Eur J Med Res (2008) 13: 205-208

Safety of Long-term Lopinavir Plasma-levels in Patients with Liver Disease

P. Langmann[2], C. Hubert[1], W. Heinz[1], A. Trein[3], E. Schnaitmann[3], M. Leyh[1], H. Klinker[1], R. Winzer[1]

[1]Department of internal Medicine II – divison of infectious diseases, University of Wuerzburg, Wuerzburg, Germany, [2]Private-Praxis, Karlstadt, Germany, [3]Private-Praxis, Stuttgart, Germany

Abstract
Chronic liver disease is often found in HIV infected patients. LPV as first choice drug is often used over long time periods. TDM as a tool in patients care is important but the knowledge of LPV-plasma-levels in patients with chronic liver disease remain uncertain. With this retrosepective analysis we want to show if there are differences in LPV-plasma-levels between patients with and without chronic liver diseases over a long-time period.

LPV-plasma-levels were analysed with an HPLC-based methode. The LPV-plasma-levels over the time course in patients with chronic liver disease (n = 30) and patients without liver disease (n = 38) was evaluated. Liver function tests, CD4-cell count and HI-viral load was also correlated with liver disease.

The LPV plasma-levels of n = 450 samples from 30 patients with liver disease (Hepatitis B: n = 17, Hepatitis C: n = 16, Alcoholic liver disease: n = 7) were determined over 18.7 ± 16,3 months (1 - 48.5 months). A median of 10 samples per patient was eligible (2 - 50 samples). There are no significant differences according to liver disease in LPV-plasma levels (mean C_{trough} without: 5917 ± 4811 ng/ml, mean C_{trough} with liver-disease: 6564 ± 4517 ng/ml, $p > 0.05$). The intraindividual and interindividual variation of LPV-plasma levels, CD-4 increase, HI-virus suppression and liver tests in patients with and without liver disease is comparable.

In this clinical setting no differences in LPV-plasma levels between patients with and without chronic liver disease could be demonstrated. LPV-therapy in patients with chronic liver disease is therefore safe. In patients with impaired liver function TDM is a helpful tool for dose adjustment.
Key words: HPLC, Lopinavir, chronic liver disease, drug monitoring

1. Introduction

Chronic liver disease is commonly found in patients with HIV, mainly due to similar ways of infection for Hepatitis B and C [1, 2]. Liver damage might sometimes be associated with microsomal enzym induction as well as with reduction in the metabolic capacity in advanced states of liver disease. Some HIV drugs themselves induce or amplify liver toxicity [1, 3, 4, 5, 6]. It is not surprising that interindividual variability of plasma drug concentrations in patients with altered liver function is very high. The risc of severe hepatotoxicity in underlying chronic lver disease is evident [6]. Therefore, regularly testing for liver function is recommended in case of longterm therapy with drugs metabolized by the liver. Accompanying TDM facilitates the detection of increased plasma levels and enables to react early by dose adaptation and therewith reduce toxicity. LPV as first choice drug is often used over long time periods. TDM as a tool in patients care is important but the knowledge of LPV-plasma-levels in patients with chronic liver disease remain uncertain. With this retrosepective analysis we want to show if there are differences in LPV-plasma-levels between patients with and without chronic liver diseases over a long-time period.

2. Methods

Since 06/00 we determine LPV-plasma-levels with an HPLC-based method [7]. Also efavirenz levels were measured routinely during patient visits [8]. All patients get the LPV hard gel capsuel at a dose of 400/100 mg/bid or 500/120 mg/bid in combination with efavirenz or nevirapine. LPV- plasma samples were drawn as trough levels. The LPV-plasma-levels over the time course in patients with chronic liver disease (n = 30) and patients without liver disease (n = 38) were evaluated. Liver function tests, CD4-cell count and HI-viral load was also correlated with liver disease status. All statistical calculations were performed with the Statistical Product and Service Solutions (SPSS) for Windows, version 12.0.1. (SPSS, Chicago, IL, USA). Correlation was considered statistically significant if the calculated value of p was 0.05 or less.

3. Results

The LPV-plasma-levels over the time course in patients with chronic liver disease (n = 30) and patients without liver disease (n = 38) were evaluated (49 male, 19 female).

The age was 42.74 ± 8.86 years (27 – 67 years), with a mean body-mass index of 23.80 ± 4.08 kg × m^{-2} . Baseline characteristics of patients, given in Table 1,

Table 1. CDC Classification of n = 68 patients with HIV infection and source of associated chronic liver disease in n = 30 patients.

