Population Pharmacokinetic Model of Human Insulin Following Different Routes of Administration

Elizabeth Potocka, PhD, Robert A. Baughman, PharmD, PhD, and Hartmut Derendorf, PhD, FCP

Multiple-compartment disposition of insulin has been demonstrated following intravenous administration; however, because of slow absorption and flip-flop kinetics, meal-time insulin pharmacokinetics have been described by a 1-compartment model. Technosphere insulin (TI) is an inhaled human insulin with rapid absorption and a distinct second compartment in its pharmacokinetics. The aim of this analysis was to develop a pharmacokinetic model for insulin administered via the intravenous, subcutaneous, and inhalation routes. A 2-compartment pharmacokinetic model with 1 (inhaled) or 2 sequential (subcutaneous) first-order absorption processes and first-order elimination was developed using data from 2 studies with a total of 651 concentrations from 16 healthy volunteers. Insulin was administered intravenously (5 U), subcutaneously (10 U), and via inhalation (25, 50, and 100 U). The data were modeled simultaneously with NONMEM VI, using ADVAN6 subroutine with FO. Typical values were clearance, 43.4 L/h; volume of distribution in the central compartment, 5.0 L; intercompartmental clearance, 23.9 L/h; volume of distribution in the peripheral compartment 30.7 L; TI first-order absorption rate constant, 2.35 h^{-1}; and first-order absorption rate constants associated with subcutaneously administered insulin, 0.63 and 1.04 h^{-1}, respectively. Absorption rate after subcutaneous dosing was found to decrease with increasing body mass index. Insulin pharmacokinetics were found to be consistent with 2-compartment disposition, regardless of route of administration, with insulin curve differences attributable to absorption differences.

Keywords: *Insulin; inhaled insulin; population pharmacokinetics*

Journal of Clinical Pharmacology, 2011;51:1015-1024
© 2011 The Author(s)

Insulin disposition following subcutaneous or pulmonary administration has been described by a 1-compartment pharmacokinetic model.[1-5] Early work also suggested a 1-compartment model following intravenous (IV) administration, but with advances in sensitive and specific analytical methods, lower concentrations of insulin could be quantitated. This increased sensitivity enabled the detection of insulin concentrations in the elimination phase, revealing multiple compartment disposition following IV administration.[6] However, the slow absorption characteristics of both subcutaneously administered insulin and early formulations for delivery via the pulmonary route obscured the distribution phase and the second compartment. Technosphere insulin (TI) is a novel, inhaled, human insulin (recombinant DNA origin) (RHI) whose administration by oral inhalation results in rapid absorption and rapid clearance and makes it possible to distinguish the second compartment of the insulin pharmacokinetic profile.[7]

TI's unique insulin pharmacokinetics are attributed to the combination of pulmonary delivery and a novel insulin formulation. TI consists of insulin adsorbed onto Technosphere microparticles, formed when fumaryl diketopiperazine, a small organic molecule, self-assembles into microspheres with a large surface area and an average diameter of 2.5 µm.[8] Following oral inhalation, at the surface of the lung, the microparticles are believed to dissolve quickly, resulting in rapid absorption of insulin.

From the College of Pharmacy, University of Florida, Gainesville, Florida (Dr Potocka, Dr Baughman, Dr Derendorf); and MannKind Corporation, Paramus, New Jersey (Dr Potocka, Dr Baughman). Submitted for publication November 18, 2009; revised version accepted June 21, 2010. Address for correspondence: Elizabeth Potocka, PhD, 1 Casper Street, Building 8, Danbury, CT 06810; e-mail: epotocka@mannkindcorp.com.
DOI: 10.1177/0091270010378520

The aim of this analysis was to develop a pharmacokinetic model for RHI administered by the IV, subcutaneous, and inhalation routes and to demonstrate that 2-compartment disposition is a characteristic of insulin regardless of route of administration, with the route-dependent concentration–time profile differences due primarily to differences in absorption rates.

METHODS

Study Population

Data for this analysis were combined from 2 separate glucose clamp studies in healthy subjects. Study 1 was conducted at the Klinik für Stoffwechselkrankheiten und Ernährung, Medizinische Klinik und Poliklinik der Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany. The protocol was reviewed and approved by the local ethics committee, the Ethikkommission der Medizinischen Fakultät der HeinrichHeineUniversität, Düsseldorf. Study 2 was conducted at Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany. The protocol was reviewed and approved by the local ethics committee of the Ärztekammer Nordrhein.

Each was a prospective, single-center, open-label, randomized, crossover euglycemic glucose-clamp study in healthy, nonsmoking male and female volunteers, 18 to 40 years of age, with a body mass index (BMI) of 18 to 27 kg/m^2 and normal pulmonary function. All subjects provided written informed consent before initiation of any study-related procedures. Before entry into either study, all subjects underwent a physical examination, pulmonary function tests, electrocardiography, and laboratory tests, including urinalysis and screening for drugs of abuse.

Study Design and Drug Administration

Both studies used a euglycemic glucose clamp procedure performed with the Biostator glucose monitoring and infusion system (Biostator, Life Science Instruments, Elkhart, Indiana) and a continuous insulin infusion to suppress endogenous insulin production. On each treatment day, after an overnight fast and before test article administration, subjects were started on a constant rate, IV RHI infusion, locked 2 hours before dose, to establish a serum insulin concentration between 10 and 15 μU/mL and to suppress endogenous insulin secretion. This infusion was continued until the end of each treatment visit. Subjects received a single dose of the test treatment on separate occasions.

