Population pharmacokinetics of clomethiazole and its effect on the natural course of sedation in acute stroke patients

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Aims This analysis was performed to investigate the population pharmacokinetics of clomethiazole and its effect on the natural course of sedation in acute stroke patients using a nonlinear mixed effects modelling approach.

Methods One thousand five hundred and forty-six acute stroke patients (774 on active treatment) from 166 centres were included in three randomized, double-blind, placebo-controlled phase III efficacy and safety studies. A total dose of 68 mg kg⁻¹ clomethiazole edisilate was given as a three-phase i.v.-infusion over 24 h. Three blood samples were drawn from all patients to characterize the pharmacokinetics. Sedation was monitored throughout the entire treatment period and the degree of sedation was measured on a discrete ordinal scale with six levels. Models were fitted to the data using the software NONMEM.

Results Clomethiazole was characterized by a two-compartment pharmacokinetic model with interindividual variability in all structural parameters. For a patient weighing 75 kg, the average CL, *V*₁, *Q*, and *V*₂ was estimated to be 52.7 l h⁻¹, 82.5 l, 167 l h⁻¹ and 335 l, respectively. The interindividual variability in CL, *V*₁, *Q* and *V*₂ was estimated to be 48%, 53%, 42% and 54%, respectively. Increasing body weight and concomitant administration of liver enzyme inducing drugs were found to increase clearance (by 0.5 l h⁻¹ kg⁻¹ and 40%, respectively). Increasing weight also increased the volume of distribution (1.1 l kg⁻¹ for *V*₁ and 4.7 l kg⁻¹ for *V*₂). A six-category proportional odds model with a component including the natural course of sedation following placebo administration, a drug component (present or absent) and an interindividual variability component described the degree of sedation. Stroke severity as measured on the NIH-stroke scale on admission and drug treatment were the most important predictors of sedation, but a nonlinear increase in sedation with increasing age was also found. Increasing body weight increased the sedative drug effect.

Conclusions The pharmacokinetics of clomethiazole were characterized in acute stroke patients and the analysis excluded several possible covariates of interest in drug development. The time course of sedation could be quantitatively described during the first 24 h following an acute stroke in the presence or absence of clomethiazole treatment.

Keywords: logistic regression, nonlinear mixed effects models, pharmacokinetics, proportional odds model, sedation, stroke

Introduction

Stroke is the third leading cause of death and the most common cause of adult disability in the Western world

[1–4]. Stroke may also cause sedation, especially when oedema occurs [5].

Clomethiazole has been shown to have neuroprotective effects in rat, gerbil, and marmoset models of cerebral ischaemia [6–12]. These findings suggested that clomethiazole might prevent neuronal degeneration following ischaemic stroke and the drug has undergone clinical development as a potential treatment. The putative mechanism of the neuroprotective effect of clomethiazole is an enhancement of γ -amino butyric acid

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(GABA)_A receptor activity, leading to prevention of the excitotoxic effects of glutamate in the ischaemic cascade [13]. The main dose limiting side-effect of clomethiazole in acute stroke patients is sedation, especially as stroke itself induces sedation [5].

Two reports on the pharmacokinetics of clomethiazole in stroke patients have been published. The first was an open pilot study of 17 stroke patients with extensive blood sampling. No relationship was found between clomethiazole concentrations and sedation [14]. The second was a phase II study involving 1360 patients treated with clomethiazole or placebo within 12 h after the onset of stroke. One steady state blood-sample per patient was drawn and used in a population pharmacokinetic analysis [15]. The study was designed to investigate the safety and efficacy of clomethiazole in acute stroke patients. The difference between clomethiazole- and placebo-treated patients on the primary efficacy end point was not statistically significant [16]. However, a *post hoc* analysis showed an apparent positive effect of clomethiazole in the patients suffering from Total Anterior Circulation Syndrome (TACS) [17].

