

Non-genetic factors play more important role in lansoprazole metabolism than *CYP2C19* pharmacogenetic profiles in European patients with burns

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Short Report

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Abstract

Single nucleotide variants in *CYP2C19* gene, as well as some non-genetic factors, are associated with the effectiveness most proton pump inhibitors used for the stress ulcer prophylaxis and should be considered in personalized treatment. In this study, we aimed to determine the *CYP2C19**2 and *17 genotypes by qPCR and the concentration of lansoprazole and its metabolites using HPLC in 50 burn patients from European population on their first-ever lansoprazole prophylaxis. While *CYP2C19* pharmacogenetic profiling in patients with burns played no significant role in predicting their ability to metabolize lansoprazole, association of non-genetic factors, such as age, sex, BMI, smoking, or substance abuse, with lansoprazole metabolism were detected. Our results suggest that when prescribing lansoprazole to prevent stress ulcers in burn patients from the European population, there is no particular need to take their genetic predispositions into consideration, as other factors have a greater effect.

1 Introduction

Proton pump inhibitors (PPIs) are drugs reducing stomach acids, often used as stress ulcer prophylaxis (SUP). In patients with burns, the SUP is recommended to prevent clinically important upper gastrointestinal bleeding. Lansoprazole (LAN), a widely prescribed PPI, is metabolized in the liver mostly by the highly polymorphic cytochrome P450 2C19 (*CYP2C19*) and secondarily by cytochrome P450 3A4 (*CYP3A4*, with relatively rare variants in the European population). Among the variant alleles, two (*CYP2C19**2 and *17) are the most common in Europeans, with allele frequencies > 10%. The variant *2 (rs4244285) leads to the expression of a non-functional *CYP2C19* protein, while the variant *17 (rs12248560) causes an increase in gene expression and enzyme activity [1]. *CYP2C19* metabolizes LAN to 5-hydroxylansoprazole (OHL), while *CYP3A4* metabolization produces lansoprazole sulphone (LS). Variations in the *CYP2C19* genetic profile may affect plasma levels of LAN and its metabolites, altering the effectiveness of PPI treatment in individual patients. Knowledge of the respective *CYP2C19* variant allows to predict the intensity of PPIs metabolism and classify the resulting *CYP2C19* phenotypes as poor metabolizers (PMs, *1*1/*2*2), intermediate metabolizers (IMs, *1*1/*1*2), extensive metabolizers (EMs, *1*1/*1*1), ultrarapid metabolizers (UMs, *1*17/*1*1 or *17*17/*1*1), and ambivalent metabolizers (AMs, *1*17/*1*2) [2].

Here, we hypothesized that the predicted *CYP2C19* phenotype in patients with minor or moderate burns will be reflected in plasma concentrations of LAN, its metabolites OHL and LS, and the metabolic ratios of these compounds. To test this hypothesis, we measured the concentrations of LAN and its metabolites, and analyzed their associations with (a) *CYP2C19* pharmacogenetic profiles of burn patients from the European population and (b) non-genetic factors (age, BMI, sex, etc.), which might also affect drug efficiency.

2 Methods

Methods are described in detail in the Supplement. Briefly, our study was conducted at the Department of Burns and Plastic Surgery, University Hospital Brno, Czech Republic. Ethical approval (No. 05-061020/EK, October 6, 2020) has been granted for this project in accordance with the principles of the Declaration of Helsinki. All participants signed an informed consent. Inclusion criteria were patients of European ancestry treated at this department aged ≥ 18 able to sign an informed consent and indicated for SUP using PPIs. Patients with second-degree (IIa–IIb) burns involving $> 20\%$ of the total body surface area (TBSA), those with hepatic dysfunction classified as Child-Pugh B or C, and those with medications that affect the metabolic activity of the CYP2C19 or interact with PPIs were excluded. Clinical data including information about smoking and substance abuse were obtained from patients' electronic medical records.

For SUP, patients took 30 mg of LAN (Lanzul®) on an empty stomach 30–60 minutes before the first meal of the day. Three hours later, whole venous blood specimens were collected and plasma separated. Later, DNA was extracted and qPCR genotyping analysis was performed on LightCycler® 480 Instrument (Roche Diagnostics, Indianapolis, USA). Plasma concentrations of LAN and its metabolites OHL and LS were analyzed using HPLC UV and HPLC MS. The results were statistically analyzed in R version 4.3.3 with the ggplot2 and stats packages using appropriate methods. Multivariate linear models were constructed using predicted CYP2C19 phenotype, sex, age, TBSA, smoking, and substance abuse as predictors and LAN/metabolites/their ratios as explained variables.

