Long-term suppression of viral replication despite low plasma saquinavir concentrations in the CHEESE Study

There is a growing interest in therapeutic drug monitoring (TDM) of protease inhibitors (PIs) as a potential tool to optimize the treatment of HIV-infection, as recently discussed in this journal [1]. A prerequisite for the introduction of TDM is the definition of minimal effective concentrations. To date, the target concentrations of the PIs are largely unknown. Proposed minimal effective concentrations for the PI saquinavir range from 100 to 200 ng ml^{-1} [1]. Results from the CHEESE study, however, suggest that the threshold concentration may be even lower for antiretroviral naive HIV-1-infected patients concomitantly treated with zidovudine (AZT) and lamivudine (3TC).

In the CHEESE study, antiretroviral naive patients were treated with saquinavir soft-gelatin capsules 1200 mg three times daily (or indinavir 800 mg three times daily), in combination with AZT 200 mg three times daily plus 3TC 150 mg twice daily [2]. To explore pharmacokinetic–pharmacodynamic (PK–PD) relationships, blood samples for the quantification of saquinavir were obtained at regular intervals. Plasma concentrations of saquinavir were determined with a sensitive and validated assay [3]. The accuracy of this assay was confirmed in a cross-validation with a commercial contract laboratory using a radioimmunoassay.

Three patients experienced virological treatment failure prior to week 48 (one had two plasma saquinavir concentrations below 100 ng ml^{-1}, one had no concentrations below 200 ng ml^{-1}, and no saquinavir concentrations were available from the remaining patient). Twenty-two patients (median baseline plasma HIV-1 RNA concentration (viral load) 4.99 $\log_{10}$ copies/ml), completed 48 weeks follow-up. After 48 weeks, 19/22 patients (86%) had a plasma viral load below 50 copies/ml. A total of 151 plasma saquinavir concentrations were available ranging from undetectable (four samples from three patients) to 3792 ng ml^{-1} (median 145 ng ml^{-1}) (Figure 1).

No PK–PD relationships were observed, possibly due to a lack of statistical power. Surprisingly, however, a potent and durable suppression of viral replication (<50 copies/ml) was observed in 86% of the patients, despite low plasma saquinavir concentrations throughout the study period. When applying the proposed threshold concentrations of 100 and 200 ng ml^{-1}, the proportion of patients with at least one 'suboptimal' saquinavir concentration was 77 and 91%, respectively. Fifteen patients continued the study drugs beyond 48 weeks. After a median follow-up of 93 weeks (range 62–106 weeks), 13/15 patients (87%) maintained a plasma HIV-1 RNA concentration below 50 copies/ml, despite continuing low plasma saquinavir concentrations (median concentration 52 ng ml^{-1}).

The satisfactory antiviral response may be explained by the intracellular pharmacokinetics of saquinavir. Compared with other protease inhibitors, saquinavir showed the most pronounced accumulation in peripheral blood mononuclear cells, resulting in a 5.45-fold higher exposure intracellularly as compared with plasma [4]. The intracellularly saquinavir concentration may be a better predictor of the virological response to therapy than the plasma concentration, since viral replication takes place within cells.

Despite low plasma concentrations, saquinavir contributed to the virological response. A decline in plasma viral load of 2.4 $\log_{10}$ copies/ml was observed after 24 weeks [2], whereas previous studies of AZT plus 3TC in naive patients showed only a drop of about 1.1 $\log_{10}$ copies/ml after 24 weeks [5].

Recent results from a randomized, prospective study on TDM (the ATHENA trial), suggested that antiretroviral naive HIV-1-infected patients may benefit from TDM of indinavir and nelfinavir [6]. TDM of PIs seems thus an attractive option to optimize antiretroviral therapy, and is increasingly advocated as the next tool in the management of HIV-1-infected patients. We argue, however, that more knowledge on the PK–PD relationships of saquinavir is required, before the introduction of TDM in daily