To determine if clomethiazole is of benefit in the treatment of this type of stroke a new phase III efficacy study, CLASS-I, was designed together with two phase III safety studies, CLASS-H and CLASS-T. All used a new dosing regimen aiming for a target steady state plasma concentration of clomethiazole above 10 µmol l⁻¹. The great majority of patients (96%) included in CLASS-I had symptoms and other clinical findings that fitted predefined criteria for an ischaemic TACS [18]. CLASS-H included patients with haemorrhagic stroke [19] and CLASS-T included patients with acute ischaemic stroke who were concomitantly treated with tissue-Plasminogen Activator (t-PA) [20]. In addition to efficacy and safety, the studies were also designed to investigate the pharmacokinetics of clomethiazole and their relationship to sedation. The findings of the efficacy study indicated that clomethiazole does not improve outcome in patients with major ischaemic stroke [18]. Sedation is an important aspect of the disease, and since clomethiazole has known sedative properties, it was important to monitor and quantify the relationships between drug treatment and sedation. Therefore the aim of the present analysis was to investigate the population pharmacokinetics and sedative effect of clomethiazole in acute stroke patients. The evaluation was performed using a nonlinear mixed effects modelling approach on data from the three phase III studies.

Methods

Study design

The three studies were randomized, double-blind, placebo-controlled and performed in accordance with Good

Clinical Practice and the Declaration of Helsinki. Informed consent was obtained before patient inclusion. In total 1600 patients (1200 for CLASS-I, 200 for CLASS-H and CLASS-T, respectively) from 166 centres in the USA and Canada were to be included in the studies. Local ethics committees approved the study at all sites, details of which can be obtained from the author. To be eligible for inclusion the patients had to have a clinical diagnosis of acute stroke within 12 h after onset. Patients were recruited to the different studies based on the results of a CT scan. Patients who had an acute ischaemic stroke and a combination of limb weakness, higher cortical dysfunction and visual field disturbance were enrolled in the CLASS-I study, patients with an intracerebral haemorrhage were enrolled in the CLASS-H study and ischaemic stroke patients treated with t-PA were enrolled in the CLASS-T study.

Treatment

Clomethiazole edisilate was given as a three-phase i.v.-infusion over 24 h in a regimen of 6 mg kg⁻¹ over 0.25 h, 31 mg kg⁻¹ from 0.25 to 8 h and 31 mg kg⁻¹ from 8 to 24 h.

Compared with the previous phase II study [16] the dose of clomethiazole edisilate was reduced from 75 mg kg⁻¹ to 68 mg kg⁻¹ and the infusion schedule modified, with the aim of achieving a target steady state plasma concentration of clomethiazole above 10 µmol l⁻¹. This was done to decrease the number of dose interruptions due to excessive sedation, since both the stroke itself and clomethiazole induce sedation.

Blood sampling

Blood samples were drawn at 15 min, at any time between 1 and 2 h and at the end of the infusion or 24 h whichever occurred first. If a dose adjustment was needed (see below), an extra sample was drawn at the first time the infusion was interrupted. To obtain more pharmacokinetic information, the above sampling times were changed for patients included in the late stage of the CLASS-I study. The new sampling times were at any time between 2 and 10 h, at any time between 10 and 23 h and at any time between 26 and 36 h after the start of the infusion.

The determination of clomethiazole concentrations in plasma was performed by the Department of Bioanalysis, AstraZeneca R & D, Södertälje, Sweden. Clomethiazole and the internal standard were extracted from plasma into 10% n-hexane in diethyl ether. Phosphate buffer pH 1.5 was added to the test tube before evaporation of the organic solvent. An aliquot (60 µl) of the buffer was assayed by reversed phase liquid chromatography with

UV detection at 255 nm. The mobile phase consisted of 28% acetonitrile in pH 1.5 buffer containing 1 mmol l⁻¹ of sodium laurylsulphate and the flow rate was 1.7 ml min⁻¹. The liquid chromatographic system consisted of a pump (Shimadzu model LC-10AD), an auto-sampler (Gilsoin model 234), a detector (TSP model, Spectra 100), an integrator (PE Nelson model 900), a column heater (model LC 22 A), a temperature regulator (Gilson model 721) and an analytical column (Prodigy 3 μ ODS (3) 100 A (50 $\times$ 4.6 mm)). The limit of quantification was 0.2 μ mol l⁻¹ and the intra-assay precision ranged from 1.4% to 5.4% at three different concentrations (0.2 μ mol l⁻¹, 2.0 μ mol l⁻¹ and 20 μ mol l⁻¹). The calibration curve was linear to at least 200 μ mol l⁻¹. The relative standard deviation was around 7% in the quality control samples with low concentrations, decreasing to 3.4% and 4.7% in the medium and high concentration groups. The relative standard deviation for the slope of the calibration graph was 1.6%. The accuracy was 98–101%.

