The time taken to reach the maximum plasma concentration (t_{max}), however, was not significantly affected by imipramine (Table 2).

The administration of imipramine together with lamotrigine induced a downward shift in the time–concentration curve of lamotrigine throughout the entire period of sample collection (Fig. 2).

All the animals which had received lamotrigine together with imipramine chronically for 5 days invariably showed a decrease in the AUC as compared to those which were given lamotrigine alone (Fig. 3).

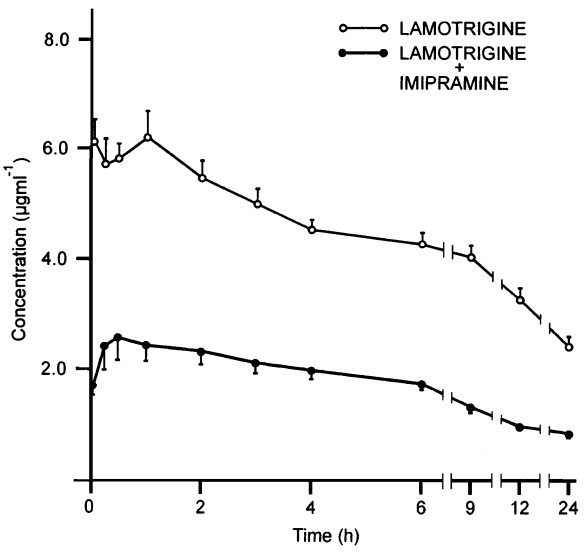

Fig. 2. Plasma lamotrigine concentration–time profiles for chronic oral administration of lamotrigine alone (○——○), or when it is given together with chronic parenteral imipramine (●——●). Each point represents the mean ± S.E.M. of nine observations.

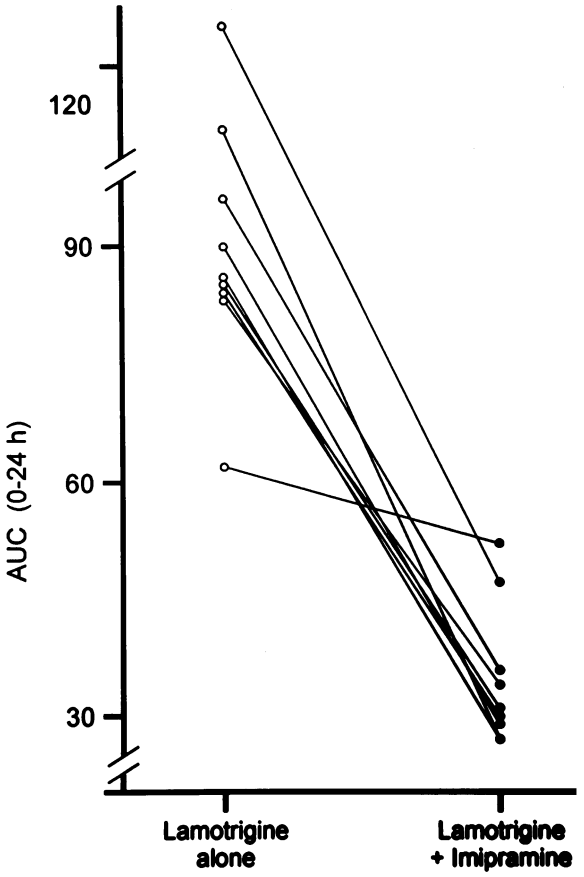

Fig. 3. Area under the plasma lamotrigine–time curves (AUC; 0–24 h) following chronic (5 days) treatment with lamotrigine alone or when it was given together with imipramine.

4. Discussion

The present results show that the acute and chronic parenteral administration of imipramine together with oral lamotrigine produces a significant decrease in the maximum plasma concentration (C_{max}), the half-life ($t_{1/2}$) and the mean area under the plasma–concentration curve (AUC) of lamotrigine, as compared to those obtained when the latter was administered alone.

Imipramine has been widely prescribed for the treatment of major depression (Sallee and Pollock, 1990). The main metabolic pathways include 2-hydroxylation form desipramine, which is further oxidized, by the hepatic cytochrome P-450 microsomal drug oxidation system, (Bickel and Aggiolini, 1966; Crammer et al., 1969) to 2-hydroxydesipramine (Rudorfer and Potter, 1987; Sallee and Pollock, 1990) The pharmacokinetic consequences of the combination of imipramine with other anti-epileptic drugs had previously been investigated in animals. For instance, the concurrent administration of carbamazepine with imipramine resulted in a decrease in the blood levels of the active metabolite (10, 11-epoxide) of the former (Daniel and Netter, 1988). It was concluded from that study that this was due to competition of the two drugs for the active centre of cytochrome P-450. Similarly, it has been shown that long-term treatment with imipramine increases the level of cytochrome P-450 in rats following chronic treatment with the antidepressant for 2 weeks (Daniel and Netter, 1990). It has been reported that lamotrigine is excreted primarily as unchanged drug in rats. Therefore, the increased levels of cytochrome P-450 induced following chronic administration of imipramine cannot explain the decrease in the plasma levels observed for lamotrigine in the present study when the two drugs were given concurrently.