Study 1 was a 3-way crossover euglycemic glucose-clamp study in 5 subjects that compared the pharmacokinetics and pharmacodynamics of single doses of 100 U of inhaled TI Inhalation Powder (MannKind Corporation, Paramus, New Jersey), 10 U of RHI (Actrapid, Novo Nordisk A/S, Bagsvaerd, Denmark) administered subcutaneously, and 5 U of RHI administered IV. Study 2 was a 4-way, crossover, euglycemic glucose clamp study in 12 subjects that compared the pharmacokinetics and pharmacodynamics of 3 different single doses of inhaled TI with a single subcutaneous dose of 10 U of RHI.[9]

Blood glucose was kept constant at 90 mg/dL throughout the procedure by a variable infusion of a dextrose solution, controlled by the Biostator. An additional external pump, controlled by study personnel, was used if the Biostator could not meet the glucose infusion requirements to maintain euglycemia. If any glucose was provided by the external pump, the glucose infusion rate (GIR) from the pump was added to the GIR from the Biostator. Subjects fasted until the end of each treatment visit. Treatment periods were separated by a washout period of 3 to 28 days.

Drug Administration and Insulin Concentrations

TI was administered using a commercially available inhaler (model M, Boehringer Ingelheim, Ingelheim, Germany) in study 1 and using the MedTone dry powder inhaler (model Alpha, MannKind Corporation, Danbury, Connecticut) in study 2. Subcutaneous RHI was administered by injection in the abdomen. All blood samples were drawn through an IV catheter in the antecubital vein of the arm contralateral to that used for the continuous insulin infusion and glucose administration. Samples for the determination of insulin concentration were drawn at 120, 90, 60, and 30 minutes before dosing and at 0, 1, 3, 7, 12, 20, 30, 45, 60, 90, 120, 180, 240, 300, and 360 minutes after dosing. Samples were analyzed for insulin concentration using radioimmunoassay (RIA) with an analytical range of 1.2 to 400 μU/mL and double determinations. A single C-peptide sample was collected between 120 and 60 minutes before dosing, and further samples were collected at 0, 30, 60, 180, and 300 minutes after dosing. The samples were cooled in an ice water bath before centrifugation; afterwards the plasma samples were immediately frozen and stored at –80°C until analysis.

15524604, 2011, 7, Downloaded from https://accp1.onlinelibrary.wiley.com/doi/10.1177/0091270010378520 by University Of Athens, Wiley Online Library on [14/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Baseline Insulin Correction Methodology

Insulin concentrations collected at 120, 90, 60, and 30 minutes before dosing were averaged, and the result was subtracted from all subsequently observed insulin concentrations. This method adjusted the serum insulin concentrations to account for the ongoing insulin infusion. This correction was conducted before the data were analyzed and used for model development.

Data Excluded From the Pharmacokinetic Analysis

Endogenous insulin secretion was assumed to be completely suppressed after insulin administration. However, to ensure that endogenous insulin was suppressed for the entire sampling period, the serum insulin and C-peptide concentration–time profile for each dosing was examined visually. In subjects with low exposure to the test treatment, endogenous insulin appeared to be contributing to the later part of the concentration–time curve. Given the small number of samples collected for C-peptide assay, a C-peptide correction method[10] could not be applied to the insulin data, and visual inspection was used to determine insulin concentrations influenced by the endogenous component. As a result of the lower doses administered in study 2, a higher incidence of elevated C-peptide concentrations was observed in the later time points following TI treatment, particularly in the lower dose groups. All insulin concentrations after 180 minutes after dosing in the 25-U dose group, 240 minutes in the 50-U dose group, and 300 minutes in the 100-U dose group were excluded. A total of 51 quantifiable insulin concentrations was excluded from the analysis.

Noncompartmental Pharmacokinetic Analysis and Absolute Bioavailability

Insulin pharmacokinetics were analyzed using noncompartmental methodology and baseline-corrected insulin concentrations. The pharmacokinetic parameters, derived using WinNonlin 5.2 (Pharsight Corporation, Mountain View, California), were observed peak insulin concentration (C_{max}), time to peak insulin (t_{max}), and total insulin exposure as measured by the area under the insulin concentration–time curve from time 0 until the last time point with nonzero insulin concentrations ($AUC_{0\text{-}last}$), calculated by the linear-trapezoidal method. The terminal elimination half-life ($t_{1/2}$) was calculated as $\ln(2)/\lambda_z$ in accordance with pharmacokinetic theory,[11] where λ_z was the terminal elimination rate constant estimated from log-linear regression analysis of the terminal elimination phase of the concentration–time profile. Insulin $AUC_{0\text{-}\infty}$ was calculated as $AUC_{0\text{-}last} + C_{last}/\lambda_z$, where C_{last} was the last quantifiable insulin concentration. Noncompartmental parameter values were used to determine starting values for pharmacokinetic modeling and were compared with parameter values estimated by the final model as part of the model fit assessment. Absolute bioavailability (%F) was determined using the mean dose-normalized insulin $AUC_{0\text{-}last}$ values, expressed as the group average dose-normalized $AUC_{0\text{-}last}$/average dose-normalized $AUC_{0\text{-}last}$ following IV administration.

Pharmacokinetic Model and Data Analysis

The software package NONMEM (version VI, level 1.2, NONMEM Project Group, ICON Development Solutions, Ellicott City, Maryland) was used for the population analysis. The ADVAN6 subroutine and first-order (FO) estimation method were used. The FOCE (first-order conditional estimation) method was tested, but given the excessively long run times associated with this model, the FO estimation method was chosen. All sampling times were coded relative to a dosing time of 0. The system was reset following each crossover dose using the EVID variable due to the complete washout of test treatment during a minimum of 3 days.

NONMEM describes the observed concentration–time data in terms of a number of fixed-effect parameters, θ, and 2 types of random-effect parameters. The fixed-effect parameters include the population values of the relevant base pharmacokinetic model parameters and may include a number of parameters that relate the base model parameters to demographic and other covariates. The random-effect parameters are ω^2, the variances of the interindividual variability (η) within the population, and σ^2, the variances of the residual intraindividual variability (ε) due to random fluctuations in an individual's parameter values, measurement error, model misspecification, and all sources of error not accounted for by the other parameters.