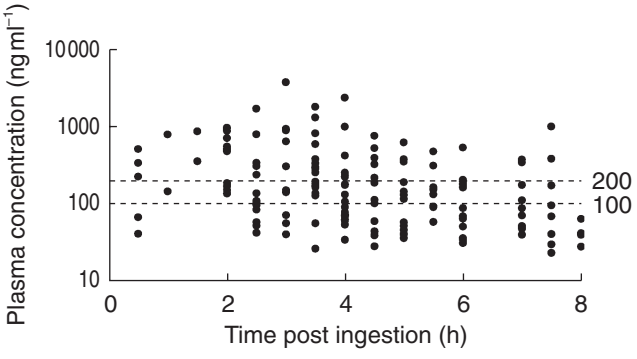

Figure 1 Scatterplot of the saquinavir plasma concentrations ($n = 151$) obtained from 22 HIV-1 infected patients at regular intervals during a 48 week period. The patients used saquinavir soft gelatin capsules 1200 mg three times daily plus zidovudine and lamivudine. The dotted lines represent threshold concentrations of 100 and 200 ng ml^{-1}.

clinical practice can be justified. Definition of target concentrations for TDM is crucial to prevent a waste of health-care resources.

The authors would like to thank the following for their contribution to the CHEESE Study: L. van Belle, B. Bravenboer, K. Brinkman, C. A. B. Boucher, W. Dorama, T. de Groot, D. Hamann, H. J. M. ter Hofstede, J. R. Jutmann, F. P. Kroon, P. P. Koopmans, N. Langebeek, R. van Leusen, P. L. Meenhorst, P. van der Meulen, C. Richter, M. Roos, R. Schuurman, R. Snijder, H. G. Sprenger, B. van der Ven, E. Waalberg-Tammeling, A. Wicherink, and B. Zomer. This research was supported by the Ministry of Public Health, Welfare, and Sports as part of the Stimulation Program on AIDS Research of the Dutch Program Committee for AIDS Research (project 1307), and by Roche Nederland BV, Mijdrecht, the Netherlands.

Rolf P. G. van Heeswijk,[1] James W. T. Cohen Stuart,[2,3] David M. Burger,[4] Jos H. Beijnen,[1] Jan C. C. Borleffs,[3] Richard M. W. Hoetelmans[1] on behalf of the Cheese Study Group

[1]*Department of Pharmacy and Pharmacology, Slotervaart Hospital, Amsterdam,* [2]*Department of Virology, Eijkman Winkler Institute, University Medical Centre, Utrecht,* [3]*Department of Internal Medicine, University Medical Centre, Utrecht, and* [4]*Department of Clinical Pharmacy, University Hospital Nijmegen, Nijmegen, the Netherlands*

Received 5 July 2001, accepted 18 September 2001

Correspondence: Rolf P. G. van Heeswijk, PharmD, PhD, The Ottawa Hospital, General Campus, Division of Infectious Diseases, 501 Smyth Road, Ottawa, ON K1H 8L6, Canada. Tel.: 613-737-8304; Fax: 613-737-8696; E-mail: rvanheeswijk@ottawahospital.on.ca

References

1 Back DJ, Khoo SH, Gibbons SE, Merry C. The role of therapeutic drug monitoring in treatment of HIV infection. *Br J Clin Pharmacol* 2001; **51**: 301–308.

2 Cohen Stuart JWT, Schuurman R, Burger DM, *et al.* Randomized trial comparing saquinavir soft-gelatin capsules versus indinavir as part of triple therapy (CHEESE Study). *AIDS* 1999; **13**: F53–F58.

3 Heeswijk van RPG, Hoetelmans RMW, Harms R, *et al.* Simulatenous quantitative determination of the HIV protease inhibitors amprenavir, indinavir, nelfinavir, ritonavir, and saquinavir in human plasma by ion-pair high-performance liquid chromatography with ultraviolet detection. *J Chromatogr B* 1998; **719**: 159–168.

4 Khoo S, Hennesy M, Mulcahy F, *et al.* Differences in intracellular drug accumulation between the protease inhibitors. *8th Conference on Retroviruses and Opportunistic Infections*, Chicago, IL, USA, February 4–8, 2001 [Abstract 258].

5 Eron JJ, Benoit SL, Jemsek J, *et al.* Treatment with lamivudine, zidovudine, or both in HIV-positive patients with 200–500 CD4+ cells per cubic millimeter. *N Engl J Med* 1995; **333**: 1662–1669.

