Slotervaart Hospital

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The Netherlands Cancer Institute
Antoni van Leeuwenhoek Hospital

Population pharmacokinetics of caffeine and its metabolites theobromine, paraxanthine and theophylline after inhalation in combination with diacetylmorphine

A.S. Zandvliet[1,2], A.D.R. Huitema[1,2], M.E. de Jonge[1,2], R. den Hoed[3], R.W. Sparidans[3], V.M. Hendriks[4,7], W. van den Brink[5,7], J.M. van Ree[6,7], J.H. Beijnen[1,2,3]

1 Department of Pharmacy & Pharmacology, Slotervaart Hospital, Amsterdam, The Netherlands
2 The Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands
3 Department of Biomedical Analysis, Section of Drug Toxicology, Utrecht University, Utrecht, The Netherlands
4 Parnassia Addiction Research Centre, The Hague, The Netherlands
5 Amsterdam Institute for Addiction Research, Amsterdam, The Netherlands
6 Rudolf Magnus Institute of Neuroscience, Utrecht, The Netherlands
7 Central Committee on the Treatment of Heroin Addicts (CCBH), Utrecht, The Netherlands

INTRODUCTION

The stimulant effect of caffeine, as an additive in legal diacetylmorphine (heroin) preparations for study purposes, may interfere with the pharmacodynamic effects of diacetylmorphine. From this perspective it is important to obtain insight into the pharmacology of caffeine as an additive to diacetylmorphine after inhalation. The current study focused on the pharmacokinetics of caffeine and its dimethylxanthine metabolites (theobromine, paraxanthine and theophylline) after caffeine inhalation in heroin users.

OBJECTIVES

I. To establish the population pharmacokinetics in this exceptional group of subjects and for this extraordinary route of administration.

II. To make a comparison to published data concerning the pharmacokinetics of caffeine after intravenous and oral administration in healthy volunteers.

METHODS

Study design:

- diacetylmorphine preparations containing 100mg caffeine
- 10 subjects, 5 consecutive days
- route of administration: inhalation, using either the method of "chasing the dragon" (fig.1) or a laboratory heating plate.

Fig. 1. The inhalation method of "chasing the dragon"

Bioanalysis: High performance liquid chromatography (HPLC) was used to determine plasma concentrations of caffeine, theobromine, paraxanthine and theophylline.

Parameter estimation: NONMEM version V, level 1.1 was used to simultaneously estimate:

I. population PK parameters of caffeine and three metabolites

II. estimation of interindividual and interoccasion variances (exponential models)

III. residual error variance (exponential models).

Method: first-order conditional estimation (FOCE) with interaction between interindividual, intraindividual and residual variability

Subroutine: ADVAN6

Model evaluation: jack-knife procedure

RESULTS

Absorption model:

- Absorption of caffeine after inhalation was rapid.
- The process of inhalation could be described as a bolus administration into the central compartment.

Structural model:

- Caffeine plasma concentrations were best described by a two compartmental model.
- Figure 2 depicts the linear multi-compartment structural model, which adequately described the pharmacokinetics of caffeine and its metabolites theobromine, paraxanthine and theophylline simultaneously after inhalation of the caffeine sublimate.

Covariate model:

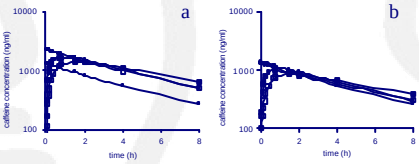
- (1) The smoking method and (2) the amount of co-administered diacetylmorphine were tested as covariables for $CL/F_{(CAF)}$ and $V_1/F_{(CAF)}$.
- No covariables were included in the full model.

Final model:

- Parameter estimates are listed in Table 1.
- Figure 3 shows PRED vs DV and IPRED vs DV plots for all compounds.
- From the results of this study only, the bioavailability of caffeine after inhalation could not be estimated.
- The extent to which the dimethylxanthines were formed was correlated within individuals and subject to high interindividual variability.

Comparison to previously published data:

- From figure 4 can be concluded that the bioavailability of caffeine administered by inhalation was approximately 60% in experienced smokers.
- $V_{1(CAF)}$ was estimated to be 45.7 L and the apparent elimination rate constant of caffeine at 8 hours after inhalation was 0.150 h^{-1} for a typical individual. These values correspond well to previously published data (Table 2).



-O- *inhalation* -●- *intravenous bolus injection*
-□- *oral intake of capsules* -■- *oral intake of coffee*

Fig. 4. Typical concentration versus time profiles of caffeine
a) after administration of 100mg and assuming that the bioavailability is complete for all routes of administration
b) after administration of 60mg for the oral and intravenous routes of administration and 100mg for inhalation

Table 2. Mean pharmacokinetic parameters of caffeine, from previous study results.