The population values of the parameters (θ), the interindividual variances (ω^2), and the residual variance (σ^2), were estimated by NONMEM. Subject-specific parameters were calculated by NONMEM using the POSTHOC option. These parameters are empirical Bayesian estimates of the individual's true

15524604, 2011, 7, Downloaded from https://accp1.onlinelibrary.wiley.com/doi/10.1177/009127001037852O by University Of Athens, Wiley Online Library on [14/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

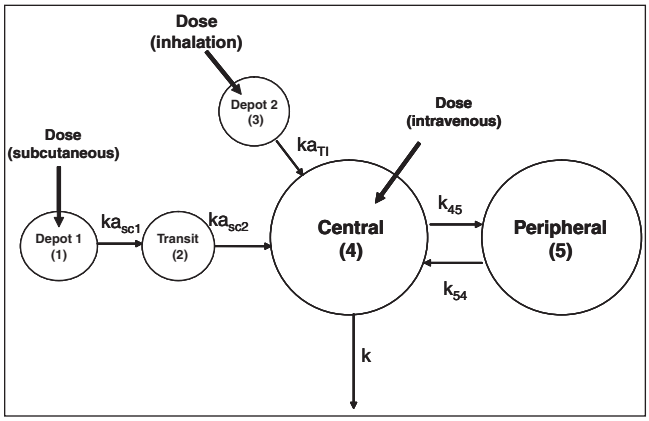

Figure 1. Pharmacokinetic model diagram.

parameters based on the population parameters and the individual's observed concentrations.

Pharmacokinetic Base Model

Data from all 3 routes of administration were modeled simultaneously. Insulin pharmacokinetics were described by a 2-compartment model with 1 (inhaled) or 2 sequential (subcutaneous) first-order absorption processes and first-order elimination. A diagram of the model is presented in Figure 1. The model was described by the following differential equations:

$$\frac{dA_1}{dt} = -ka_{sc1} \cdot A_1 \quad (1)$$

$$\frac{dA_2}{dt} = ka_{sc1} \cdot A_1 - ka_{sc2} \cdot A_2 \quad (2)$$

$$\frac{dA_3}{dt} = -ka_{TI} \cdot A_3 \quad (3)$$

$$\frac{dA_4}{dt} = ka_{TI} \cdot A_3 + ka_{sc2} \cdot A_2 + k_{54} \cdot A_5 - k_{45} \cdot A_4 - k \cdot A_4 \quad (4)$$

$$\frac{dA_5}{dt} = k_{45} \cdot A_4 - k_{54} \cdot A_5 \quad (5)$$

where A_i is the amount of insulin in compartment *i*, ka_{TI} is the TI first-order absorption rate constant, ka_{sc1} and ka_{sc2} are the 2 first-order absorption rate constants associated with subcutaneously administered insulin, and the k_{ij} values are the intercompartmental transfer rates between the central and peripheral compartment (k_{45}) and peripheral and central compartment (k_{54}).

The pharmacokinetic structural model was parameterized in terms of clearance (CL); volume of distribution in the central compartment (V_4); intercompartmental clearance (Q); volume of distribution in the peripheral compartment (V_5); ka_{TI}, ka_{sc1}, and ka_{sc2}; and the absolute bioavailability for subcutaneous insulin and TI (F_{sc}, F_{TI}), where

$$CL = k \cdot V_4 \quad (6)$$

$$Q = k_{45} \cdot V_4 \; or \; k_{54} \cdot V_5 \,. \quad (7)$$

Error Model

Fixed-effects parameters were used to describe the typical population estimates, and an exponential random-effect model was used to describe interindividual variability for each model parameter:

$$\theta_i = \theta^{\eta_i} \quad (8)$$

where θ_i was the estimated parameter value for the *i*th individual, θ was the fixed-effect typical parameter value in the population, and η_i values were individual-specific random effects for the *i*th individual symmetrically distributed with 0 mean and variance ω^2.

A combined proportional and additive error model was used to model the residual unexplained variability, as described by the following equation:

$$Cp_{ij} = \tilde{C}p_{ij} \cdot (1 + \varepsilon_{1ij}) + \varepsilon_{2ij} \quad (9)$$

where Cp_{ij} was the observed value of the *j*th plasma concentration of individual *i*; Cp_{ij} was the predicted *j*th plasma concentration of individual *i*; and the ε_{ij} are random variables that represent the discrepancy between the observed and predicted *j*th concentration.

Considerable interoccasion variability (IOV) was observed within the TI groups. The variability was attributed to natural variation in inhalation on different occasions, resulting in differences in relative bioavailability at different visits, as described by

$$F_{TI} = \theta_{FTI}^{\eta_{FTI} + \eta_{OCC1} \cdot OCC1 + \eta_{OCC2} \cdot OCC2 + \eta_{OCC3} \cdot OCC3} \quad (10)$$

where *OCC*1, *OCC*2, and *OCC*3 were set to 1 at the corresponding occasion and 0 otherwise. This IOV error model was used in the base and full models.

Reparameterization and Individual Predicted Values

Individual-specific values of each pharmacokinetic parameter were obtained by Bayesian analysis with the final model. The following pharmacokinetic parameters could subsequently be calculated for each individual according to the following equations based on compartment modeling theory:

15524604, 2011, 7, Downloaded from https://accp1.onlinelibrary.wiley.com/doi/10.1177/0091270010378520 by University Of Athens, Wiley Online Library on [14/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

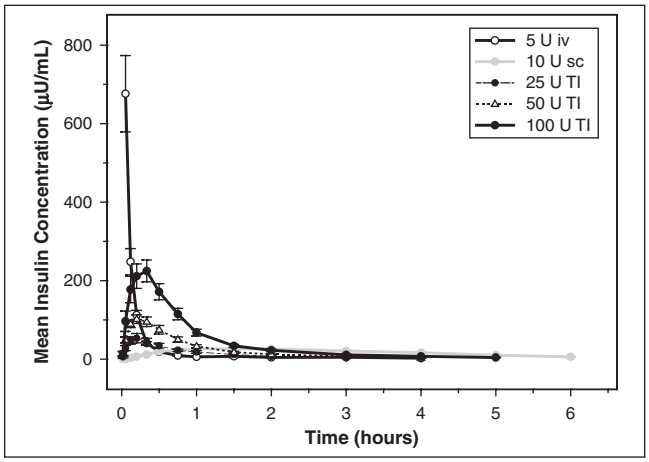

Figure 2. Mean (±SE) insulin concentration–time profiles for all dose groups. Following IV treatment, data past 4 hours were available from only 2 subjects; mean data not shown.