CDC-Classfication	n	%
A1	5	5.97 %
A2	11	16.42 %
A3	5	7.46 %
B1	1	1.49 %
B2	8	11.94 %
B3	12	17.91 %
C1	0	0.00 %
C2	2	2.99 %
C3	24	35.82 %
Chronic Liver disease	n	%
Chronic liver disease	30	44.1176 %
Hepatitis B	17	25.0000 %
Hepatitis C	16	23.5294 %
Hepatitis D	2	2.9412 %
Zirrhosis	1	1.4706 %
Alcoholism	4	5.8824 %
Severe hepatic steatosis	1	1.4706 %
Other toxic hepatitis	1	1.4706 %

indicate mainly CDCstage C patients. Liver disease was diagnosed as chronic hepatitis C (n = 14), hepatitis B (n = 13), coinfection of HBV/HCV (n = 3) or other chronic liver disease like alcoholic (n = 4) or toxic (n = 1) liver disease (Table 1).

The median duration of LPV-intake was 18.7 ± 16.3 months with maximal 4.04 years. A median of 10 samples per patient was taken in this longterm observation.

The LPV plasma levels of all patients showed no significantly change during the observation period. (Fig. 1) The wide intraindividual variance is statistically not different in patients with or without liver disease, There are no significant differences according to liver disease in LPV-plasma levels (mean C_{trough} without: 5917 ± 4811 ng/ml, mean C_{trough} with liver-disease: 6564 ± 4517 ng/ml, $p > 0.05$). (Fig. 2 and 3) CD-4 cell increase in patients with chronic liver disease from CD4-cell counts of 300/µl to 395/µl is significantly lower as in patients without liver disease with an increase of CD4-cells from 205/µl to 500/µl (Fig. 4). HI-virus suppression rates in both groups were comparable.

Change of liver function tests (AST, ATT, GGT, Bilirubin and Cholinesterase) were not different in patients with liver disease and without liver disease. As shown in Figure 5 the increase of AST from 17 U/l to 35 U/l in all patients was mainly in the normal range. Also the individual course of AST during the follow up of 4 years is well for all patients.

No patient has to stop LPV because of adverse effects. 12 patients had mild diarrhoe, 4 patients suffered from lipodystrophy, 1 patient had mild nausea. In 4 patients virologic failure occurred. LPV plasma-levels of all failing patients were over 3500 ng/ml.

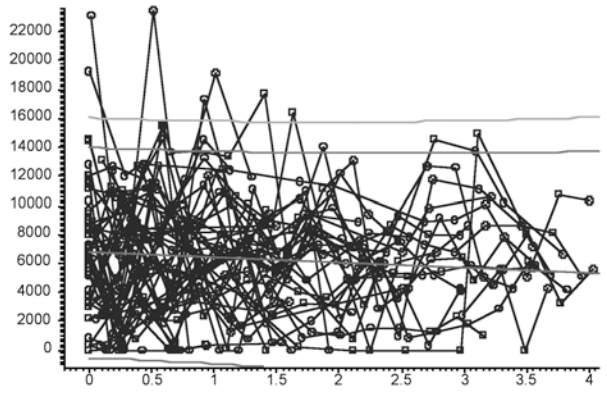

Fig. 1. LPV-plasma-levels (ng/ml) (n = 450 samples) of 68 patients up to 4 years.

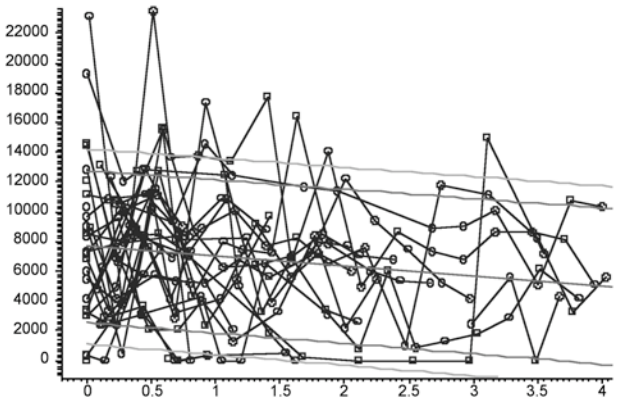

Fig. 2. LPV-plasma-levels 8ng/ml) (n = 235 samples) in 38 patients without liver disease up to 4 years of therapy.

