International Journal of Antimicrobial Agents 50 (2017) 557–563

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Linezolid in liver failure: exploring the value of the maximal liver function capacity (LiMAx) test in a pharmacokinetic pilot study

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ARTICLE INFO

Article history:
Received 4 April 2017
Accepted 24 June 2017

Keywords:
Liver failure
Liver function test
Dosing
Linezolid

ABSTRACT

Patients in the intensive care unit frequently require antibiotic treatment. Liver impairment poses substantial challenges for dose selection in these patients. The aim of the present pilot study was to assess the novel maximal liver function capacity (LiMAx test) in comparison with conventional liver function markers as covariates of drug clearance in liver failure using linezolid as a model drug. A total of 28 patients with different degrees of liver failure were recruited. LiMAx test as well as plasma, dialysate and urine sampling were performed under linezolid steady-state therapy (600 mg twice daily). NONMEM® was used for a pharmacometric analysis in which the different clearance routes of linezolid were elucidated. Linezolid pharmacokinetics was highly variable in patients with liver failure. The LiMAx score displayed the strongest association with non-renal clearance ($CL_{non\text{-}renal}$) [= 4.46·(body weight/57.9) $^{0.75}$·(LiMAx/221.5)$^{0.388}$ L/h], which reduced interindividual variability in $CL_{non\text{-}renal}$ from 46.6% to 33.6%, thereby being superior to other common markers of liver function (international normalised ratio, gamma-glutaryl transferase, bilirubin, thrombocytes, alanine aminotransferase, aspartate aminotransferase). For LiMAx < 100 µg/kg/h, 64% of linezolid trough concentrations were above the recommended trough concentration of 8 mg/L, indicating the necessity of therapeutic drug monitoring in these patients. This is the first pilot application of the LiMAx test in a pharmacokinetic (PK) study demonstrating its potential to explain PK variability in linezolid clearance. Further studies with a larger patient collective and further drugs are highly warranted to guide dosing in patients with severe liver impairment.

1. Introduction

Patients in the intensive care unit frequently suffer from bacterial infections. Management of infectious diseases in critically ill patients is challenging due to severely altered pharmacokinetic (PK) characteristics [1–3]. Dose-finding studies are usually performed in healthy volunteers or in patients who are not critically ill [4–6] and extrapolation of the dosage recommendations to critically ill patients may not be reasonable due to pathophysiological changes in this specific patient population.

Inadequate dosing is a major risk factor contributing to underexposure or overexposure to antimicrobials in these patients. Underexposure may lead to potential therapeutic failure and the development of drug-resistant bacterial strains. Overexposure may result in a higher risk of drug-related toxicity [7]. Altered pharmacokinetics in critically ill patients supports a change of dosing strategy favouring an individualised approach [2,8]. In renal failure, for renally eliminated drugs dosing recommendations are often based on measurement of creatinine clearance (CL_{cr}) as a reasonable proxy of renal function. However, hepatic dysfunction can also reduce drug metabolism and clearance, especially of mainly hepatically metabolised drugs and antibiotics [9,10]. Owing to a lack of reliable liver function tests, few data are available to guide antibiotic dose adjustments in critically ill patients with liver dysfunction [11,12].

The recently introduced maximal liver function capacity (LiMAx) test provides a non-invasive diagnostic tool for determining quantitative liver function in different settings. The LiMAx test determines the maximal liver function capacity based on a non-invasive breath test. In several previous studies, the LiMAx test was successfully evaluated as a dynamic liver function test prior to and following liver resection and liver transplantation as well as in septic patients [13–16].

Linezolid is an oxazolidinone antibiotic used for the treatment of infections caused by Gram-positive bacteria. It is metabolised

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https://doi.org/10.1016/j.ijantimicag.2017.06.023
0924-8579/

non-enzymatically and enzymatically in the lactone and lactam pathways. Clearance of linezolid is ca. 65% non-renal and up to 30% appears unchanged in the urine [17]. Based on this PK profile, linezolid clearance was not expected to vary significantly in patients with renal or hepatic failure [18]. However, recent studies reported increased PK variability in critically ill patients with renal and/or hepatic failure presenting wide interindividual variability of linezolid trough levels during treatment with the recommended standard dosing of 600 mg twice daily [19–22]. The reason for the variability remained unknown and dosing recommendations could not be derived from their findings.

The aim of this prospective study was to evaluate linezolid trough serum concentrations (C_{min}) in patients with or without liver dysfunction. To define the influence of liver failure precisely, the correlation between linezolid C_{min} values and the degree of liver dysfunction, as quantified by the LiMAx test, was evaluated, facilitated by a population PK approach.

2. Patients and methods

2.1. Ethics

This study was approved by the Ethics Review Board of the Charité medical faculty (Berlin, Germany) in accordance to the provisions of the Declaration of Helsinki. Written informed consent was obtained from all of the participants or their responsible legal representatives prior to study inclusion.