$$\alpha = \frac{1}{2}\left[(k_{45} + k_{54} + k) + \sqrt{(k_{45} + k_{54} + k)^2 - 4k_{54}k}\right] \quad (11)$$

$$\beta = \frac{1}{2}\left[(k_{45} + k_{54} + k) - \sqrt{(k_{45} + k_{54} + k)^2 - 4k_{54}k}\right] \quad (12)$$

$$\alpha\, half - life = \frac{0.693}{\alpha} \quad (13)$$

$$\beta\, half - life = \frac{0.693}{\beta}. \quad (14)$$

Model Fit Assessment

Goodness-of-fit was determined by the objective function value (OFV) and visual inspection of scatter plots of predicted versus observed concentrations and weighted residuals. For nested models, hypothesis tests were performed based on the likelihood ratio test, in which the change in OFV approximates the χ^2 distribution. A more complicated model was preferred when the decrease in OFV was more than 3.84 (the critical value for the χ^2 distribution at $P < .05$ with 1 degree of freedom).

Covariate Analysis

After determination of the base population model, potential covariates were examined to determine whether they improved the overall fit and reduced variability in the model. These covariates included age, body weight, body height, and BMI. Covariates were initially evaluated for possible relationships with the model estimated pharmacokinetic parameters using the generalized additive model (GAM) procedure in Xpose,[12] which incorporates the Akaike information criterion (AIC) for covariate identification. Covariates associated with a reduction in the AIC were evaluated using NONMEM in a stepwise manner. Each covariate added to the base model, and the resulting univariate model was then compared with the reduced model for significant improvement in fit. Covariates were included in the model if the nested model criterion (a 3.84 point drop in the OFV) was observed ($P < .05$). Backward elimination was then performed whereby each covariate was independently removed from the model to confirm its relevance. An increase in the OFV of 6.7 ($P < .01$) was necessary to confirm that the covariate was significant.

RESULTS

Study Population

Fourteen men and 2 women were enrolled; 15 subjects were Caucasian and 1 was Asian. Demographic characteristics were mean (standard deviation) age, 28 (4) years; weight, 76 (11) kg, BMI, 24 (2) kg/m^2; and height, 179 (9) cm. All subjects completed the studies and received all scheduled doses. In study 1, a subject in the 5-U IV dose group had an insulin concentration–time profile that did not match the dosing and sampling times, indicating that errors may have been made when dosing or sampling times were recorded. Because the elapsed time since dose could not be determined with certainty, the subject was excluded from the analysis. In study 2, a subject was excluded from analysis in the 10-U subcutaneous treatment group because 3 consecutive BLQ values were observed in the pharmacokinetic profile below the limit of quantification, suggesting a possible analytical error. Furthermore, on visual inspection of the insulin concentration–time profiles, data from 1 subject appeared to differ markedly from the other subjects, with almost no insulin exposure within the first few hours after dosing, suggesting that the subject may have had difficulty with inhalation. Statistical analysis determined the subject was an outlier with respect to at least 1 pharmacokinetic parameter for each dose group ($P < .05$); consequently, the subject was excluded from both the noncompartmental analysis (NCA) and population analysis. Dixon's test was used on all log-transformed pharmacokinetic parameters, except t_{max}, which was tested using nontransformed values and Tukey's test.

15524604, 2011, 7, Downloaded from https://accp1.onlinelibrary.wiley.com/doi/10.1177/009127001037852O by University Of Athens, Wiley Online Library on [14/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table I Mean (% Coefficient of Variation) Noncompartmental Pharmacokinetic Parameter Estimates

Treatment	n	t_{max}[a], h	C_{max}, µU/mL	$AUC_{0\text{-last}}$, µU/mL·h	t_{last}[a], h	Half-life, (h)	$AUC_{0\text{-}\infty}$, µU/mL·h	Dose-normalized $AUC_{0\text{-last}}$
5 IU IV	4	NA	NA	100.0 (21)	4.5	1.7 (23)	103.2 (19)	20.1
10 IU SC	15	1.5	30.7 (34)	107.0 (26)	6	NA	NA	10.7
25 U TI	11	0.2	54.6 (72)	50.0 (61)	3	1.1 (61)	57.4 (62)	2.0
50 U TI	11	0.2	105.3 (38)	101.5 (39)	4	1.3 (31)	111.2 (39)	2.0
100 U TI	16	0.33	240.9 (52)	218.6 (43)	5	1.4 (57)	230.6 (41)	2.2

$AUC_{0\text{-}\infty}$, area under the concentration–time curve from zero to infinity; C_{max}, peak insulin concentration; IV, intravenous; NA, not applicable; SC, subcutaneous; TI, Technosphere Insulin Inhalation Powder; t_{last}, last observed insulin concentration; t_{max}, time to peak insulin.
a. Median.

A total of 651 insulin concentrations from 16 subjects and 57 profiles were included in the analysis.

Noncompartmental Pharmacokinetic Analysis

The highest average insulin concentration–time profiles were observed following IV dosing, the lowest were observed following subcutaneous administration, and average insulin concentration–time profiles appeared to increase with increasing TI dose (Figure 2). Insulin bioavailability, based on mean dose-normalized $AUC_{0\text{-last}}$, was approximately 53% after subcutaneous administration, was between 10% and 11% following TI administration, and did not appear to depend on TI dose (Table I). Because this calculation was based on $AUC_{0\text{-tlast}}$, which was truncated at 6 hours following subcutaneous RHI, absolute bioavailability may have been underestimated for this treatment, but because the 6-hour subcutaneous RHI samples were at or nearing baseline, no appreciable difference was expected. Terminal insulin half-life and $AUC_{0\text{-}\infty}$ could not be calculated following subcutaneous dosing because the prolonged absorption from the tissue and the flip-flop kinetics associated with this route of insulin administration.

