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*Original Research Article.*

# Effect of CYP3A4 Inhibitor Erythromycin on the Pharmacokinetics Of Lignocaine in Subjects with Liver Dysfunction

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## ABSTRACT

**Background:** Lignocaine is a local anaesthetic agent that is also effectively in the acute intravenous treatment of ventricular arrhythmias. The aim of this study was to evaluate the effect of erythromycin, as a prototypical CYP3A4 inhibitor, on the disposition kinetics of lignocaine in healthy volunteers and patients with liver cirrhosis.

**Materials & Methods:** A double-blind, randomized control study, thirty male subjects (10 healthy volunteers and 20 patients with biopsy-proven liver cirrhosis) participated in the study, after giving their informed written consent. The study design was approved by the Institutional Ethics Committee. Patients were excluded from this study if they had a history of gastrointestinal bleeding, severe encephalopathy or any other disease. None of the participants was a smoker or a heavy consumer of alcohol. They were requested to abstain from alcohol during the preceding week and throughout the period of investigation.

**Results:** In our study showed that there were no statistically significant differences between the three groups for age, weight, height, or body mass index. Our study indicates that only in decompensated (Child's class C) cirrhotic patients were the disposition kinetics of lignocaine profoundly altered compared with healthy volunteers. In particular, CL was approximately halved, whereas Vss was increased and, consequently, t1/2 was more than doubled.

**Conclusion:** This study has shown that concomitant administration of erythromycin causes a moderate but statistically significant decrease in lignocaine clearance that, contrary to predictions, is quantitatively similar in healthy subjects and cirrhotic patients. Because, erythromycin also significantly increases the AUC of MEGX, which has been shown to have 80–90% of the antiarrhythmic potency of lignocaine.

**Keywords:** Erythromycin, Liver Cirrhosis, Lignocaine.

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## INTRODUCTION

Lignocaine is a local anaesthetic agent that is also effectively in the acute intravenous treatment of ventricular arrhythmias. Owing to its high lipophilicity, it is eliminated mainly by metabolism, <5%being excreted unchanged in urine.[1] The principal metabolic pathway of lignocaine in human beings is oxidative deethylation to monoethylglycinexylidide (MEGX), which is further de-ethylated to glycinexylidide (GX). The latter is hydrolysed to xylidine and then oxidized to 4- hydroxy-xylidine, the main metabolic product found in urine.[1] Cytochrome P450 (CYP) 3A4 has been proposed as the main CYP isoform responsible for MEGX formation.[2]

Erythromycin has been shown to produce quasiirreversible inhibition of CYP3A4 in vitro, via formation of a CYP3A4-iron-metabolite complex, and to cause clinically important drug interactions with CYP3A4 substrates.[3,4] According to a previous study in healthy volunteers[5], erythromycin causes a statistically significant but limited increase in lignocaine half-life, and a more pronounced increase in the MEGX area under the concentration-time curve. While the present study was in progress, a further investigation on healthy volunteers was published, which found no significant effect of erythromycin on lignocaine disposition kinetics.[6] The aim of this study was to evaluate the effect of erythromycin, as a prototypical CYP3A4 inhibitor, on the disposition kinetics of lignocaine in healthy volunteers and patients with liver cirrhosis.

## MATERIALS & METHODS

A double-blind, randomized control study, thirty male subjects (10 healthy volunteers and 20 patients with biopsy-proven liver cirrhosis) participated in the study, after giving their informed written consent. The study design was approved by the Institutional Ethics Committee. Healthy volunteers were recruited from outpatients attending the Rama Medical College Hospital & Research Centre, Hapur, Uttar Pradesh (India) for routine laboratory tests. They were diagnosed as healthy by means of a thorough clinical examination, including medical history, physical examination, electrocardiogram and standard laboratory tests.

Patients were excluded from this study if they had a history of gastrointestinal bleeding, severe encephalopathy or any other disease. None of the participants was a smoker or a heavy consumer of alcohol. They were requested to abstain from alcohol during the preceding week and throughout the period of investigation.

### Methods

On the morning of study day 1, after an overnight fast, all participants received either 600 mg erythromycin ethylsuccinate or a matched placebo orally at 07.00, 15.00 and 22.00 h. On day 2 they received a fourth dose of erythromycin or placebo at 07.00 h, and 1 h later, 1 mg kg-1 intravenous lignocaine, infused over 1 min by means of a precise volumetric infusion pump. A final erythromycin or placebo dose was given at 15.00 h. A similar erythromycin dosage has been shown to decrease markedly the elimination of the CYP3A4 substrate triazolam.[7] After lignocaine administration, all subjects remained supine for 2 h. They were asked to report any subjective adverse effects and their vital signs were closely monitored.