6 Burger DM, Hugen PWH, Droste J, *et al.* Therapeutic drug monitoring (TDM) of nelfinavir (NFV) and indinavir (IDV) in treatment naive patients improves therapeutic outcome after 1 year: Results from ATHENA. *The 1st IAS Conference on HIV Pathogenesis and Treatment*, Buenos Aires, Argentina, July 8–11, 2001 [Abstract 30].

Pharmacokinetics of methadone in HIV-positive patients receiving the non-nucleoside reverse transcriptase efavirenz

We find that the work titled 'The pharmacokinetics of methadone in HIV-positive patients receiving the non-nucleoside reverse transcriptase efavirenz', authored by Clarke *et al.* [1], adequately describes an interaction with possible clinical significance between methadone and efavirenz. Nevertheless, from a pharmacokinetic viewpoint the study lacks the exploration or discussion of some important issues.

In the introduction the authors write, 'we designed a study to assess the effect of efavirenz, EFV, on methadone pharmacokinetics, the timing of withdrawal symptoms, and the requirement for a dose escalation in methadone'. Then, based only on C_{max} (obtained by inspection of the data) and the area under the curve of plasma levels (AUC) from 0–24 h (noncompartmental analysis) Clarke *et al.* make prescription recommendations for efavirenz to injection drug users receiving oral methadone concurrently.

The authors do not discuss any kinetic parameter that could serve to predict dosification schedules such as volume of distribution after a single dose, clearance at steady state, or half-life (in order to adjust the dosage interval).

Methadone is characterized by large interindividual variation in pharmacokinetics and by a rapid and extensive distribution phase (half-life of 2–3 h) and a slow elimination phase (λ_z half-life of 15–60 h) [2, 3]. This alone could have important clinical implications.

In a recent study [4], of steady state pharmacokinetics and pharmacodynamics in methadone maintenance patients, the only difference between individuals with strong and weak withdrawal symptoms was the significantly more rapid hourly rate of decline in the plasma concentration within the period from C_{max} until the next dose. Also, no differences in methadone AUC were observed between the two symptom extremes. Clarke *et al.* do not discuss this possibility which could explain, at least in part, their finding of small changes (increases) required in methadone dosage after efavirenz (22%) although the AUC was reduced by over 50% (since the latter appears not be an adequate correlate of symptom severity.)

© 2002 Blackwell Science Ltd

Also, the pharmacokinetics of methadone in maintenance treatment for opiate users show adaptive changes. In a recent population study, changes in CL and V with the time of methadone treatment had to be considered in order to explain and predict plasma drug concentrations during continuous administration [5]. These authors attributed the time-dependence in the kinetics of methadone to an increase in CL with time due to an autoinduction of CYP3A4. The changes in V with time can reflect both up- and down-regulation of α_1-acid glycoprotein (AAG), the major binding site for methadone in plasma [6, 7]. One more recent study [8] has evaluated the quantitative importance of the metabolic pathway and concludes that it is not possible to adapt the daily doses to the hepatic metabolic activity of the patients, suggesting that intestinal CYP3A4 is involved in the metabolism (efavirenz and the other antiretroviral drugs are administered orally). An effect of P-glycoprotein in intestinal absorption of methadone has also been suggested [9].

The results of Clarke *et al.* (Figure 1 [1]) with a lower AUC do not lead to the conclusion that the interaction described is only due to induction in the hepatic metabolism of methadone by efavirenz. A change in AUC, without primary pharmacokinetic changes, can be due to changes at the intestinal level (CYP3A4 or glycoprotein). Also, the fact of not observing appreciable changes, in this figure, in the elimination slope seems to be more in accord with this last mechanism, which is not discussed. Given that methadone is administered as a racemic mixture (*R*-(+)-methadone and *S*-(–)-methadone of which only the former shows significant opioid receptor affinity) the possibility of stereoselective interaction [10] could also be explored.

Another possibility which the authors do not contemplate is the interaction with AAG binding which would lead to lower plasma levels of methadone as a result of elevated V and CL (methadone is a low extraction ratio drug). The half-life could again remain unaltered if V and CL changed proportionally [11]. Although there are no specific data about the degree of binding of efavirenz, other non-nucleoside reverse transcriptase inhibitors, such as GW420867X, are highly bound to plasma proteins (range 89% to 94%) [12].