2.2. Patients

Patients from the surgical intensive care unit of the Charité University Hospital were included in this observational study. Inclusion criteria were a medical indication for an intravenous (i.v.) anti-infective therapy with linezolid and an age between 18–99 years. Exclusion criteria were methacetin allergy, co-medication with substances metabolised by cytochrome P450 1A2 (CYP1A2) (e.g. ciprofloxacin, mexiletine, propafenone) or with substances affecting the clearance of linezolid (e. g. rifampicin), and/or missing informed consent.

2.3. Study design

Enrolled patients ($n = 28$) were repeatedly measured at up to five different time points during the course of anti-infective therapy with linezolid. At each time point, the LiMAx test was performed, a serum sample, 24-h urine sample and dialysate sample in patients on continuous venovenous haemodialysis were taken, and routine blood parameters were determined. To assess linezolid plasma C_{min} in a steady-state condition, the first probe sampling was carried out ≥36 h after the first dosage of the drug. All patients received recommended standard dosing of 600 mg linezolid twice daily with an infusion time of 30 min. A 10 mL blood sample was drawn from a central venous or arterial line 15 min prior to administration of the next linezolid dose. Following centrifugation at 4000 rpm for 5 min, serum was separated in cryotubes and was stored at –80 °C until assayed.

2.4. Linezolid assay

Linezolid serum concentrations were analysed by high-performance liquid chromatography (HPLC) [23]. Briefly, samples were prepared by mixing aliquots of 250 µL of serum (patient sample or linezolid-spiked serum) with 50 µL of internal standard and 500 µL of extraction solution (methanol/acetonitrile 50/50). After mixing and centrifugation at 4000 rpm at 4 °C for 10 min, 200 µL of the supernatant was diluted and was mixed with 600 µL of water for injection and was injected onto the HPLC column. For each day of analysis, calibrator and control samples were defrosted, processed and consecutively analysed. The HPLC system consisted of a Shimadzu LC-20AD pump (Shimadzu, Kyoto, Japan), an autoinjector (SIL-10AF; Shimadzu) and a controller unit (SCL-10A VP; Shimadzu). Detection was performed with a diode array detector (SPD-M20A; Shimadzu) at 204 nm and 260 nm. The relative standard deviation of interday and intraday precision was <10% for the assay, and the limit of detection and quantification was 0.2 mg/L and 1.0 mg/L, respectively.

2.5. LiMAx test

The LiMAx test was performed using the FLIP™ Analyzer (Humedics GmbH, Berlin, Germany). The test substrate, ^{13}C-labelled methacetin (Humedics GmbH), was applied as an i.v. bolus of 2 mg/kg body weight (WT). ^{13}C-labelled methacetin is metabolised by the specific liver enzyme CYP1A2 into $^{13}CO_2$ and acetaminophen. $^{13}CO_2$ is exhaled and leads to an alteration of the normal $^{13}CO_2$:$^{12}CO_2$ ratio in the exhaled breath. Liver function capacity is calculated from the kinetic analysis of the $^{13}CO_2$:$^{12}CO_2$ ratio over a period of 60 min. The normal range is defined as >315 µg/kg/h. In mechanically ventilated patients, a special tube was used to dissipate the total amount of exhaled gas to the $^{13}CO_2$ detector [16,24].

2.6. Exploratory statistical analysis

According to their LiMAx result at the respective measurement point, parameters of each time point were matched into one of the following groups: (A) LiMAx < 100 µg/kg/h; (B) LiMAx 100–199 µg/kg/h; (C) LiMAx 200–299 µg/kg/h; and (D) LiMAx ≥ 300 µg/kg/h. The groups were investigated in terms of severity of illness using the Acute Physiology and Chronic Health Evaluation (APACHE) II score, the Sepsis Organ Failure Assessment (SOFA) score and the Simplified Acute Physiology Score II (SAPS II). Liver function was evaluated by biochemical testing of aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutaryl transferase (γGT), pseudocholinesterase (PCHE), glutamate dehydrogenase (GLDH), bilirubin, lactate, thrombocytes and international normalised ratio (INR).

For better illustration, investigation of baseline characteristics between liver failure and normal liver function were carried out by comparison of groups A (LiMAx < 100 µg/kg/h) and D (LiMAx ≥ 300 µg/kg/h).

Statistical analysis of demographic and clinical parameter was carried out using the statistical software package IBM SPSS Statistics v.19.0 (IBM Corp., Armonk, NY). For comparison of two or more independent samples of equal or different sample sizes, the non-parametric Kruskal–Wallis test was performed. Categorical data were investigated using the Pearson χ^2 test. Non-normally distributed data are presented as median with interquartile range. A P-value of <0.05 was considered statistically significant.

The target concentration range was defined according to findings published recently. The minimum inhibitory concentration inhibiting the growth of 90% of relevant infectious pathogens (MIC_{90}) was determined as 2 mg/L [25] as was set the lower threshold of the target concentration range. In agreement with previous observations, the upper threshold was set at 8 mg/L [19,20,26–28].

2.7. Pharmacometric analysis

NONMEM® 7.3 (Icon Development Solutions, Ellicott City, MD) was utilised for population PK modelling and was executed via