3 Results

In total, 50 patients were included (15 women and 35 men), mean age 44.8 ± 14.3 years. The basic demographic characteristics are presented in Supplementary Table S1, the observed allele frequencies observed allele frequencies for both *CYP2C19* variants are presented in Supplementary Table S2 (since only one patient belonged to the PM group, this group was merged with the IM group). No differences between the groups of burn patients with predicted CYP2C19 phenotypes were observed in any of the demographic variables (Kruskal-Wallis test, see Fig. 1). However, several significant associations between the LAN or its metabolites and demographic variables (age, sex, BMI, smoking, and substance abuse) were observed (Fig. 2). In the multivariate linear models, only those for LAN and LAN/OHL ratio were borderline significant (F-test *p*-values 0.037 and 0.040, respectively), with sex and age as significant regressors. Full results of the multivariate linear models are presented in Supplementary Tables S3 and S4.

4 Discussion

Contrary to the expectations, we found no evidence of differences in the concentrations of LAN, its metabolites, or their ratios between the groups of burn patients stratified according to their predicted CYP2C19 phenotypes. LAN concentrations positively correlated only with age. On the other hand, a strong positive association was detected between OHL concentrations and female sex, along with

significant negative correlations between the OHL concentrations and BMI, smoking, and substance abuse.

The negative correlation between BMI and OHL could be possibly explained by the presence of chronic inflammatory state associated with obesity, which is generally linked to the reduced activity of some CYP enzymes and decreased CYP2C19 activity in obese patients was repeatedly found in comparison to those with normal weight [3].

A significant negative correlation between substance abuse and OHL levels and a positive correlation between the LAN/OHL metabolic ratio and substance abuse were observed in our study. A significant negative correlation was also observed between smoking and OHL levels. This pattern may suggest a greater contribution of CYP3A4-mediated LAN metabolism in smokers. CYP2C19 plays an important role in the conversion of cotinine to cotinine-N-oxide (COX), while CYP3A4 contributes only minimally to cotinine metabolism, primarily at elevated cotinine concentrations [4]. Increased involvement of CYP2C19 in smokers could potentially favor the CYP3A4-mediated metabolism of LAN, resulting in lower OHL levels. However, the underlying mechanism remains unclear and requires further investigation.

A significant positive correlation between age, LAN, LS, and associated ratios suggests reduced CYP2C19 metabolic activity and, contrary, higher metabolic activity of CYP3A4 in older patients (leading to higher LAN metabolization to LS in these patients). In other words, the metabolism of LAN through CYP2C19 is slower in older patients, resulting in higher active plasma concentrations (and, in effect, higher effectiveness of the drug). At the same time, the relative importance of metabolization to LS increases with age. This is consistent with findings by Hussein et al. reporting longer LAN half-life in older patients [5].

The presented study is the first dealing with personalized SUP in burn patients. However, several limitations need to be acknowledged. Firstly, a relatively small sample size limits the statistical power when analysing a wide range of factors involved in the LAN metabolism. Also, alcohol and drug abuse can influence the liver metabolization capacity and, considering a relatively high number of such individuals in our patient group (which is, however, typical of patients with burns), this may outweigh the effects of genetic factors in LAN metabolization.

5 Conclusion

This study investigated the effect of genetic variants *2 and *17 in the *CYP2C19* gene, as well as of non-genetic factors, on the plasma level of LAN and its metabolites OHL and LS in burn patients from European population using LAN for the SUP. The predicted CYP2C19 phenotype did not play any significant role in actual metabolization of LAN, and any such possible effects were overwhelmed by effects of non-genetic factors, such as BMI, age, smoking or substance abuse. Our results suggest that when prescribing LAN to prevent stress ulcers in burn patients from European population, there is no special need to take their genetic predispositions into consideration, as other factors have a greater effect.

Declarations

7 Funding

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8 Ethics

This study was approved by the Ethics Committee of University Hospital Brno on 6 October 2020 under reference number 05-061020/EK. All procedures performed in this study were conducted in accordance with the ethical standards of the responsible committee and the Declaration of Helsinki.

9 Informed Consent

All participants signed an informed consent.

10 Use of Generative AI

The authors declare that no Generative AI was used in the preparation of this manuscript.

11 Data Availability

The data supporting this study are available in the Zenodo repository. DOI: 10.5281/zenodo.21451936

12 Clinical Trial Number

Not applicable.