Pharmacokinetic Model

A 2-compartment open model with 1 (inhaled) or 2 sequential (subcutaneous) first-order absorption processes and first-order elimination described the insulin concentration data well. The population typical parameter values (Table II) in the structural model were clearance, 43.7 L/h; volume of distribution in the central compartment, 5.11 L; volume of distribution in the peripheral compartment, 31.6 L.

Table II Population Pharmacokinetic Parameters of Insulin

	Base Model	Full Model
	Estimate (%RSE)	Estimate (%RSE)
CL, L/h	43.70 (8.6)	43.4 (8.6)
V_4, L	5.11 (10.0)	5.02 (9.6)
Q, L/h	24.5 (15.4)	23.9 (13.3)
V_5, L	31.6 (18.5)	30.7 (15.4)
ka_{sc1}, h^{-1}	0.52 (17.3)	2.37 (14.4)
ka_{sc2}, h^{-1}	1.28 (25.4)	1.04 (22.8)
ka_{TI}, h^{-1}	2.34 (8.7)	2.35 (8.9)
F_{sc}, %	53 (13.4)	52 (13.0)
F_{TI}, %	11 (12.7)	11 (13.0)
BMI covariate effect	NA	0.74 (8.0)
Estimates of Interindividual and Residual Variability (%)	**Base Model**	**Full Model**
ω_{CL}	9.2	9.9
ω_{V4}	37.8	36.9
ω_{Q}	31.5	30.7
ω_{V5}	29.5	27.7
ω_{kasc1}	57.4	50.1
ω_{kaTI}	19.1	19.6
ω_{Fsc}	23.2	24.1
ω_{FTI}	24.0	23.7
$\omega_{IOV\ FTI}$	30.7	30.2
σ_1	26.1	25.1
σ_2	1.3[a]	1.51[a]

BMI, body mass index; CL, clearance; F_{sc}, absolute bioavailability for subcutaneous insulin; F_{TI}, absolute bioavailability for TI; ka_{sc1} and ka_{sc2}, first-order absorption rate constants associated with subcutaneously administered insulin; ka_{TI}, TI first-order absorption rate constant; Q, intercompartmental clearance; RSE, root square error; V_4, volume of distribution in the central compartment; V_5, volume of distribution in the peripheral compartment interindividual error.
a. σ_2 (additive residual error) is expressed in µU/mL; The magnitude of interindividual and residual variability was approximated by the square root of the variance estimate.

15524604, 2011, 7, Downloaded from https://accp1.onlinelibrary.wiley.com/doi/10.1177/0091270010378520 by University Of Athens, Wiley Online Library on [14/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table III Covariate Selection

Covariate Model Tested	OFV	Change in OFV
Base model	3695.551	
BMI on ka_{sc1}	3686.141	9.410
Body weight on V_4	3694.240	1.311
Age on V_5	3691.658	3.893
BMI on ka_{sc1} and age on V_5	3682.352	3.789

BMI, body mass index: ka_{sc1} first-order absorption rate constant associated with subcutaneously administered insulin; OFV, objective function value; V_4, volume of distribution in the central compartment; V_5, volume of distribution in the peripheral compartment.

Covariate Analysis

A GAM analysis identified BMI as a potential covariate for absorption rate constant associated with subcutaneous insulin and body weight as a potential covariate for volume of distribution in the central compartment; to a lesser extent, age was identified as a potential covariate for the peripheral volume of distribution (Table III). Visual inspection of covariate versus parameter scatter plots and graphs of weighted residuals versus covariates confirmed these findings. Because different inhalers were used in the 2 studies, a possible effect on TI bioavailability was examined by adding the effect into the univariate analysis. The lack of inhaler effect seen visually was confirmed by a lack of change in OFV when the covariate was tested.

The results of a stepwise forward addition showed that following the addition of BMI ($P < .01$) as a covariate to the subcutaneous absorption rate constant, the further addition of weight or subject age on any of the identified parameters did not significantly contribute to the model. BMI effect was described by the following equation:

$$ka_{sc1} = \theta_{kasc1}(1 - \theta_{BMI,kasc1}) \cdot (BMI / 23.7) \qquad (15)$$

where BMI was centered around the population median value (23.7 kg/m^2). The addition of this covariate decreased the OFV by 9.41 points and also reduced the interindividual CV% on ka_{sc1} from 57% to 50% (Tables II and III).

Final Model

The overall model fit was good, with individual predicted versus observed values distributed along the line of unity and no significant trends in the weighted residuals (Figure 3). Thus, the structural and error models appeared to adequately describe insulin pharmacokinetics and explain the variability in the data.

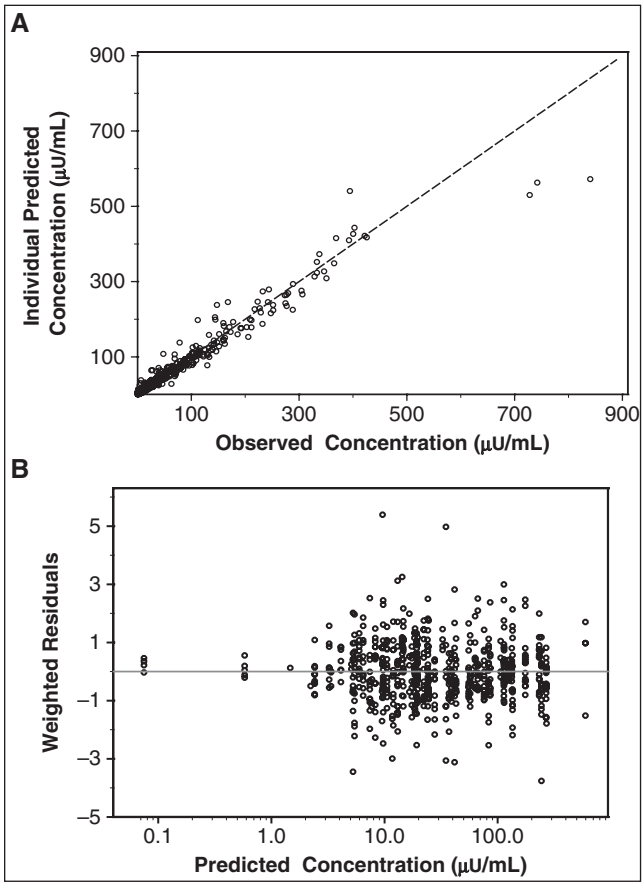

Figure 3. (A) Individual predicted vs observed insulin concentrations; (B) weighted residuals vs predicted insulin concentrations.