Sampling design for the sedation score data

Sedation was monitored through the entire treatment period. The degree of sedation was measured on a discrete ordinal scale with six levels (Table 1).

If the patient became excessively sedated, defined as a score of 4 or above, the infusion of clormethiazole was stopped and optionally resumed at half the previous rate as soon as the subject scored 3 or less on the sedation scale. Sedation was measured at least every 3 h up to 24 h after the start of infusion, but if a score of 3 or greater was observed, sedation was checked approximately every 15 min.

Covariate data

Demographic covariates and information on concomitant use of other drugs were also collected from each patient and the distributions of the covariates are presented in Table 2. Creatinine clearance was estimated from the Cockcroft-Gault formula [21], based on the serum creatinine value at admission and was truncated upwards at 140 ml min⁻¹. Concomitantly used drugs were coded as

present or absent. They were classified on the basis of having a theoretical possibility to influence the pharmacokinetics of clomethiazole or to affect the sedation or of being frequently used by the patient population. The NIH stroke scale score [19] at admission was used as the covariate representing stroke severity.

Model building

The population pharmacokinetic and pharmacodynamic models were built using a nonlinear mixed effects approach as implemented in the NONMEM software (version VI β). The first-order conditional estimation method with interaction was used to derive population

Table 2 Distribution of covariates, all studies.

Covariate	Median (range)
Body weight (kg)	75 (31–157)
Age (years)	74 (19–90)
Height (cm)	168 (122–201)
BMI (kg m ⁻²)	26.0 (13.4–57.6)
Creatinine clearance (ml min ⁻¹)	74.12 (6.7–140)
Sex (male/female)	761/785
Race (Caucasian/Black/Oriental/Other/Hispanic)	1293/168/40/11/34
S-ASAT (U l ⁻¹)	23 (8–323)
S-ALAT (U l ⁻¹)	18 (4–287)
S-GT (U l ⁻¹)	26 (4–1121)
S-BILI, TOT (mg dl ⁻¹)	0.5 (0.1–2.4)
S-ALB (g dl ⁻¹)	3.9 (1.9–5.0)
S-ALP (U l ⁻¹)	83 (30–625)
NIH-stroke scale	16 (1–34)
Concomitant medication	Present/Absent (number of patients)
Liver enzyme inducers	100/1446
CYP2E1 substrates	590/956
Dicumarol group	212/1334
Heparin group	671/875
Inhibition of thrombocyte aggregation	825/721
β -adrenoceptor blockers	608/938
Thiazides	184/1362
Loop diuretics	437/1109
Potassium saving	70/1476
Calcium antagonists	428/1118
ACE inhibitors	508/1038
Cardiac glycosides	424/1122
Anti-arrhythmia agents	73/1473
Ataractic drugs	171/1375
Hypnotics	98/1448
Acetylsalicylic acid	842/704
CYP3A4 inhibitors	59/1487
Angiotensin-II antagonists	63/1483
Neuroleptics	57/1489
Sedative drugs	285/1261

Table 1 The sedation scale.

1	Fully awake
2	Drowsy but answers when spoken to
3	Answers slowly when spoken to
4	Reacts when spoken to but does not answer
5	Reacts only to pain
6	Does not react to pain

means and variances for the pharmacokinetic data, whereas the Laplacian estimation method was used for the pharmacodynamic data [22]. All final models were re-run using NONMEM version V, and gave the same results.

Pharmacokinetic model

The pharmacokinetic model was developed by first identifying a suitable structural model, for example a one or two compartment model. During this part of model development, the stochastic model had the form of exponential etas on all structural model parameters, together with a proportional residual error. This was followed by the development of the covariate part of the model. Finally, the form of the stochastic submodel was determined, that is on which parameters interindividual variability terms were supported and their correlation structure. The model for the residual error is also part of the stochastic submodel. To ensure that previous model building steps were not invalidated by later additions, all parts of the model were regularly scrutinized and changed if necessary.

Model discrimination was based on goodness of fit plots, simulations and changes in NONMEM's objective function value (OFV). For two nested models, the more complex one was selected if the OFV decreased by more than 10.8 (one parameter difference). This decrease corresponds to a nominal P value <0.001 .

