

The Annotated Bibliography of the UCSF HIV Solid Organ Transplantation Project

ARV Dosing in End Stage Liver Disease (ESLD)

1. Veronese, L., Rautureau, J., Sadler, B. M., Gillotin, C., Petite, J. P., Pillegand, B., Delvaux, M., Masliah, C., Fosse, S., Lou, Y., & Stein, D. S. (2000). Single-dose pharmacokinetics of amprenavir, a human immunodeficiency virus type 1 protease inhibitor, in subjects with normal or impaired hepatic function. *Antimicrobial Agents and Chemotherapy*, 44(4), 821-6

ABSTRACT: Amprenavir (141W94) is extensively metabolized by P450 cytochromes, specifically, CYP3A4. Because hepatic insufficiency reduces P450-mediated metabolism, the concentrations in plasma of drugs metabolized through this pathway are often increased in subjects with liver disease. Following administration of a single, oral dose of 600 mg of amprenavir, pharmacokinetic parameters were determined for 10 subjects with severe cirrhosis, 10 subjects with moderate cirrhosis, and 10 healthy volunteers. Model-independent methods for determining the area under the plasma concentration-time curve (AUC) from time zero to infinity (AUC(0-infinity)) showed an increase in amprenavir AUC(0-infinity) of 2.5-fold in the group with moderate cirrhosis and 4.5-fold in the group with severe cirrhosis compared with that in the control group of healthy volunteers ($P < 0.05$). AUC(0-infinity) was linearly related to the severity of liver disease, as assessed by the Child-Pugh score. Of the laboratory data used to calculate the Child-Pugh score, only the mean total bilirubin concentration showed a significant relationship with AUC(0-infinity). The relationship between the total bilirubin concentration and the AUC(0-infinity) of amprenavir was well characterized by a simple E(max) model, suggesting that the total bilirubin concentration may be a useful parameter for predicting the amprenavir AUC in subjects with hepatic insufficiency. Finally, the sera of cirrhotic subjects showed significant decreases in the levels of alpha(1)-acid glycoprotein, the primary plasma binding protein for amprenavir. On the basis of the results of this study, for an exposure equivalent to a clinical dose of 1,200 mg twice daily in subjects without cirrhosis, subjects with Child-Pugh scores of 5 to 8 should receive a twice-daily 450-mg dose of amprenavir, and subjects with Child-Pugh scores of 9 to 15 should receive a twice-daily 300-mg dose of amprenavir.

2. GlaxoWellcome. (2000). *Potential Safety Concerns with the large amount of propylene glycol in AGENERASE (amprenavir) Oral Solution*. Research Triangle Park, NC: GlaxoWellcome Inc.

3. Citation: Abstracts of the 40th Interscience

**Conference on Antimicrobial Agents and Chemotherapy, September 2000, page 331
Pharmacokinetics of, and Tolerability to, a Single, Oral, 600mg Dose of Abacavir in HIV-
Positive Subjects with or without Liver Disease.
F. Raffi¹, Y. Benhamou², D. Sereni³, T. Poynard², C. Brunet-Francois¹, A. Emmanuel⁴, C.
Gillotin⁴, S. Fosse⁴, G. Yuen⁵**

**1 Hopital Hotel-Dieu, Nantes, France; 2Hopital Pitie-Salpetriere, Paris, France; 3 Hopital
Saint-Louis, Paris,France; 4 Glaxo Wellcome, Marly le Roi, France; 5 Glaxo Wellcome
Inc., Res. Triangle Park, NC**

Abacavir, a synthetic carbocyclic nucleoside analog with specific anti HIV activity, is extensively metabolized by the liver. Primary pathway for metabolism in man is by alcohol-aldehyde dehydrogenase and by glucuronidation to produce the 5-carboxylate (2269W93) and the 5-glucuronide (361W94) metabolites. Because changes in the metabolism due to hepatic insufficiency could potentially be of clinical significance, a study was designed to evaluate the kinetics of, and tolerability to, a single, oral, 600mg dose of abacavir in HIV+ subjects with or without liver disease. Pharmacokinetic (PK) parameters of abacavir and its two major metabolites were determined in 9 HIV+ subjects with clinically diagnosed moderate cirrhosis and 9 normal controls, matched for sex, age and weight. PK analyses were performed using model-independent methods and statistical analysis of primary PK parameters was performed by analysis of variance. All adverse events (AEs) were recorded throughout the study. Results: All patients in the moderate cirrhosis group had Child-Pugh scores of 5-6 (mild impairment). Results showed that the PK profile of abacavir was altered in subjects with cirrhosis. There were concomitant increases in AUC_∞ and t_{1/2} of abacavir, 89% and 58% respectively, and a 47% decrease in CL/F of abacavir in the cirrhosis group compared with the control group (p<0.01). Furthermore, there were marked increases in t_{1/2} of 2269W93 (31%; p<0.05) and in t_{1/2} of 361W94 (21%) but no statistically significant differences for AUC_∞ of the metabolites. No previously unknown AEs related to abacavir were observed during this study.

Conclusion: The changes in abacavir kinetics suggest that abacavir daily dose should be reduced to 150mg BID in patients with mild hepatic impairment with cirrhosis.