In the final model, the population typical parameter values were CL, 43.4 L/h; V_4, 5.0 L; and V_5, 30.7 L. The %F for subcutaneous insulin and TI was 52% and 11%, respectively, matching both results reported with TI[13] and subcutaneous RHI[14] and the results of the noncompartmental analysis (Table I). Based on the median BMI value, ka_{sc1} was 0.63 h^{-1}. The pharmacokinetic parameter estimates are summarized in Table II.

The α and β half-lives of 5 minutes and 93 minutes, respectively, were calculated from the individual predicted parameters and were in close agreement with both the insulin half-life estimates after IV administration reported previously[6] and the terminal half-life approximated following noncompartmental analysis (Table III). The population predicted concentration–time profiles (Figure 4) showed

15524604, 2011, 7, Downloaded from https://accp1.onlinelibrary.wiley.com/doi/10.1177/009127001037852O by University Of Athens, Wiley Online Library on [14/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

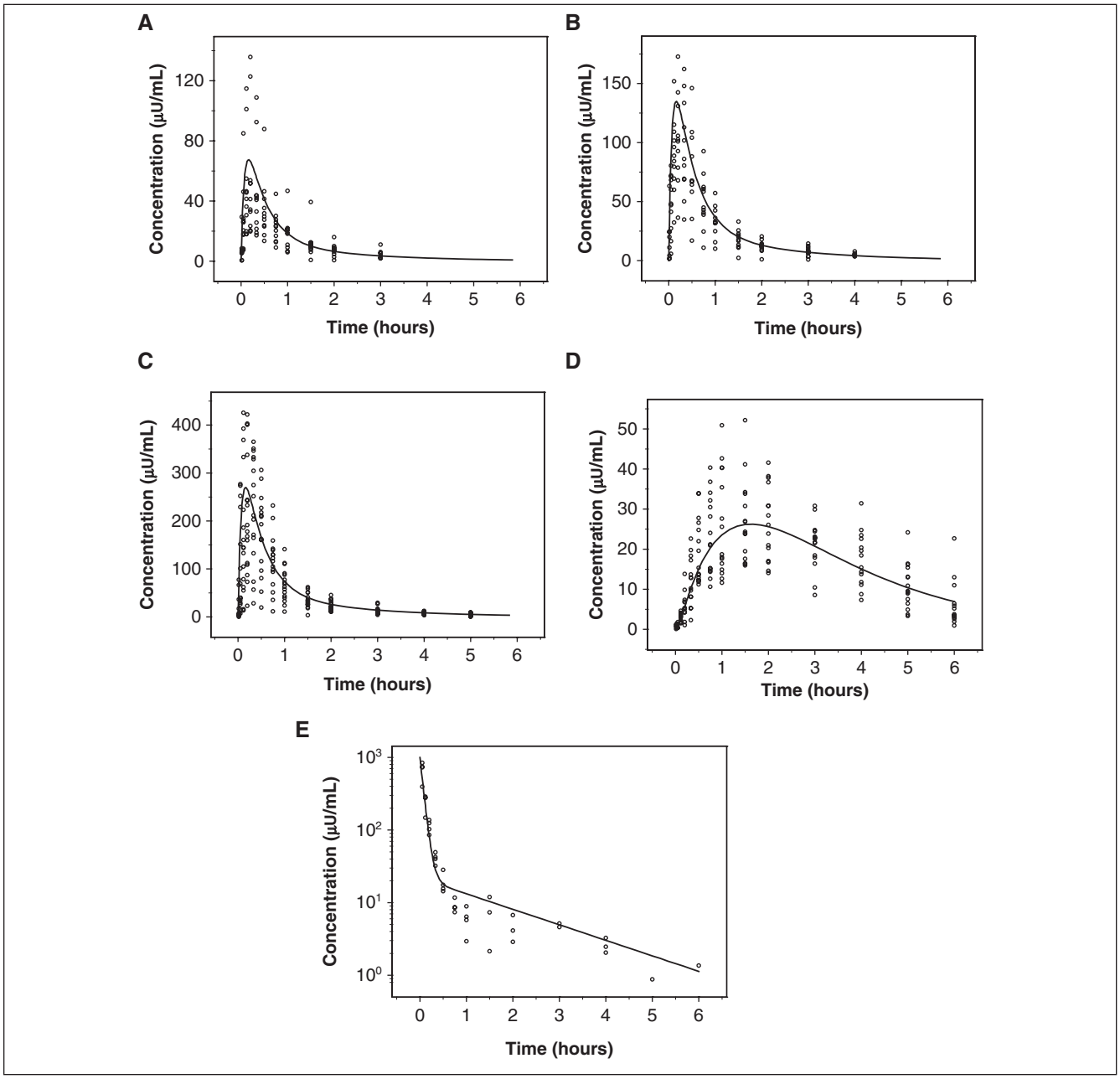

Figure 4. Population predicted concentration–time profiles and observed data by dose group: (A) TI 25-U dose; (B) TI 50-U dose; (C) TI 100-U dose; (D) subcutaneous RHI, 10-U dose; (E) intravenous RHI, 5-U dose.

that following IV dosing, the distribution phase was approximately 30 minutes. The apparent distribution phase was longer after TI administration and was indistinguishable from the elimination phase after subcutaneous dosing due to prolonged absorption from the injection site.

