The effect of rifampicin-based antitubercular therapy and co-trimoxazole on the population pharmacokinetics of stavudine (d4T) in HIV-1 infected patients

PAGE 2009 Poster 58

J-S van der Walt [1], K Cohen [1], HM McIlleron [1], PJ Smith [1], G Maartens [1], MO Karlsson [2]

[1] Division of Clinical Pharmacology, University of Cape Town, South Africa, [2] Department of Biopharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

BACKGROUND AND AIMS

- The coadministration of antiretroviral and antitubercular therapy is known to result in drug-drug interactions due primarily to the induction of metabolising enzymes and drug transporters by rifampicin.[1,2]
- Nucleoside analogue reverse transcriptase inhibitors, including stavudine (d4T), are predominantly eliminated by renal tubular secretion and not affected by this interaction.[3]
- Co-trimoxazole reduces the apparent clearance of lamivudine (3TC) , but an interaction with stavudine has not been reported.[4]
- The aims of our analysis were to describe the population pharmacokinetics of stavudine during and after antitubercular treatment, to assess the effects of co-trimoxazole on stavudine pharmacokinetics and to quantify the between-occasion variability in this population.

METHODS

DATA

- Stavudine concentration-time data from 16 patients on antiretroviral therapy containing d4T, 3TC and nevirapine, during and at least 10 days after completing rifampicin-based antitubercular therapy, were available for pharmacokinetic modelling.[5,6]
- Blood samples collected at 0 (pre-dose) and at 0.5, 1, 1.5, 2, 4, 6, 10 and 12 hours after a fasted dose were analysed.
- Blood samples were analysed using a validated LC/MS-MS method (LOQ set at 20 ng/mL).

PHARMACOKINETIC MODELLING

- One- and two-compartment models with first-order absorption and first-order elimination from the central compartment were fitted to the data.
- Between-subject (BSV) and between-occasion (BOV) variability was modelled using an exponential model.
- Residual variability was modeled using a combined additive and proportional error model.
- The effects of concomitant medications were modelled as categorical covariates:

$$P_i = \theta_{pop} \cdot (1 + INTER) \cdot e^{BSV+BOV}$$

The parameter value of the i^{th} individual (P_i) was described by the population parameter value (θ_{pop}), an interaction term to describe the effect of concomitant therapy (INTER), and the random effects(η_i) comprising both BSV and BOV. The value of INTER was fixed to zero in the absence of concomitant therapy.

- The first-order conditional estimation method with η-ε interaction (FOCE INTER) of NONMEM version VI (level 2.0) was used to estimate typical population values.
- Models were compared using the NONMEM objective function value (OFV), goodness-of-fit plots and scientific plausibility. A decrease in the OFV of more than 3.84 was considered significant ($p < 0.05$) for model improvement at one degree of freedom.
- Models were evaluated with the nonparametric bootstrap method (1000 samples) and visual predictive checks (1000 samples) using Perl-speaks-NONMEM.

RESULTS

- A one-compartment disposition model with absorption lag time best described the data.
- The pharmacokinetics of stavudine in this population was highly variable.
- Adding between-occasion variability in the relative bioavailability and k_a improved the model fit (OFV decreased by 18.45 points).
- Antitubercular therapy did not have a significant effect the relative bioavailability or absorption rate of stavudine. During antitubercular therapy:
  - bioavailability was 3% lower (95%% CI: -24%, 17%)
  - K_a was 30% higher (95% CI -71%, 131%).
- During antitubercular treatment 14 of 16 patients used co-trimoxazole prophylaxis and 10 patients remained on prophylaxis after completion of antitubercular treatment.
- Stavudine clearance was 18% higher (95% CI: 3% - 32%) in patients taking concomitant co-trimoxazole. However, improvement in health after completing antitubercular treatment and the small sample size should be taken into account.

CONCLUSIONS

- Rifampicin-based antitubercular therapy did not significantly affect the population pharmacokinetics of stavudine.
- In patients using co-trimoxazole and stavudine concomitantly, the apparent clearance of stavudine increased by 18% (95% CI 3% - 32%,). Although stavudine dose adjustment is unlikely when coadministered with co-trimoxazole, this interaction may be relevant as lower doses of stavudine are now recommended to reduce toxicity.

FIGURE 1

Stavudine concentrations (nmol/mL) *vs* time after dose (h) during and after rifampicin-based antitubercular (TB) therapy.

Observed data are superimposed on the 50th(solid line), 5th and 95th percentiles (dashed lines) of the observed data. The coloured areas represent the 95% CI of the 5th, 50th and 95th percentiles of the simulated data (1000 data sets), respectively .