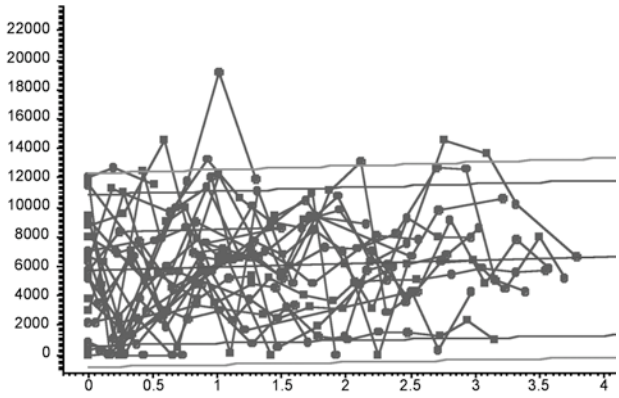

Fig. 3. LPV-plasma-levels (ng/ml) (n = 215 samples) in n = 30 patients with liver disease up to 4 years of therapy.

4. Discussion

LPV pharmacokinetics are well described [10, 11, 12]. In this longterm study of LPV plasmalevels no change

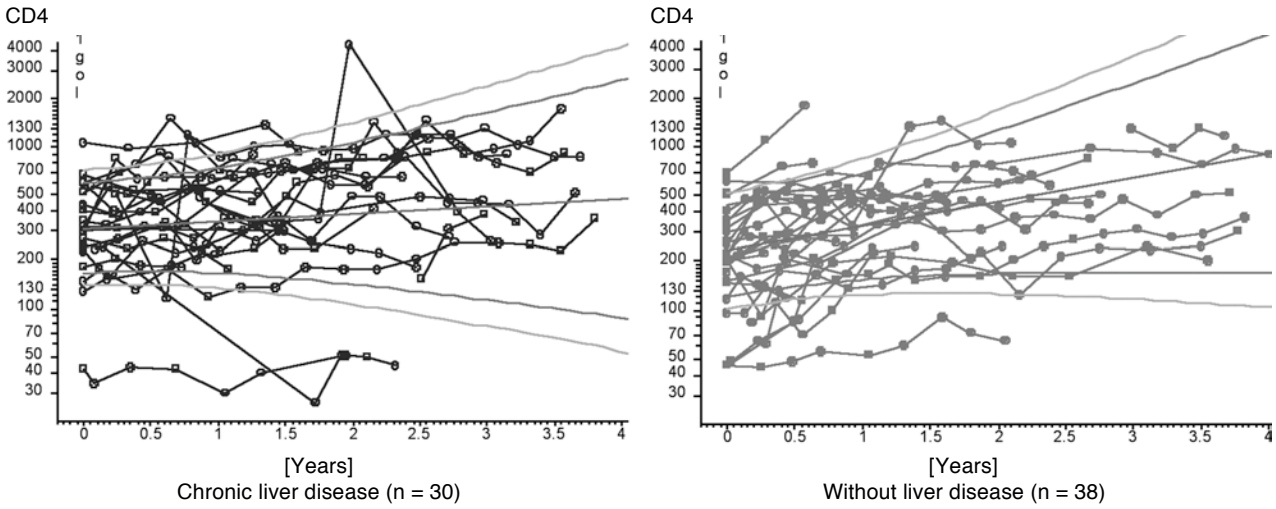

Fig. 4. CD-4 cell course of n = 68 patients during LPV therapy.

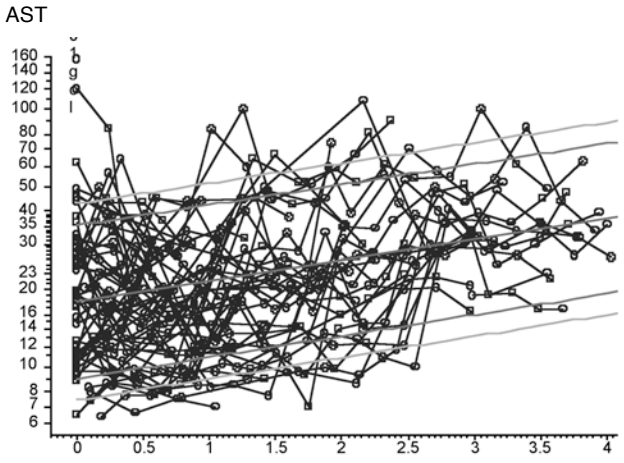

Fig. 5. Liver function test in n = 68 patients under therapy with LPV.

over the time of 4 years is eligible. The longterm efficacy of therapy in this collective of difficult to treat patients is comparable to present studies [11].