Interoccasion variability following TI administration was approximately 30%. The interindividual variability for all pharmacokinetic parameter estimates ranged from 10% to 52%. The residual error was described by a combined proportional (25.1%) and additive (1.51 µU/mL) model, with the additive component close in value to the lower limit of quantification of the insulin assay (1.2 µU/mL). Example observed and predicted concentration–time profiles are shown in Figure 5.

15524604, 2011, 7, Downloaded from https://accp1.onlinelibrary.wiley.com/doi/10.1177/0091270010378520 by University Of Athens, Wiley Online Library on [14/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

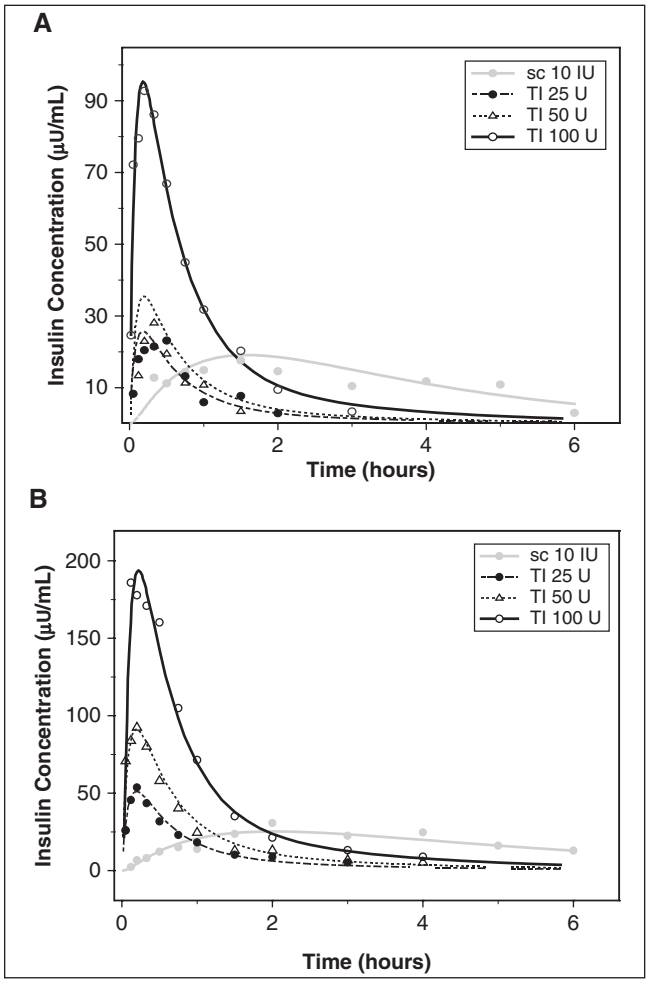

Figure 5. Example observed and predicted concentration–time profiles: (A) subject A and (B) subject B.

DISCUSSION

Insulin pharmacokinetics have been described by a 2-compartment disposition after IV administration, and the α half-life has been previously reported as approximately 5 to 6 minutes.[6] Because the α phase is short compared with the duration of absorption following subcutaneous administration, the absorption phase obscures the initial distribution, rendering it difficult to distinguish the second compartment. Furthermore, slow absorption dominates the pharmacokinetics of subcutaneously administered insulin in a phenomenon commonly termed *flip-flop* kinetics.[4] As a result, the differences in insulin profiles, especially the terminal phase, observed among the various non-IV routes of administration reflect the differences in absorption, not elimination.

Most available assessments of insulin pharmacokinetics use the pharmacokinetic profiles of subcutaneously administered formulations, as this route of administration has been the dominant route since insulin's initiation as a therapeutic agent. Hence, the pharmacokinetic profiles following non-IV routes of insulin administration have been described using a 1-compartment model.[2,4,15]

TI is a novel inhaled insulin with unique delivery characteristics that result in rapid absorption and systemic clearance, making it possible to clearly distinguish a second compartment in its pharmacokinetic profile. This is unique for an insulin formulation and may be due to the combination of the quick dissolution of the delivery microparticles upon contact with the lung surface[16] and delivery of TI to the lung as an insulin monomer,[8] the most readily absorbed form of insulin.[17]

Because insulin pharmacokinetic properties are expected to be consistent once insulin is available systemically,[18] the inclusion of data from TI and IV dosing, both of which have distinct α and β phases, made it possible to demonstrate the 2-compartment disposition of all 3 routes of insulin administration. Furthermore, the differences in absorption rate between TI and subcutaneously administered insulin could be estimated. A model incorporating 2 sequential absorption rates and a transit compartment was used to describe the slower absorption seen with the subcutaneously administered insulin. This model was described by Puckett et al[19] and was based on the physiology of subcutaneous insulin administration, where the depot compartment represents the subcutaneous tissue, and the second compartment represents the interstitial space.

Interoccasion inhalation variability can result in differences in the bioavailability of treatments administered through the lung. Although this variability may be reduced with repeated dosing, treatment-naïve or inexperienced subjects may exhibit significant interoccasion differences in exposure. In this analysis, subjects in 1 of the studies received 3 different doses of TI on 3 different occasions. The interoccasion variability was successfully modeled to reflect inhalation differences that resulted in a difference in insulin bioavailability, with no difference in other pharmacokinetic parameters. For this group of subjects, the interoccasion variability was estimated by the model to be approximately 30%. The overall interindividual variability estimate associated with TI absorption rate (19.6 %) was considerably lower compared with subcutaneously administered insulin (50.1 %).

15524604, 2011, 7, Downloaded from https://accp1.onlinelibrary.wiley.com/doi/10.1177/009127001037852O by University Of Athens, Wiley Online Library on [14/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Covariate analysis was not expected to result in many findings because the number of subjects was small and the subjects were young, healthy volunteers. However, even in this population, increases in BMI were associated with a decreased absorption rate when insulin was administered subcutaneously. Although the small number of patients in the analysis may inflate type I error with forward stepwise covariate addition[20] and the significance of this finding should be treated with caution, it is consistent with results reported previously[21] and may be attributed to the increased thickness of the subcutaneous tissue slowing absorption from the depot compartment. Because this relationship was detected in the healthy population with BMI within the normal range, it is expected that a greater impact would be observed in patients taking subcutaneous insulin who have higher BMI, as is often the case in subjects with type 2 diabetes. However, a larger number of subjects, with preferably a greater range of BMI values, are needed to better define a dependency between this covariate and absorption rate following subcutaneous insulin administration.