Xpose 3.0 was used for data checkout, graphics and other diagnostic techniques to assist the model building [23]. This program was run in an S-PLUS environment (Insightful Corp., version 5.1 for Linux).

Stochastic submodel

Parameters were assumed to vary between individuals according to lognormal distributions. During the development of the structural and covariate submodels the parameters were assumed not to be correlated. After the covariate model building, this assumption was challenged and models with correlated parameters were tested.

The residual error model was chosen by examination of goodness of fit plots. Those considered were the additive error model, the proportional error model and the combined additive and proportional error model on untransformed or on log-transformed plasma concentrations.

Covariate model identification

Important covariate relationships were identified using a stepwise covariate model building routine described elsewhere [24]. Briefly, for each parameter covariate combi-

nation, a set of possible models including nonlinear relations was defined. Covariates were added to the model until no more added parameter-covariate combination significantly improved the fit, defined as a decrease in the OFV of 6.8 (corresponding to a nominal P value <0.01). Following the forward inclusion was a backward elimination step with stricter significance criteria for keeping a covariate in the model. Any parameter-covariate combinations that failed to decrease the OFV by 10.8 were omitted from the model.

Graphical analysis of individual parameters *vs* covariates was used to assess the possible influence of outlying individuals, together with scientific judgement to ensure that the identified covariate relationships were reasonable.

For clomethiazole, demographic covariates were tested on all the pharmacokinetic parameters, whereas concomitant medications were tested on clomethiazole clearance only. In the model for the sedation scores (see below), only covariates judged to have potential to influence sedation were tested. These were NIH stroke scale score on admission, sex, weight, age and concomitant medication with sedative drugs.

Pharmacodynamic models

The sedation score data were described using a proportional odds model for the probabilities of observing a particular degree of sedation [25]. The model estimated the cumulative probabilities of the sedation scores. Let S denote an observed sedation score, the logits, l_x , of the probabilities that $S \geq 2$, $S \geq 3$, $S \geq 4$, $S \geq 5$, $S = 6$, given no drug or natural course of sedation were then modelled as:

$$\begin{aligned} l_{S \geq 2} &= b_2 + \eta_1 \\ l_{S \geq 3} &= b_2 + b_3 + \eta_1 \\ l_{S \geq 4} &= b_2 + b_3 + b_4 + \eta_1 \\ l_{S \geq 5} &= b_2 + b_3 + b_4 + b_5 + \eta_1 \\ l_{S=6} &= b_2 + b_3 + b_4 + b_5 + b_6 + \eta_1 \end{aligned} \quad (1)$$

The b_x s are fixed effects parameters of the model and η_1 is a random variable with mean 0 and standard deviation ω_1 . The corresponding probabilities are given by:

$$PC_x = \frac{e^{l_x}}{1 + e^{l_x}} \quad (2)$$

The actual probabilities, p_x , of observing a particular score is given by: $p_{S=1} = 1 - PC_{S \geq 2}$, $p_{S=2} = PC_{S \geq 2} - PC_{S \geq 3}$, $p_{S=3} = PC_{S \geq 3} - PC_{S \geq 4}$, $p_{S=4} = PC_{S \geq 4} - PC_{S \geq 5}$, $p_{S=5} = PC_{S \geq 5} - PC_{S \geq 6}$, $p_{S=6} = PC_{S=6}$.

The first stage of the model development established a model for the disease progression, that is the natural course of sedation over time in the presence of placebo

treatment only. In the second stage, the effect of active treatment on sedation was determined on the basis of the data from both the placebo and active treatment groups. The relative contributions to the sedative effect of clomethiazole were accounted for through the predicted plasma concentrations.

Results

In total 1546 patients (774 on active treatment) of the 1600 patients from all three studies were available for the analysis. One thousand five hundred and forty-five of these patients had recorded sedation score measurements and were included in the sedation analysis. Several patients had dose-interruptions as directed by the protocol when reaching a sedation score of 4 or greater (43% of those treated with clomethiazole, 6% of those treated with placebo). The pharmacokinetics were evaluated on the 774 patients on active treatment. All clomethiazole concentrations used together with the model prediction for the typical individual are shown in Figure 1.