The wide intra- and interpatient variablity of LPV-levels in our investigation is comparable to findings of others [10].

In a retrospective TDM database analysis of interpatient variability in the pharmacokinetics of lopinavir in HIV-infected adults of 802 patients (607 males; 150 females; 45 unknown) female patients had a significantly higher lopinavir level than males [12].

A prospective study was conducted to investigate the plasma levels of lopinavir in 26 HIV-infected pregnant women. The lopinavir trough-level was found to be subtherapeutic in four women (15.4%) [18].

We didn`t find any sex associated difference in LPV plasma-level in our retrospective longterm analysis with repeated measurements.

A study of population pharmacokinetics of lopinavir in combination with ritonavir in HIV-1-infected patients using NONMEM showed that the only factor with significant effect on the pharmacokinetics was concurrent use of non-nucleoside reverse transcriptase inhibitors (NNRTI), which increased the clearance rate of LPV and is associated with lower LPV-plasma levels [13].

In our study all patients get LPV 500/120 mg/bid in combination with the NNRTI efavirenz. Also in patients with liver disease and the higher LPV dosage had no unexpected high LPV plasma-levels.

The interpretation of LPV-plasma levels requires knowledge of the time after intake of medication. In a clinical setting like our retrospective analysis there may be some causes for variance of the LPV-levels. [14, 15]

The critical review of all factors reflected in one single LPV plasma-level often necessitates the indiviual clinical situation.

An computer-based system to aid in the interpretation of plasma concentrations of antiretrovirals for therapeutic drug monitoring may be helpful but did not replace an expert [15].

In our study target level of 3500ng/ml was reached of 90% of patients. In an other investigation a lower virological efficacy was shown for experienced or naive patients with plasma trough lopinavir concentrations<3000 ng/ml at the beginning of treatment [11].

In patietents with liver disease the influence of liver fibrosis stage on plasma levels of antiretroviral drugs in HIV-infected patients with chronic hepatitis C was studied before. Plasma drug levels were measured in hepatitis C virus (HCV)/human immunodeficiencyvirus (HIV)-coinfected patients receiving nevirapine, efavirenz, LPV/r, or atazanavir with or without ritonavir. Liver fibrosis was measured using elastometry. In a total 268 coinfected patients with compensated liver disease were analyzed. Mean plasma LPV levels were 5800 μg/mL for LPV (56 patients). In contrast to EFV and NVP levels, plasma levels of protease inhibitors did not differ significantly between patients with and those without cirrhosis [16].

In our retrospective study only one patient with cirrosis was included. He showed no different LPV plasmalevel.

In another study of pharmacokinetics of lopinavir/ritonavir in HIV/hepatitis C virus-coinfected subjects

with mild hepatic impairment and moderate hepatic impairment showed similar effects on lopinavir pharmacokinetics. Hepatic impairment increased lopinavir AUC12 by 68% and Cmax by 56%. The effect of hepatic impairment on low-dose ritonavir pharmacokinetics was more pronounced in the moderate impairment group (181% and 221% increase in AUC12 and Cmax, respectively) than in the mild impairment group (39% and 61% increase in AUC12 and Cmax, respectively) [17].

While lopinavir/ritonavir dose reduction is not recommended in subjects with mild or moderate hepatic impairment, therapeutic drug monitoring of LPV and RTV should be performed in this population.

LPV-therapy in patients with chronic liver disease is safe. TDM is a helpful tool in patients with impared liver function.