13 Credit Author Statement

NM – Investigation, Methodology, Writing – original draft

JB – Data curation, Formal analysis, Visualization

JJ – Writing – review and editing

OZ – Methodology, Supervision, Writing – review and editing

JG – Methodology, Investigation

OP – Methodology, Investigation

MF – Investigation, Writing – review and editing

BL – Conceptualization, Writing – review and editing, Supervision

PBL – Conceptualization, Funding acquisition, Supervision, Writing – review and editing

14 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Figures

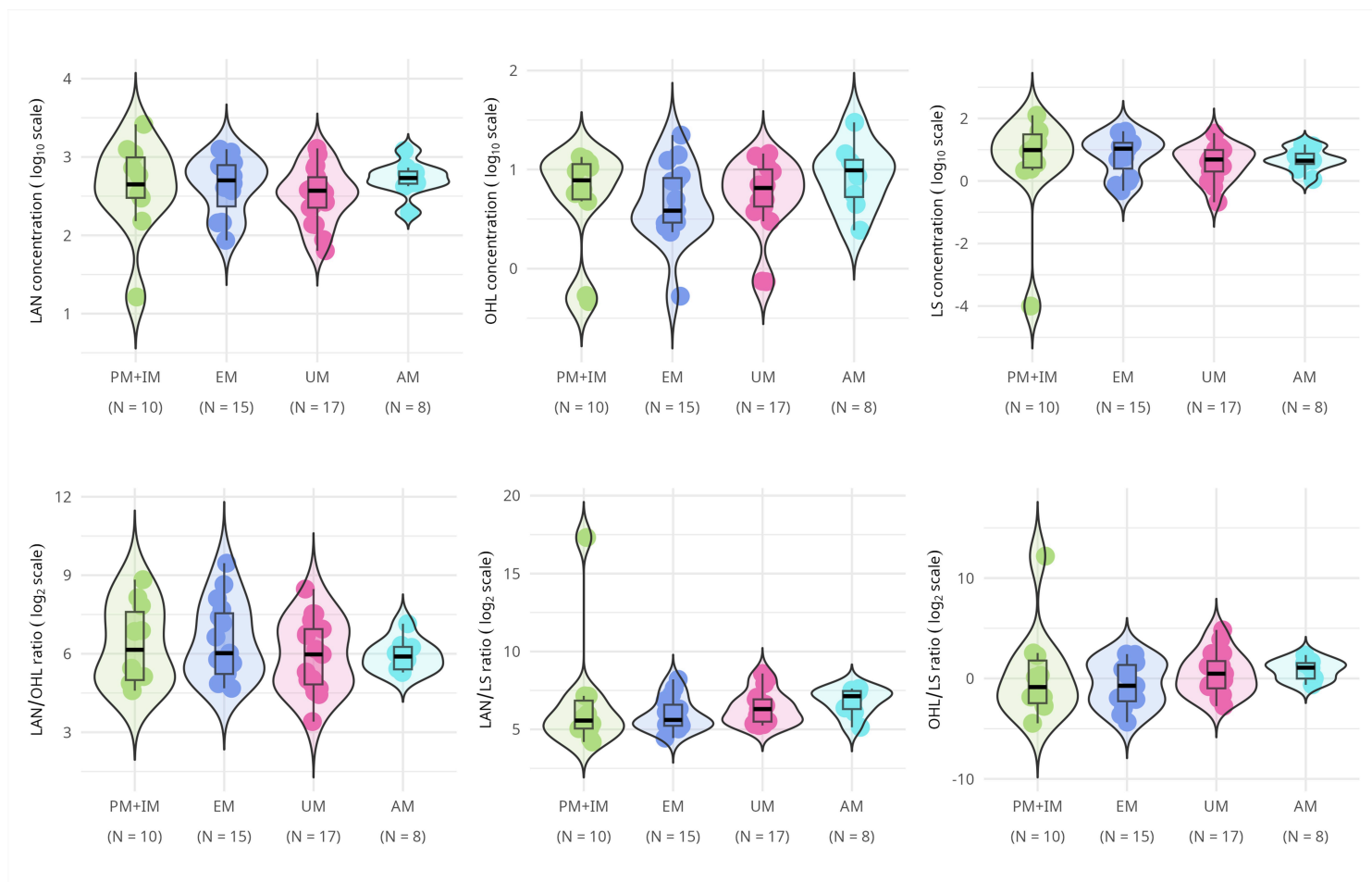


Figure 1

Violin plots of measured drug, its metabolites and their ratios (logarithmically scaled) for 50 burn patients stratified according to their predicted CYP2C19 phenotypes.