Pharmacokinetics

Concentration data for clomethiazole exceeding $150 \mu\text{mol l}^{-1}$ were considered to be unrealistically high, based on experience from phase I studies, and were omitted from the analysis. Missing data and concentration measurements where the sampling times were not in accordance with the dosing times, e.g. the presence of drug before any drug administration, were also omitted from the analysis. In total 111 out of 2288 observations were not used. Missing covariate information was imputed by the median value or with the mode (categorical covariates). Less than 5% of all covariate information was missing.

Figure 1 Observed clomethiazole concentrations and the model prediction for the typical individual.

A two-compartment model was found sufficient to describe the data (with a decrease in the OFV of 790 points compared with a one-compartment model). The model was parameterized in terms of CL, V_1 , Q and V_2 . The final clomethiazole model included terms for the interindividual variability on all four of these structural model parameters which were found to be correlated. The interindividual variabilities were modelled in an exponential fashion with a parameter specific term for the interindividual variability model and a term common to all parameters for the correlations. The interindividual models used all had the form:

$$P_i = \tilde{P}(z_i) \exp(\eta_{P_i} + \eta_{Q_i}) \quad (3)$$

where P_i represents the value of the pharmacokinetic parameter P for the i th subject, whereas $\tilde{P}(z_i)$ is the population mean of that parameter P in the structural model (given the covariate vector z of subject i). The random deviation from that mean is given by η_{P_i} and η_{Q_i} , where η_{P_i} corresponds to the interindividual variability of a specific parameter and η_{Q_i} corresponds to the joint interindividual variability for all parameters, which is probably caused by adsorption of clomethiazole to the tubing used for the infusion. These deviations were assumed to be distributed symmetrically with a mean of 0 and variance of ω_k^2 . Goodness of fit plots for the final model, are shown in Figure 2. To evaluate the relevance of the small trends seen in Figure 2, the final model was used to simulate a new dataset. The final model was then fitted to the simulated dataset and the resulting goodness of fit plots (Figure 3) were compared with the plots in Figure 2. The lack of differences between the plots from the real and the simulated data showed that the model adequately described the experimental data.

The skewed distributions of residuals justified a log-transformation of the concentration data. An additive

Figure 2 Observed concentrations *vs* individual and population predictions (log-transformed data).

Figure 3 Observed (simulated) concentrations *vs* individual and population predictions (log-transformed data).

residual error model on the log-transformed data was sufficient to account for the residual variability. The model used was:

$$\log C_{it} = \log \hat{C}_{it} + \epsilon_{it} \quad (4)$$

The residual errors ϵ_{it} were assumed to be independently symmetrically and identically distributed with a mean of 0 and a variance of σ^2 .

The stepwise covariate model building procedure showed that CL, V_1 and V_2 all were related linearly to weight (WT) and parameterized as:

$$\tilde{V}_1 = \theta_{V1} \cdot (1 + (WT - 75) \cdot \theta_{V1|WT}) \quad (5)$$

$$\tilde{V}_2 = \theta_{V2} \cdot (1 + (WT - 75) \cdot \theta_{V2|WT}) \quad (6)$$

where θ_{V1} and θ_{V2} are the typical V_1 and V_2 for a patient weighting 75 kg $\theta_{V1|WT}$ and $\theta_{V2|WT}$ are the linear relationships between body weight and V_1 and V_2 , respectively. Mean V_1 was estimated to increase by 1.3% kg^{-1} and mean V_2 by 1.4% kg^{-1} . No other demographic covariate was found to influence the pharmacokinetics.

For CL the linear relationship with weight was considered to be unphysiological. Clomethiazole is a middle to high extraction ratio drug and therefore its elimination will be mainly influenced by the size of the liver and by liver blood flow. It is not reasonable to believe that liver size and blood flow increases linearly over the entire body weight range (31 kg to 157 kg) of our population. At some point, a further increase in weight will only result from increase in the body fat independent of liver size and liver blood flow. There are also relatively few data points that support the upper range of the weight-clearance relationship. Therefore, it was assumed that clearance increased linearly to a certain weight, and above which it was constant. This relationship would be different in patients concomitantly treated with liver

enzyme inducing drugs. Thus a function Φ was defined as:

$$\Phi = \frac{WT^{50}}{WT^{50} + WT_{50}^{50}} \quad (7)$$

where WT^{50} is weight raised to the power of 50. This makes Φ achieve a shape almost identical to a step-function, but without the numerical problems the latter could cause. The parameterization of the clearance model was then described by the equation:

$$\tilde{CL} = \theta_{CL,ni} \cdot ((1 + \theta_{CL,ni,WT}) \cdot (WT_{50} - 75) \cdot \Phi) \cdot ((1 + \theta_{CL,ni,WT}) \cdot (WT - 75) \cdot (1 - \Phi)) \quad (8)$$

where $\theta_{CL,ni}$ is the typical clearance in a patient not also taking inducing drugs, $\theta_{CL,ni,WT}$ is the linear relationship between CL and body weight and WT_{50} is the estimated weight where the linear increase in clearance becomes constant. For patients on liver enzyme inducing drugs, that is, carbamazepine, phenytoin, rifampicine, a similar model was used:

$$\tilde{CL} = \theta_{CL,i} \cdot ((1 + \theta_{CL,i,WT}) \cdot (WT_{50} - 75) \cdot \Phi) \cdot ((1 + \theta_{CL,i,WT}) \cdot (WT - 75) \cdot (1 - \Phi)) \quad (9)$$

where $\theta_{CL,i}$ is the typical clearance in a patient taking inducing drugs and $\theta_{CL,i,WT}$ is the linear relationship between CL and body weight in those patients.

In the final covariate model, the mean CL was estimated to increase with WT by 0.88% kg^{-1} in patients not taking enzyme inducing drugs, and for patients taking enzyme inducing drugs this relationship was 1.33% kg^{-1} to a body weight of 100 kg, above which clearance was constant.

The typical parameter estimates for V_1 , V_2 and CL are shown in Table 3 and a graph depicting the parameter-covariate relationships for CL is shown in Figure 4.

Concomitant medications were evaluated for their effect on the clearance of clomethiazole, but no drug or drug class fulfilled the specified criteria for being a statistically significant covariate. However, the effect of enzyme inducing drugs, was of borderline statistical significance. When this covariate was included in the model, there was a decrease in OFV of 7.5, which was significant at the $P < 0.01$ level. The typical value of CL increased by 40% (from 53 l h^{-1} to 74 l h^{-1}) in patients treated with an inducing drug.

Pharmacodynamics

As the degree of sedation in the placebo patients seemed to change during the observation period, it was necessary to develop a model for this time dependence. In the final

Table 3 Population pharmacokinetic parameter estimates for the basic model without covariates and from the final clomethiazole model.

Parameter	Estimate (RSE)	Basic model	Estimate (RSE)	Final covariate model
		Estimated interindividual coefficient of variation (%) (RSE) ^h		Estimated interindividual coefficient of variation (%) (RSE) ^h
CL (l h ⁻¹) ^a	53.4 (0.027)	44 (0.17)	52.7 (0.029)	43 (0.19)
V1 (l) ^b	73.6 (0.048)	17 (1.72)	82.5 (0.058)	48 (0.46)
Q (l h ⁻¹)	191 (0.066)	76 (0.17)	167 (0.092)	36 (0.44)
V2 (l) ^b	320 (0.059)	31 (0.62)	335 (0.092)	49 (0.42)
Correlation between the PK parameters	NA	28 (0.22)	NA	22 (0.32)
WT ₅₀ ^c	NA	NA	100 (89.3, 110.7) ⁱ	NA
WT on CL (%) ^d	NA	NA	0.009 (0.006, 0.011) ⁱ	NA
WT on CL (%) ^e	NA	NA	0.013 (0.005, 0.021) ⁱ	NA
WT on V1 (%) ^f	NA	NA	0.013 (0.009, 0.017) ⁱ	NA
WT on V2 (%) ^g	NA	NA	0.014 (0.010, 0.017) ⁱ	NA
Inducer effect on CL ^b	NA	NA	0.399 (0.076, 0.722) ⁱ	NA
Residual error	NA	43 (0.10)	NA	44 (0.12)

^aFor a patient with a weight of 75 kg and not on treatment with an inducer. ^bFor a patient with a weight of 75 kg. ^cWT₅₀ is the point where the linear relationship between CL disappears. ^dCL increases with WT at a rate of 0.9% of the 75 kg value of CL per kg increase in weight in patients not on treatment with an inducer. ^eCL increases with WT at a rate of 1.3% of the 75 kg value of CL per kg increase in weight in patients on treatment with an inducer. ^fV1 increases by 1.3% of the 75 kg value of V1 per kg increase in weight. ^gV2 increases by 1.4% of the 75 kg value of V2 per kg increase in weight. ^hRelative standard error of ω^2 . ⁱ95% confidence intervals.