REFERENCES

1. Sulkowski MS, ThomasDL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. JAMA, 2000, 283, 74.
2. Thomas DL. Hepatitis C and human immunodeficiency virus infection Hepatology, 2002, 36 Supp1, 201.
3. Bonfati P, Landonio S, Ricci E. Risc factors for hepatotoxicity in patients treated with highly active antiretroviral therapy. J Acquir Immune Defic Syndr, 2001, 27, 316.
4. Orenstein R, Tsogas N. Looking beyond highly active antiretroviral therapy: drug related hepatotoxicity in patients with human immunodeficiency virus infection. Pharmacotherapy, 2002, 22, 1468.
5. Puoti M, Torti C, Ripamonti D. Severe hepatotoxicity during combination antiretroviral treatment: incidence, liver histology, and outcome. J Acquir Immune Defic Syndr, 2003, 32, 259.
6. Wit FW, Weverling GJ, Weel J, Jurriaans S, Lange JM. Incidence of and risc factors for severe hepatotoxicity associated with antiretroviral combination therapy. J Infect Dis, 2002, 186, 23.
7. Langmann P, Klinker H, Schirmer D. High-performance liquid chromatographic method for the silmultaneous determination of HIV-1 protease inhibitors indinavir, saquinavir and ritonavir in plasma of patients during highly active antiretroviral therapy. J Chromatogr B Biomed Sci Appl, 1999, 735, 41.
8. Langmann P, Schirmer D, Väth T. High-performance liquid chromatographic method for the simultaneous determination of HIV-1 non-nucleoside reverse transcriptase inhibitor efavirenz in plasma of patients during highly active antiretroviral therapy. J Chromatogr B Biomed Sci Appl, 2001, 755, 151.
9. Johnson MA, Gathe JC Jr, Podzamczer D, Molina JM, Naylor CT, Chiu YL, King MS,Podsadecki TJ, Hanna GJ, Brun SC. A once-daily lopinavir/ritonavir-based regimen provides noninferior antiviral activity compared with a twice-daily regimen. J Acquir Immune Defic Syndr. 2006 Oct 1;43(2):153-60.
10. Boffito M, Back DJ, Hoggard PG, Caci A, Bonora S, Raiteri R, Sinicco A, Reynolds HE, Khoo S, Di Perri, G. Intra-individual variability in lopinavir plasma trough concentrations supports therapeutic drug monitoring. AIDS, 2003, 17;7:1107-1111
11. Wateba MI, Billaud E, Dailly E, Jolliet P, Raffi F. Low initial trough plasma concentrations of lopinavir are associated with an impairment of virological response in an unselected cohort of HIV-1-infected patients. HIV Med. 2006 Apr;7(3):197-9
12. van der Leur MR, Burger DM, la Porte CJ, Koopmans PP. A retrospective TDM database analysis of interpatient variability in the pharmacokinetics of lopinavir in HIV-infected adults. Ther Drug Monit. 2006 Oct;28(5): 650-3
13. Crommentuyn KM, Kappelhoff BS, Mulder JW, Mairuhu AT, van Gorp EC, Meenhorst PL,Huitema AD, Beijnen JH. Population pharmacokinetics of lopinavir in combination with ritonavir in HIV-1-infected patients. Br J Clin Pharmacol. 2005 Oct;60(4):378-89
14. Goicoechea M, Vidal A, Capparelli E, Rigby A, Kemper C, Diamond C, Witt MD, Haubrich R; California Collaborative Treatment Group. A computer-based system to aid in the interpretation of plasma concentrations of antiretrovirals for therapeutic drug monitoring. Antivir Ther. 2007;12(1):55-62.
15. Kappelhoff BS, Crommentuyn KM, de Maat MM, Mulder JW, Huitema AD, Beijnen JH. Practical guidelines to interpret plasma concentrations of antiretroviral drugs. Clin Pharmacokinet, 2004, 43, 845-53.
16. Barreiro P, Rodriguez-Novoa S, Labarga P, Ruiz A, Jimenez-Nacher I, Martin-Carbonero L, Gonzalez-Lahoz J, Soriano V. Influence of liver fibrosis stage on plasma levels of antiretroviral drugs in HIV-infected patients with chronic hepatitis C. J Infect Dis. 2007 Apr 1;195(7):973-9.
17. Peng JZ, Pulido F, Causemaker SJ, Li J, Lorenzo A, Cepeda C, Garcia Cabanillas JA, DaSilva B, Brun SC, Arribas J. Pharmacokinetics of lopinavir/ritonavir in HIV/hepatitis C virus-coinfected subjects with hepatic impairment. J Clin Pharmacol. 2006 Mar;46(3):265-74.

Received: January 8, 2008 / Accepted: March 12, 2008

Address for correspondence:
Priv.- Doz. Dr. Peter Langmann
Internist-Gastroenterologie
Am Tiefen Weg 2
97753 Karlstadt
09353-4242
p_langmann@yahoo.de