Finally, the ranges of C_{max} and AUC are very broad, even in those individuals only under methadone, which implies possibly appreciable interindividual variability in the kinetics. In this situation it is not advisable to establish dosage regimens without performing a proper population analysis and establishing subject-specific covariate models for the parameters. With these parameter estimates the authors could then perform simulations to explore the appropriate dose intervals for coadministration of oral methadone with efavirenz.

Rosario Calvo,[1] John C. Lukas, Monica Rodriguez, M. Angeles Carlos & Elena Suarez

Department of Pharmacology, Faculty of Medicine, University of the Basque Country, Leioa, Vizcaya, Spain and [1]Department of Phamacy, School of Pharmacy, University of Washington, Seattle, WA 98195, USA

Received 24 May 2001, accepted 9 October 2001

Correspondence: Dr Rosario Calvo, Department of Pharmacy, School of Pharmacy, Mail Stop 357630, University of Washington, Seattle, WA 98195, USA. Tel.: 206 5436788; Fax: 206 5433835; E-mail: charo@u.washington.edu

References

1 Clarke SM, Mulcahy FM, Tjia J, *et al.* The pharmacokinetics of methadone in HIV-positive patients receiving the non-nucleoside reverse transcriptase inhibitor efavirenz. *Br J Clin Pharmacol* 2001; **51**: 213–217.

2 Nilsson MI, Gronbladh L, Widerlov E, Anggard E. Pharmacokinetics of methadone in methadone maintenance treatment: characterization of therapeutic failures. *Eur J Clin Pharmacol* 1983; **48**: 361–366.

3 Wolf K, Rostami-Hodjegan A, Shires S, *et al.* The pharmacokinetics of methadone in healthy subjects and opiate users. *Br J Clin Pharmacol* 1997; **44**: 325–334.

4 Dyer KR, Foster DJR, White JM, Somogyi AA, Menelaou A, Bochner F. Steady-state pharmacokinetics and pharmacodynamics in methadone maintenance patients: Comparison of those who do and do not experience withdrawal and concentration-effect relationships. *Clin Pharmacol Ther* 1999; **65**: 685–694.

5 Rostami-Hodjegan A, Wolf K, Hay AWM, Raistrick D, Calvert R, Tucker GT. Population pharmacokinetics of methadone in opiate users: Characterization of time-dependent changes. *Br J Clin Pharmacol* 1999; **48**: 43–52.

6 Garrido MJ, Aguirre C, Troconiz IF, *et al.* Alpha-1acid glycoprotein (AAG) and serum protein binding of methadone in heroin addicts with abstinence syndrome. *Int J Clin Pharmacol Ther* 2000; **38**: 35–40.

7 Oie S, Jacobson MA, Abrams DI. Alpha 1-acid glycoprotein levels in AIDS patients before and after short-term treatment with zidovudine (ZDV) (letter). *J Acquir Immune Defic Syndr* 1993; **5**: 531–533.

8 Charlier C, Desalles M, Plomteux G. Methadone maintenance treatment. Is it possible to adapt the daily doses to the metabolic activity of the patient? *Ther Drug Monit* 2001; **23**: 1–3.

9 Bouer R, Barthe L, Philibert C, Tournaire C, Woodley J, Houin G. The roles of P-glycoprotein and intracellular metabolism in the intestinal absorption of methadone: In vitro studies using the rat everted intestinal sac. *Fundam Clin Pharmacol* 1999; **13**: 494–500.

10 Holladay JW, Dwey MJ, Michniak BB, *et al.* Elevated alpha-1-acid glycoprotein reduces the Volume of distribution and systemic clearance of saquinavir. *Drug Metab Dispos* 2001; **29**: 299–303.

11 Moore KHP, Cass LM, Dallow N. HardmanTC, Jones A, Boyce M, Prince WT. Pharmacokinetics and safety of

escalating single and repeat oral doses of GW420867X, a novel non-nucleoside reverse transcriptase inhibitor. *Eur J Clin Pharmacol* 2001; **56**: 805–811.
12 Foster DJR, Somogyi AA, Dyer KR, White JM, Bochner F. Steady-state pharmacokinetics of (R)- and (S)-methadone in methadone maintenance patients. *Br J Clin Pharmacol* 2000; **50**: 427–440.