Figure 4 Individual predictions of the relationship between CL and weight from a model without weight as a covariate together with the predicted lines from the final pharmacokinetic model. The upper thick line is the model prediction for patients treated with liver enzyme inducing drugs and the thin line is a smoothing of the individual predictions. The thin dotted line is a smoothing of the individual predictions for noninduced patients and the dashed line is the model prediction. The circles are data from noninduced patients and x represents data from patients taking enzyme-inducing drugs.

model time dependence was included in the logits as an exponential model and defined as:

$$P_T = \theta_1 - \theta_2 e^{-\theta_3 t} \quad (10)$$

where θ_1 , θ_2 and θ_3 are parameters of the model and t is the time after the start of the first infusion. The only constraint used in placebo model development was that θ_3 could only be positive.

During placebo model development it was noted that the values of η_1 were bi-modally distributed (Figure 5). Further investigation of the individuals who had η_1 values in the lower modal of the distribution revealed that they had primarily sedation scores of 1. In other words, these individuals seemed to be less sensitive to stroke induced sedation. To accommodate this phenomenon, a mixture model in b_2 was used. Here the model is defined so that two or more different states are allowed. The parameters of the different states are estimated together with the proportions of the likelihood that can be ascribed to each state. The inclusion of the mixture in b_2 significantly improved the fit and the classification of individuals into sensitive and nonsensitive to stroke-induced sedation agreed well with Figure 5. The proportion of nonsedation sensitive patients in the placebo data set was estimated to be 0.18.

Figure 5 Distribution of η_1 from a model for the placebo data not including a mixture for b_2 .

Covariate effects were evaluated on the term P_T . Stroke severity was found to be the most important predictor of sedation. The relationship was found to be nonlinear and sedation increased by 0.041 per NIH point for scores below 16 (the median value) and by 0.0095 per NIH point for scores above 16. Age was also found to increase sedation in a nonlinear way. Sedation increased by 0.3% per year below the age of 74 (the median value) and by 1.6% per year above 74. The models were parameterized with one slope for values below the median value of the covariate and another slope for values above the median:

For NIH less than 16:

$$\text{cov}_1(\text{NIH}) = \theta_{\text{cov}_1} \cdot (1 + (\text{NIH} - 16) \cdot \theta_{\text{slp1|NIH}}) \quad (11)$$

For NIH above than 16:

$$\text{cov}_1(\text{NIH}) = \theta_{\text{cov}_1} \cdot (1 + (\text{NIH} - 16) \cdot \theta_{\text{slp2|NIH}}) \quad (12)$$

For AGE less than 74:

$$\text{cov}_2(\text{AGE}) = \theta_{\text{cov}_2} \cdot (1 + (\text{AGE} - 74) \cdot \theta_{\text{slp1|AGE}}) \quad (13)$$

For AGE above than 74:

$$\text{cov}_2(\text{AGE}) = \theta_{\text{cov}_2} \cdot (1 + (\text{AGE} - 74) \cdot \theta_{\text{slp2|AGE}}) \quad (14)$$

From Figure 6 it is clear that patients treated with clomethiazole reach a higher level of sedation than patients on placebo. To accommodate this, a drug effect parameter D was added to the logits. The latter now contain terms for both stroke-induced sedation and clomethiazole-induced sedation, where D is zero for placebo patients. D could either be a single parameter, i.e. a step

effect, or a function of the predicted clomethiazole concentrations from the final PK model. The functions tested in the latter case were the Emax model, the sigmoid Emax model, an exponential model, a power model or an effect-compartment model with and without lag time between the concentrations and the sedation.

Based on the objective function value, the graphics and parameter estimates, it was concluded that a step model best described the effect of clomethiazole on sedation. No improvement to this model could be gained by taking the clomethiazole concentrations into account. For example, in an Emax model, EC_{50} was found to be as low as $0.25 \mu\text{mol l}^{-1}$ with no improvement in the objective function value compared with the step model.