Route of administration	Formulation	k_a	V (L)	CL (L/h)	k_e (h^{-1})	Ref.
Intravenous	Injection		44.8[1]	8.48[1]	0.189	(1)
Oral	Coffee	5.6	53.5	7.14	0.133	(2)
Oral	Capsule	1.3-2.4 [2]	51.5[1]	8.70[1]	0.169	(3)

[1] Result was normalised to a parameter value for 70kg subjects.
[2] No absorption rate constant was reported by Lelo et al. (3). Therefore, the reported value for k_a was adopted from Kamimori et al. (4)

CONCLUSIONS

I. The presented model adequately describes the population pharmacokinetics of caffeine and its metabolites theobromine, paraxanthine and theophylline after inhalation of the caffeine sublimate of a 100mg tablet. Validation by the jack-knife procedure proved the stability of the model.

II. The pharmacokinetics of caffeine administered by inhalation are to a large extent similar to the pharmacokinetics of intravenously administered caffeine. The bioavailability of inhaled caffeine is approximately 60%.

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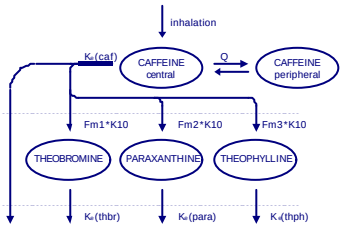

Fig. 2. Structural model of the pharmacokinetics of caffeine and three metabolites.

Table 1. Parameter estimates of the final population pharmacokinetic model.

Pharmacokinetic parameters		Estimate	(CV%)
$V_1/F_{(CAF)}$	(L)	76.2	(17.8)
$CL/F_{(CAF)}$	(L/h)	8.37	(18.5)
$V_2/F_{(CAF)}$	(L)	214	(17.1)
$Q/F_{(CAF)}$	(L/h)	9.74	(16.5)
$F_{(THBR)}/V_{(THBR)}$	(L^{-1})	0.00537	(36.8)
$F_{(PARA)}/V_{(PARA)}$	(L^{-1})	0.0288	(27.5)
$F_{(THPH)}/V_{(THPH)}$	(L^{-1})	0.00342	(31.9)
$k_{e(THBR)}$	(h^{-1})	0.117	(19.1)
$k_{e(PARA)}$	(h^{-1})	0.308	(16.4)
$k_{e(THPH)}$	(h^{-1})	0.313	(26.9)
Interindividual variability			
$\eta\ V_1/F_{(CAF)}$	(%)	51.9	(12.5)
$\eta\ CL/F_{(CAF)}$	(%)	56.3	(27.8)
$\eta\ F/V_{(THBR)}$	(%)	124	(20.3)
$\eta\ F/V_{(PARA)}$	(%)	65.5	(24.1)
$\eta\ F/V_{(THPH)}$	(%)	64.4	(27.5)
$\rho\ (\eta V_1/F_{(CAF)}, \eta CL/F_{(CAF)})$		0.42	(107.4)
$\rho\ (\eta F/V_{(THBR)}, \eta\ F/V_{(PARA)})$		0.55	(95.9)
$\rho\ (\eta F/V_{(PARA)}, \eta\ F/V_{(THPH)})$		0.74	(80.8)
$\rho\ (\eta F/V_{(THBR)}, \eta\ F/V_{(THPH)})$		0.83	(84.4)
Interoccasion variability			
$\kappa\ V_1/F_{(CAF)}$	(%)	29.8	(16.2)
$\kappa\ CL/F_{(CAF)}$	(%)	17.9	(17.4)
$\rho\ (\kappa V_1/F_{(CAF)}, \kappa CL/F_{(CAF)})$		0.67	(34.8)
Residual variability			
$\varepsilon_{(CAF)}$	(%)	26.2	(11.5)
$\varepsilon_{(THBR)}$	(%)	22.6	(14.9)
$\varepsilon_{(PARA)}$	(%)	21.3	(11.1)
$\varepsilon_{(THPH)}$	(%)	22.2	(16.5)

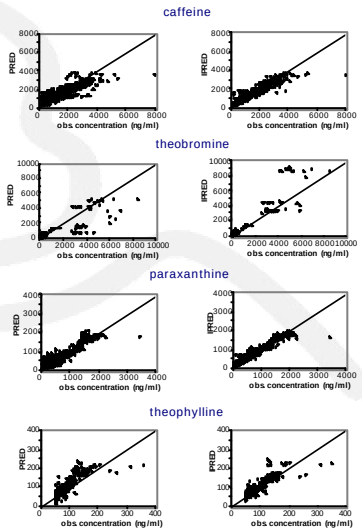

Fig. 3. Model predicted (PRED) and individual Bayesian predicted concentrations (IPRED) (ng/ml) versus observed concentrations (ng/ml)