Recreational bupropion abuse in a teenager

There are a few reports of intentional overdose of the antismoking drug, bupropion (amfebutamone/Zyban) amongst teenage patients, but no reports of recreational use. Significant overdose has led to reports of cardiotoxicity [1], and seizure activity that has resulted in hypoxia and death [2]. A case of overdose is reported in an adolescent girl who took bupropion believing the drug to be a stimulant.

A 13-year old Caucasian girl with a past history of deliberate illicit drug ingestion and evidence of a conduct disorder and mood upset symptoms was admitted to the paediatric ward after intentionally swallowing four bupropion tablets (600 mg total) that were supplied by a friend. She had been persuaded that the tablets would give her a 'better high than amphetamine', and had willingly experimented. She had no suicidal intent. She admitted her overdose 10 h after ingestion, and was referred to the local hospital. No adverse effects were reported and clinical examination revealed no abnormalities over a further 16 h period. Serum electrolytes and creatinine were normal. No seizures or side-effects of the bupropion were observed, and she was discharged home the following day.

Bupropion is licensed for smoking cessation and augments validated cessation rates from using a combination of willpower and nicotine replacement therapies [3]. It is a monocyclic antidepressant that is thought to aid smoking cessation by its dopaminergic and noradrenergic effects in the brain [4]. Rather than replacing the nicotine, bupropion increases dopamine levels that fall during cigarette abstinence, thus reducing the 'craving' associated with quitting smoking. The reduction in the normal noradrenergic responses to nicotine deprivation seen with bupropion may alter the withdrawal symptoms experienced by the patient. The side-effect profile of bupropion makes it an unlikely candidate for abuse. The adverse events most commonly reported include insomnia, dry mouth, anxiety and dizziness. Indeed, human studies have confirmed that bupropion does not provide any amphetamine-like or stimulant effects [5].

Bupropion overdose has previously been reported as attempted suicide by Ayers *et al*. [6] who reports a 14 year old who ingested between 1.5 and 3 g. A fatal overdose has been recorded in a man who ingested 23 g that resulted in seizures, hypoxia and cardiac arrest [2]. In the largest published series from Philadelphia, adverse effects including sinus tachycardia, lethargy, tremors and seizures were reported [7].

This case broadens the experience of bupropion overdose in the paediatric population and represents the first documented case of recreational use of bupropion. There is no evidence of other teenagers in the area experimenting with bupropion. This patient did not experience her desired effect, nor did she suffer any adverse effects from her overdose. Although bupropion overdose is rare in the paediatric population, the threshold for toxicity remains to be fully defined.

Jonathan McCormick
Perth Royal Infirmary, Perth, Scotland, PH1 1NX

Received 5 September 2001, accepted 25 September 2001

Correspondence: Dr J. McCormick, Paediatric Specialist Registrar, Perth Royal Infirmary, Perth, Scotland, PH1 1NX. Tel.: 01738 623311; Fax: 01738 473462; E-mail: jdmccormick@btinternet.com

References

1 Shrier M, Diaz JE, Tsarouhas N. Cardiotoxicity associated with bupropion overdose. *Ann Emergency Med* 2000; **35**: 100.
2 Harris CR, Gualtieri J, Stark G. Fatal bupropion overdose. *J Toxicol Clin Toxicol* 1997; **35**: 321–324.
3 Jorenby DE, Leischow SJ, Nides MA, *et al*. A controlled trial of sustained release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 1999; **340**: 685–691.
4 Glaxo Wellcome. *Zyban 150 mg prolonged release tablets (bupropion hydrochloride)*. Summary of Product Characteristics, May 2001.
5 Miller L, Griffith J. A comparison of bupropion, dextramphetamine and placebo in mixed substance abusers. *Psychopharmacology* 1983; **80**: 199–205.
6 Ayers S, Tobias JD. Bupropion overdose in an adolescent. *Pediatric Emergency Care* 2001; **17**: 104–106.
7 Spiller HA, Ramoska EA, Krenzelok EP, *et al*. Buproprion overdose: a 3-year multi-center retrospective analysis. *Am J Emergency Med* 1994; **12**: 43–45.

© 2002 Blackwell Science Ltd