The oral bioavailability of drugs is affected by physiochemical and physiological factors such as gastric emptying and time of food administration in relation to dose. Gastric emptying is an important factor in the absorption of drugs that are mainly absorbed in the small intestine. For instance, the prokinetic drug, metoclopramide, increases the rate and extent of absorption of levodopa and paracetamol (Pinder et al., 1976), diazepam (Gamble et al., 1976), aspirin (Ross-Lee et al., 1982) and lamotrigine (Al-Humayyd, 1996).

On the other hand, drugs that delay gastric emptying such as the anticholinergic, propantheline, (Levy et al., 1972), atropine (Adjepon-Yamoah et al., 1973) and tricyclic antidepressants (Consolo et al., 1970) have been shown to reduce the rate and extent of absorption of other drugs given concurrently with them. For example, it has been shown that propantheline significantly reduces the absorption of paracetamol when the analgesic was given concurrently with it (Nimmo et al., 1973). Lamotrigine is absorbed principally in the small intestine, and the rate and extent of oral lamotrigine absorption may be dose-depen-

dent. Any treatment that decreases the rate of gastric emptying may be expected to reduce the fractional absorption of lamotrigine. In the present study the co-administration of lamotrigine and imipramine resulted in a significant decrease in AUC and C_{max} of lamotrigine. These findings are similar to the results observed with other drugs when the latter were co-administered with tricyclic antidepressants (Levy et al., 1972). Our present data suggest that there were significant changes in the pharmacokinetic parameters of lamotrigine when it was given concurrently with imipramine. The present results are consistent with decreased gastric emptying of lamotrigine when it was given concomitantly with imipramine.

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References

Adjepon-Yamoah, K.K., Scott, D.B., Prescott, L.F., 1973. Impaired absorption and metabolism of oral lignocaine in patients undergoing laparoscopy. Br. J. Anaesth. 45, 143–147.

Al-Humayyd, M.S., 1996. Effect of metoclopramide on lamotrigine absorption in rabbits. Int. J. Pharm. 144, 171–175.

Bickel, M.H., Aggiolini, M.B., 1996. The metabolism of imipramine and its metabolites by rat liver microsomes. Biochem. Pharmacol. 15, 1155–1169.

Binnie, C.D., 1990. Progress in the treatment of epilepsy (editorial. J. Neurol. Neurosurg. Psychiatr. 53, 273–274 (Editorial).

Brodie, M.J., 1992. Lamotrigine. Lancet 339, 1397–1400.

Cohen, A.F., Land, G.S., Breimer, D.D., Yuen, W.D., Winton, C., Peck, A.W., 1987. Lamotrigine, a new anticonvulsant: pharmacokinetics in normal humans. Clin. Pharm. Ther. 42, 535–541.

Consolo, S., Morselli, P.L., Zacala, M., Garratini, S., 1970. Delayed absorption of phenylbutazone caused by desmethylimipramine in humans. Eur. J. Pharmacol. 10, 239–242.

Crammer, J.L., Scott, B., Rolfe, B., 1969. Metabolism of ^{14}C-imipramine: II. Urinary metabolites in man. Psychopharmacologia 15, 207–225.

Daniel, W., Netter, K.J., 1988. Metabolic interaction between imipramine and carbamazepine in vivo and in vitro in rats. Naunyn. Schmiedebergs Arch. Pharmacol. 377, 105–110.

Daniel, W., Netter, K.J., 1990. Alteration of cytochrome P-450 by prolonged administration of imipramine and/or lithium to rats. Naunyn. Schmiedebergs Arch. Pharmacol. 342, 234–240.

Fraser, A.D., MacNeil, W., Isner, A.F., Camfield, P.R., 1995. Lamotrigine analysis in serum by high performance liquid chromatography. Ther. Drug Monit. 17, 174–178.

Gamble, J.A.S., Gaston, J.H., Nair, S.G., Dundee, J.W., 1976. Some pharmacological factors influencing the absorption of diazepam following oral administration. Br. J. Anaesth. 48, 118–125.