### Pharmacokinetic Analysis

The lignocaine plasma concentration-vs-time data were modelled by means of Graph Pad Prism 3.0 software. The pharmacokinetics of MEGX and GX were characterized by areas under the plasma concentration-time curves from 0 h to 12 h ($AUC_{0-12}$), peak plasma concentrations (Cmax) and peak times (tmax). Because of the irregular shapes of the curves, AUC0-12 was calculated by means of the trapezoidal rule. Cmax and tmax were estimated from the experimental data.

**Table 1: Summary of patient characteristics**

| Characteristics | Healthy subjects | Patients with cirrhosis | |
|---|---|---|---|
| | | Child's class A | Child's class C |
| Age (years) | 53 ± 12 | 54 ± 6 | 53 ± 8 |
| Weight (kg) | 77 ± 7 | 81 ± 10 | 78± 7 |
| Height (cm) | 174 ± 5 | 171 ± 6 | 169 ± 7 |
| Body mass index (kg/m$^2$ ) | 25.3 ± 3.3 | 27.0 ± 2.2 | 27.7 ± 2.5 |
| Albumin (35-55 g/dl) | 41.4 ± 4.2 | 39.5 ± 3.3 | 27.7 ± 3.2** |
| Bilirubin (5-17 mmol/l ) | 13.1 ± 2.9 | 17.4 ± 5.0 | 49.7 ± 25.7** |
| Prothrombin level (70-100%) | 88.9 ± 8.3 | 81.3 ± 7.5 | 68.6 ± 14.7* |
| Pugh score (5)† | 5 (5) | 5 (5–6) | 10.4 (10–14)** |

**Table 2: Effect of erythromycin coadministration on the pharmacokinetic parameters of lignocaine.**

| Characteristics | Healthy subjects | | Patients with cirrhosis | | | |
|---|---|---|---|---|---|---|
| | Placebo | Erythromycin | Child's class A | | Child's class C | |
| | | | Placebo | Erythromycin | Placebo | Erythromycin |
| CL (ml kg, 1 min, 1) | 9.83 ± 3.02 | 8.15 ± 3.39* | 9.56 ± 2.03 | 7.79 ± 2.43* | 5.46 ± 1.83 | 4.26 ± 1.77** |
| Ratio % (95% CI) | 82 (65, 98) | | 81 (63, 99) | | 77 (62, 91) | |
| $V_c$ | 0.66 ± 0.35 | 0.61 ± 0.31 | 0.38 ± 0.18 | 0.40 ± 0.13 | 0.38 ± 0.13 | 0.42 ± 0.13 |
| Ratio % | 102 (79, 125) | | 105 (75, 135) | | 110 (89, 129) | |
| $V_{ss}$ | 1.47 ± 0.27 | 1.34 ± 0.34 | 1.95 ± 0.38 | 2.08 ± 0.74 | 2.44 ± 0.72 | 2.42 ± 0.68 |
| Ratio% | 92 (77, 106) | | 105 (87, 124) | | 100 (89, 111) | |
| t 1 /2 (h) | 2.23 ± 0.55 | 2.80 ± 0.45** | 3.15 ± 0.94 | 4.09 ± 2.13** | 5.77 ± 1.19 | 7.74 ± 2.31** |
| Ratio % | 130 (109, 151) | | 124 (104, 145) | | 132 (118, 147) | |

## RESULTS

In our study showed that the there were no statistically significant differences between the three groups for age, weight, height, or body mass index. On the basis of the conventional liver function tests, minor differences were apparent between patients with Child's grade A cirrhosis and healthy volunteers. In contrast, test results were indicative of advanced hepatocellular insufficiency in Child's class C cirrhotic patients. No significant changes in blood pressure or pulse rate were observed after lignocaine injection.

Subjective adverse effects (paraesthesia, dizziness or drowsiness) were mild and transient, and only occurred in a few subjects (1–3) in each of the three study groups (table 1).

Our study indicates that only in decompensated (Child's class C) cirrhotic patients were the disposition kinetics of lignocaine profoundly altered compared with healthy volunteers. In particular, CL was approximately halved, whereas Vss was increased and, consequently, t1/2 was more than doubled (table 2).