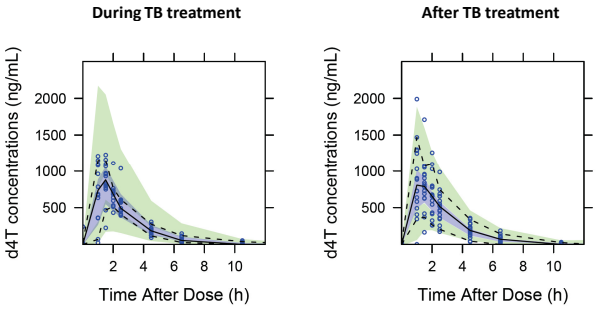

TABLE 1

Population pharmacokinetics parameters.

Population pharmacokinetic parameters	Base model	Final model with effect of anti-tubercular and co-trimoxazole therapy	Nonparametric Bootstrap of Final model (N=1000)
	Mean (%RSE)	Mean (%RSE)	Median (%RSE)
NONMEM OFV	2307.07	2297.738	2303.191
CL/F (L/h)	17.8 (7.13)	15.2 (12.1)	14.9 (8.6)
V/F (L)	33 .5 (6.42)	32.2 (10.7)	32.3 (6.4)
k_a (/h)	11.1 (39.5)	10.6 (55.6)	9.5 (135.1)
Absorption lag time (h)	0.41 (3.91)	0.41 (5.41)	0.43 (13.5)
Effect of antitubercular therapy			
Effect on k_a (95% CI)	NE	0.30 (-0.71 – 1.31)	0.28 (-0.68 – 1.20)
Effect on F (95% CI)	NE	-0.03 (-0.24 – 0.17)	-0.01 (-0.20 – 0.17)
Effect of co-trimoxazole			
Effect on CL/F	NE	0.18 (0.03 -0.32)	0.20 (-0.03 -0.41)
Between-subject variability (%CV)			
ω^2 CL/F	16.95% (43.4)	15.9 % (44.7)	14.8% (44.4)
ω^2 k_a	124.5% (46.4)	142.7% (52.9)	138.2% (97.6)
ω^2 F	15.1% (111)	15.1% (100)	15.3% (60.3)
Between-occasion variability (%CV)			
ω^2 k_a	43.6% (79.5)	26.9% (112)	29.2% (164.7)
ω^2 F	17.8 % (45.6)	16.1% (47.3)	14.3% (66.4)
η-shrinkage (%)			
ω^2 BSV CL/F	8%	9%	NC
ω^2 BSV k_a	19%	14%	NC
ω^2 BSV F	39%	37%	NC
ω^2 BOV F	12%	15%	NC
ω^2 BOV k_a	61%	76%	NC
Residual error			
$\sigma_{proportional}$	0.27 (8.4)	0.27 (8.5)	0.25 (12.8)
$\sigma_{additive}$ (ng/mL)	9.7 (14.1)	9.7 (13.9)	10.5 (93.2)
ε-shrinkage (%)	11%	10%	NC

RSE = relative standard error
NE = not estimated NC = not calculated

REFERENCES

1. Barrett JS, Labbé L, Pfister M. Application and impact of population pharmacokinetics in the assessment of antiretroviral pharmacotherapy. Clin Pharmacokinet. 2005;44(6):591-625.
2. Chen J, Raymond K. Roles of rifampicin in drug-drug interactions: underlying molecular mechanisms involving the nuclear pregnane X receptor. Ann Clin Microbiol Antimicrob. 2006 Feb 15;5:3. Review.
3. Johnson MA, Moore KHP, Yuen GJ, Bye A, Pakes GE. Clinical Pharmacokinetics of lamivudine. Clin Pharmacokinet 1999 Jan; 36 (1): 41-66.
4. Sabo JP, Lamson MJ, Leitz G, Yong CL, MacGregor TR. Pharmacokinetics of nevirapine and lamivudine in patients with HIV-1 infection. AAPS PharmSci. 2000;2(1):E1.
5. Cohen K, van Cutsem G, Boulle A, McIlleron H, Goemaere E, Smith PJ, Maartens G. Effect of rifampicin-based antitubercular therapy on nevirapine plasma concentrations in South African adults with HIV-associated tuberculosis. J Antimicrob Chemother. 2008 Feb; 61(2):389-93.
6. Elsherbiny D, Cohen K, Jansson B, Smith P, McIlleron H, Simonsson US. Population pharmacokinetics of nevirapine in combination with rifampicin-based short course chemotherapy in HIV- and tuberculosis-infected South African patients. Eur J Clin Pharmacol. 2009 Jan; 65(1):71-80.