Goa, K.L., Ross, S.R., Chrisp, P., 1993. Lamotrigine: a review of its pharmacological properties and clinical efficacy in epilepsy. Drugs 46, 152–176.

Heading, R.C., Nimmo, J., Prescott, L.F., Tothill, P., 1973. The dependence of paracetamol absorption on the rate of gastric emptying. Br. J. Pharmacol. 47, 415–421.

Kaka, J.S., Al-Khamis, K.I., 1986. Effect of domperidone on acetylsalicylic acid and acetaminophen absorption in rabbits. Int. J. Pharm. 28, 133–137.

Lamb, R.J., Leach, M.J., Miller, A.A., Wheathley, P.L., 1985. Anticonvulsant profile in mice of lamotrigine, a novel anticonvulsant. Br. J. Pharmacol. 86, 365P.

Leach, R.J., Marden, C.M., Miller, A.A., 1986. Pharmacological studies on lamotrigine, a novel potential antiepileptic drug: II. Neurochemical studies on the mechanism of action. Epilepsia 27, 490–497.

Levy, G., Gibaldi, M., Prockna, J.A., 1972. Effect of an anticholinergic agent on riboflavin absorption in man. J. Pharm. Sci. 61, 798–799.

Mikati, M.A., Schachter, S.C., Schomer, D.L., Keally, M., Osborne-Shafer, P., 1989. Long-term tolerability, pharmacokinetic and preliminary efficacy study of lamotrigine in patients with resistant partial seizures. Clin. Neuropharmacol. 12, 312–321.

Nimmo, J., Heading, R.C., Tothill, P., Prescott, L.F., 1973. Pharmacological modification of gastric emptying effects of propantheline and metoclopramide on paracetamol absorption. Br. Med. J. 1, 587–589.

Pinder, R.M., Brogden, R.N., Sawyer, P.R., Speight, T.M., Avery, G.S., 1976. Metoclopramide: a review of its pharmacological properties and clinical use. Drugs 12, 18–131.

Posner, J., Cohen, A.F., Land, G., Winton, C., Peck, A.W., 1989. The pharmacokinetics of lamotrigine (BW430C) in healthy subjects with unconjugated hyperbilirubinaemia (Gilbert's syndrome). Br. J. Clin. Pharm. 28, 117–120.

Posner, J., Holdich, T., Crome, P., 1991. Comparison of lamotrigine pharmacokinetics in young and elderly healthy volunteers. J. Pharm. Med. 1, 121–128.

Ramsay, R.E., Pellock, J.M., Garnett, W.R., Sanchez, R.M., Valakas, A.M., Wargin, W.A., Lai, A.A., Hubbell, J., Chern, W.H., Allsup, T., 1991. Pharmacokinetics and safety of lamotrigine (Lamictal®) in patients with epilepsy. Epilepsy Res. 10, 191–200.

Ross-Lee, L., Heazlewood, V., Tyrer, J.H., Eadie, M.J., 1982. Aspirin treatment of migraine attacks. Plasma drug level data. Cephalgia 2, 9–14.

Rudorfer, M.V., Potter, W.C., 1987. Pharmacokinetics of antidepressants. In: Meltzer, H.Y. (Ed.), Psychopharmacology, The Third Generation Progress. Raven Press, New York, pp. 1353–1363.

Sallee, F.R., Pollock, B.G., 1990. Clinical pharmacokinetics of imipramine and desipramine. Lin. Pharmacokinet. 18, 346–364.

Sinz, M.W., Remmel, R.P., 1991. Isolation and characterization of a novel quaternary ammonium-linked glucuronide of lamotrigine. Drug Metab. Dispos. 19, 149–153.

Wadhwa, N.K., Schroeder, T.J., O'Flaherty, E.O., Pesce, A.J., Myre, S.A., First, M.R., 1987. The effect of oral metoclopramide on the absorption of cyclosporine. Transplantation 43, 211–213.

Yau, M.K., Garnett, W.R., Wargin, W.A., Pellock, J.M., 1991. A single dose, dose proportionality and bioequivalence study of lamotrigine in normal volunteers. Epilepsia 32 (Suppl. 3), 8 (Abstract).

Yuen, A.W.C., 1994. Lamotrigine: a review of clinical efficacy. Epilepsia 35 (Suppl. 5), S33–S36.

Yuen, A.W.C., Peck, A.W., 1988. Lamotrigine pharmacokinetics: oral and infusion in man. Br. J. Clin. Pharmacol. 26, 242 (Abstract).