PM, poor metabolizer; IM, intermediate metabolizer; EM, extensive metabolizer; AM, ambivalent metabolizer; UM, ultrarapid metabolizer; LAN, lansoprazole; OHL, 5-hydroxylansoprazole; LS, lansoprazole sulphone

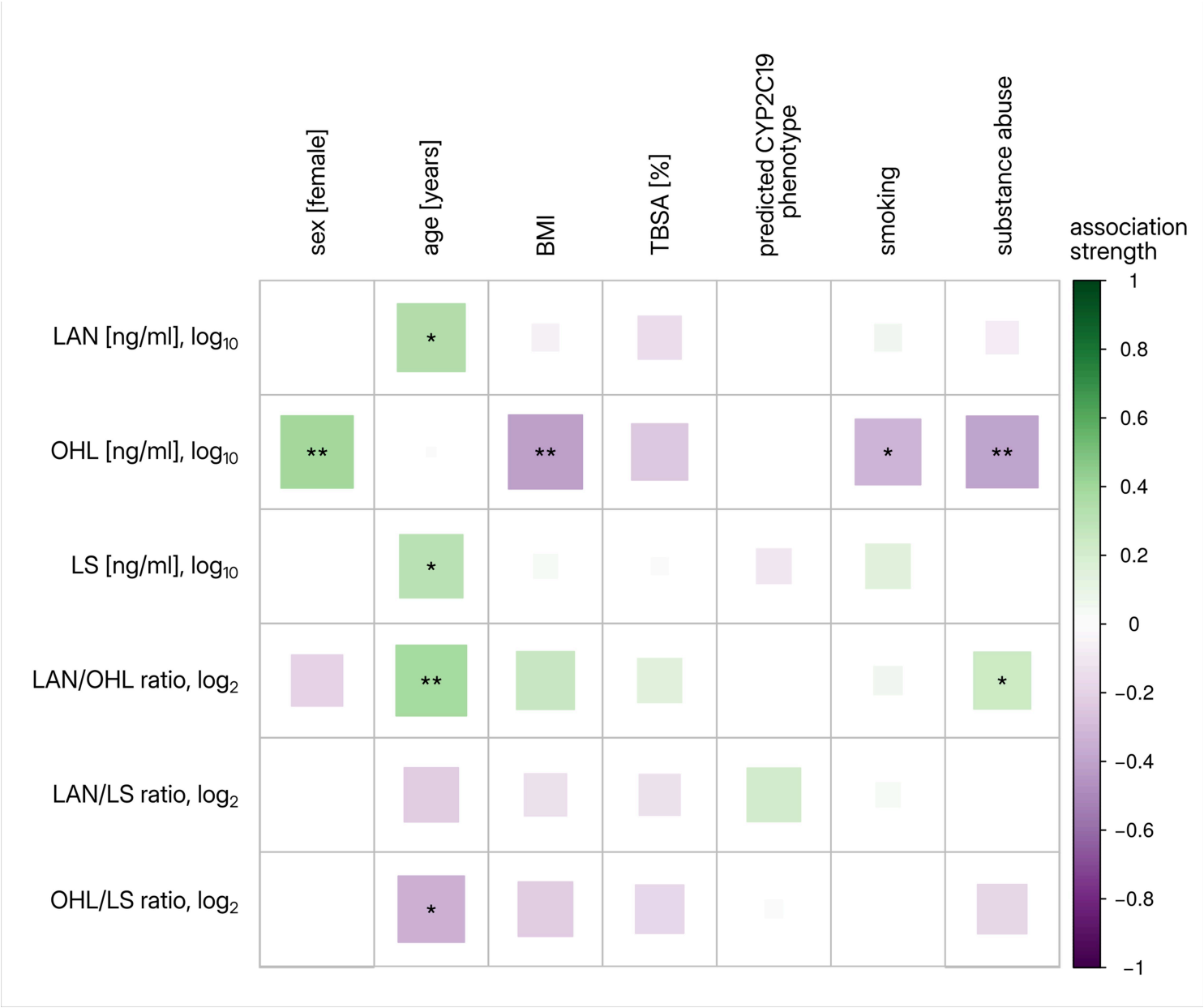


Figure 2

Associations between clinical variables of 50 burn patients and measured drug/metabolite concentrations evaluated using Spearman correlation, rank-biserial correlation with the Wilcoxon rank-sum test, or Kruskal–Wallis test as appropriate, with effect size estimated using signed epsilon-squared–based correlation coefficients.

BMI, body mass index; TBSA, total burns surface area; LAN, lansoprazole; OHL, 5-hydroxylansoprazole; LS, lansoprazole sulphone

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryMethods.docx](#)
- [SupplementaryTables.docx](#)