CONCLUSIONS

Insulin pharmacokinetics were consistent with a 2-compartment model, with a distribution phase following IV dosing of approximately 30 minutes. The apparent distribution phase was longer after TI administration and was indistinguishable after subcutaneous dosing given the prolonged duration of absorption. BMI was a significant covariate on insulin absorption rate after subcutaneous dosing, with an associated decrease in the rate of absorption with increasing BMI. In the model presented here, differences in the shape of the insulin curve after different routes of administration were successfully attributed to differences in absorption.

Financial disclosure: Elizabeth Potocka and Robert A. Baughman are employees of MannKind Corporation, which funded these studies. Hartmut Derendorf has no conflicts of interest to disclose.

REFERENCES

1. Gopalakrishnan M, Suarez S, Hickey AJ, Gobburu JV. Population pharmacokinetic pharmacodynamic modeling of subcutaneous and pulmonary insulin in rats. *J Pharmacokinet Pharmacodyn*. 2005;32:485-500.

2. Landsdorfer C. PK/PD modeling of glucose clamp effects of inhaled insulin. Paper presented at: American Conference on Pharmacometrics; March 9-12, 2008; Tucson, Ariz.

3. Osterberg O, Erichsen L, Ingwersen SH, Plum A, Poulsen HE, Vicini P. Pharmacokinetic and pharmacodynamic properties of insulin aspart and human insulin. *J Pharmacokinet Pharmacodyn*. 2003;30:221-235.

4. Tornoe CW, Jacobsen JL, Madsen H. Grey-box pharmacokinetic/pharmacodynamic modelling of a euglycaemic clamp study. *J Math Biol*. 2004;48:591-604.

5. Woodworth JR, Howey DC, Bowsher RR. Establishment of time-action profiles for regular and NPH insulin using pharmacodynamic modeling. *Diabetes Care*. 1994;17:64-69.

6. Hooper SA, Bowsher RR, Howey DC. *Pharmacokinetics and Pharmacodynamics of Intravenous Regular Human Insulin. Pharmacokinetics and Pharmacodynamics. Vol 3: Peptides, Peptoids, and Proteins*. Cincinnati, Ohio: Harvey Whitney; 1991.

7. Boss AH, Yu W, Ellerman K. Prandial insulin: is inhaled enough? *Drug Dev Res*. 2008;69:138-142.

8. Leone-Bay A. Technosphere ®/Insulin: mimicking endogenous insulin release. In: Rathbone MHJ, Roberts M, Lane M, eds. *Modified Release Drug Delivery Technology*. 2nd ed. New York, NY: Informa Healthcare USA; 2008:673-680.

9. Rave K, Potocka E, Boss AH, Marino M, Costello D, Chen R. Pharmacokinetics and linear exposure of AFRESA compared with the subcutaneous injection of regular human insulin. *Diabetes Obes Metab*. 2009;11:715-720.

10. Owens DR. Human insulin. Intermediate-acting insulin preparations "initial ratio" method. In: Owens DR, ed. *Clinical Pharmacological Study in Normal Man*. Saarbrucken, Germany: MTD Press Limited; 1986:138.

11. Muir KT. Non-compartmental analysis. In: Bonate P, ed. *Pharmacokinetics in Drug Development: Clinical Study Design and Analysis*. Arlington, VA: American Association of Pharmaceutical Scientists, 2004:235-266.

12. Jonsson EN, Karlsson MO. Xpose—an S-PLUS based population pharmacokinetic/pharmacodynamic model building aid for NONMEM. *Comput Methods Programs Biomed*. 1999;58:51-64.

13. Steiner S, Pfutzner A, Wilson BR, Harzer O, Heinemann L, Rave K. Technosphere/insulin—proof of concept study with a new insulin formulation for pulmonary delivery. *Exp Clin Endocrinol Diabetes*. 2002;110:17-21.

14. Humalog® Insulin Lispro Injection, USP (rDNA origin), 100 units per mL (U-100) [prescribing Information]. Indianapolis, Ind: Eli Lilly; 2009.

15. Nucci G, Cobelli C. Models of subcutaneous insulin kinetics: a critical review. *Comput Methods Programs Biomed*. 2000;62: 249-257.

16. Richardson PC, Boss AH. Technosphere insulin technology. *Diabetes Technol Ther*. 2007;9(suppl 1):S65-S72.

17. Brain JD. Inhalation, deposition, and fate of insulin and other therapeutic proteins. *Diabetes Technol Ther*. 2007;9(suppl 1): S4-S15.

18. Gad SC. *Drug Safety Evaluation*. New York, NY: J. Wiley, 2002.

19. Puckett WR, Lightfoot EN. A model for multiple subcutaneous insulin injections developed from individual diabetic patient data. *Am J Physiol*. 1995;269:E1115-E1124.

20. Ribbing J, Jonsson EN. Power, selection bias and predictive performance of the population pharmacokinetic covariate model. *J Pharmacokinet Pharmacodyn*. 2004;31:109-134.

21. Sindelka G, Heinemann L, Berger M, Frenck W, Chantelau E. Effect of insulin concentration, subcutaneous fat thickness and skin temperature on subcutaneous insulin absorption in healthy subjects. *Diabetologia*. 1994;37:377-380.

For reprints and permission queries, please visit SAGE's Web site at http://www.sagepub.com/journalsPermissions.nav

15524604, 2011, 7, Downloaded from https://accp1.onlinelibrary.wiley.com/doi/10.1177/0091270010378520 by University Of Athens, Wiley Online Library on [14/03/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License