## DISCUSSION

At variance with previous investigations[5,6], this study has shown that concomitant administration of erythromycin decreases lignocaine clearance in healthy volunteers to a statistically significant extent. A greater increase in terminal half-life (30%, compared with the 16% reported)[5] was also observed. Unlike that on other CYP3A4 substrates[3,4], the modest effect of erythromycin on lignocaine disposition may be due to the following reasons. (i) Lignocaine has a high extraction ratio (62–81%)[1], therefore, its systemic clearance depends more on liver blood flow than metabolic capacity and, consequently, may not be very sensitive to the action of metabolic inhibitors. (ii) Other CYP isoforms may contribute to lignocaine biotransformation.

According to a recent report[8], CYP1A2 catalyses the 3-hydroxylation of lignocaine and is also involved in its de-ethylation (MEGX formation), although the relative contribution of this isoform to the metabolic clearance of lignocaine has not been quantified. In accordance with Isohanni et al.[5], we found that erythromycin coadministration increased MEGX AUC. To explain this observation, Isohanni et al.[5] hypothesized that erythromycin inhibits further MEGX metabolism. Three metabolic routes have been identified for MEGX elimination: 3-hydroxylation, further deethylation to GX, and hydrolysis of the amide bond with generation of 2,6-xylidine. However, it has been shown that 3-hydroxy-MEGX production is negligible in man (0.3% of a lignocaine dose)[9]. Inhibition of MEGX hydrolysis seems unlikely as, to our knowledge; no effect of erythromycin on amidases has ever been reported. In order to test whether the effect of erythromycin on MEGX concentrations is due to inhibition of MEGX de-ethylation, we also measured GX concentrations. Although the latter were found to be lower after erythromycin coadministration, differences did not reach statistical significance.

Liver cirrhosis causes progressive alteration of hepatic microcirculation, leading to capillarization of the sinusoids and consequent decrease in drug uptake. Thus, as liver function worsens, the clearance of highly extracted drugs progressively loses its flow-dependence and becomes capacity-limited, as shown for lignocaine.[10]

Hence, inhibition of lignocaine metabolizing enzymes should result in a more marked reduction of clearance in patients with liver cirrhosis. Contrary to this hypothesis, erythromycin caused very similar changes in lignocaine clearance in healthy volunteers and the two groups of cirrhotic patients. The lack of a more marked reduction in clearance in cirrhotic patients may be due to reduced uptake of the inhibitory drug by the cirrhotic liver, resulting in decreased enzyme inhibition. In this context, decreased or absent enzyme induction has been observed in liver disease.[11,12]. Alternatively, a macrolide antibiotic such as erythromycin may not be the ideal drug to test this hypothesis, as its inhibitory action is consequent upon the formation of a nitrosoalkane metabolite[4], which might be produced to a lesser extent in subjects with liver dysfunction.

On the other hand, the other currently used CYP3A4 inhibitors, the azole antifungals, have been shown to have no effect on lignocaine and MEGX kinetics.[5] Further tests with highly extracted drugs metabolized by other CYP isoforms are necessary for a definitive assessment of whether or not the clearance of flow-dependent drugs becomes more sensitive to enzyme inhibition in liver cirrhosis.

With regard to the effect of liver dysfunction on lignocaine disposition kinetics, this study has shown that the extent of the kinetic modifications is closely dependent on the stage of liver cirrhosis. No significant modifications in CL or t1/2 were observed in patients with compensated (Child's grade A) liver cirrhosis, whereas profound alterations of both parameters were found in decompensated (Child's class C) cirrhotic patients. At variance with the changes in these two parameters, Vss also increased to a significant extent in compensated patients. No such modification had been reported in a previous study[13]; but our results are in good agreement with the observation of Barry et al.[14] that the concentration of a1-acid glycoprotein and, consequently, lignocaine plasma protein binding, start to decrease significantly in Child's grade A liver cirrhosis. Collectively, these findings indicate that only in patients with decompensated liver cirrhosis is a reduction of lignocaine dose required.

## CONCLUSION

In conclusion, unlike previous investigations[5,6], this study has shown that concomitant administration of erythromycin causes a moderate but statistically significant decrease in lignocaine clearance that, contrary to predictions, is quantitatively similar in healthy subjects and cirrhotic patients. Because erythromycin also significantly increases the AUC of MEGX, which has been shown to have 80–90% of the antiarrhythmic potency of lignocaine[1], maintenance of the rate of lignocaine infusion at the lower end of the therapeutic range (1- 4 mg kg-1) may be prudent and it may be advisable to monitor closely patients in the event that inadequate clinical response requires upward dose adjustment.

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