Covariate effects on the term D were then evaluated and age and weight were found to influence clomethiazole-induced sedation. The latter increased linearly with weight. The covariate was modelled as a slope intercept model, centred around the median values:

$$\text{cov}_3(\text{WT}) = \theta_{\text{cov}_3} \cdot (1 + (\text{WT} - 75) \cdot \theta_{\text{cov}_3|\text{WT}}) \quad (15)$$

Clomethiazole-induced sedation increased (on the logit scale) by 0.7% per kg increase in weight.

The final model for stroke and clomethiazole-induced sedation was a proportional odds model with the logits given by:

$$\begin{aligned} l_{S \geq 2} &= b_2 + P_T + D + \eta_1 \\ l_{S \geq 3} &= b_2 + b_3 + P_T + D + \eta_1 \\ l_{S \geq 4} &= b_2 + b_3 + b_4 + P_T + D + \eta_1 \\ l_{S \geq 5} &= b_2 + b_3 + b_4 + b_5 + P_T + D + \eta_1 \\ l_{S=6} &= b_2 + b_3 + b_4 + b_5 + b_6 + P_T + D + \eta_1 \end{aligned} \quad (16)$$

where D is zero for patients on placebo and $D = \theta_D \cdot (1 + \text{cov}_3)$ for clomethiazole-treated patients where cov_3 included covariate effects of weight, cov_1 included covariate effects of NIH and cov_2 included covariate effects of age.

The final parameter estimates (relative standard error) are shown in Table 4. The observed and predicted sedation score frequencies from the final pharmacodynamic model for both placebo and clomethiazole treated patients are displayed in Figure 6.

Discussion

This analysis characterized the pharmacokinetics of clomethiazole, its interindividual variabilities and covariate relationships and the natural course of sedation after stroke. It also explored the relationship between clomethiazole treatment and sedation in acute stroke patients. The findings were in accordance with pharmacokinetic data in healthy subjects and in stroke patients [14, 15,

Figure 6 Goodness of fit plots for the final pharmacodynamic model showing the sedation scores over 10 time intervals with an equal number of observations in each category. The upper panel shows the observed data for the clomethiazole and placebo treatment groups, respectively, and the bottom panel shows the predicted sedation scores from the final pharmacodynamic model. The sedation scale (see Table 1): 1, □; 2, ▨; 3, ▩; 4, ■; 5, ▤; 6, ■.

26], although the intraindividual variabilities were somewhat higher than anticipated. From three blood samples per patient, it was possible to use a two-compartment pharmacokinetic model and also to estimate interindividual variabilities in all pharmacokinetic parameters compared with the previous analysis [15], where data only

supported a one-compartment model without any inter-individual variability. The concentration–time profile for the typical patient was similar to the predicted profile and the target steady state concentration of clomethiazole, of $10 \mu\text{mol l}^{-1}$ and above, was reached.

Most of the evaluated covariates did not have any

Table 4 Parameter estimates from the final pharmacodynamic model.

Parameter	Estimate (RSE)
b_2 sedation sensitive	-4.71 (0.06) ^a
b_2 nonsedation sensitive	-8.81 (0.06) ^a
b_3	-3.16 (0.02) ^a
b_4	-1.57 (0.04) ^a
b_5	-1.88 (0.05) ^a
b_6	-2.09 (0.13) ^a
Proportion nonsedation sensitive	0.18 (0.22) ^a
θ_1	5.07 (0.07) ^a
θ_2	1.75 (0.07) ^a
θ_3	0.27 (0.14) ^a
D (effect of clomethiazole)	2.40 (0.06) ^a
$\theta_{slp1 NIH}$	0.041 (0.031, 0.051) ^b
$\theta_{slp2 NIH}$	0.0095 (-0.001, 0.020) ^b
$\theta_{slp1 AGE}$	0.0031 (-0.001, 0.007) ^b
$\theta_{slp2 AGE}$	0.016 (0.001, 0.031) ^b
$\theta_{cov3 WT}$	0.007 (0.004, 0.010) ^b
ω	3.19 (0.11) ^c

^aRelative standard error. ^b95% confidence intervals. ^cRelative standard error of ω^2 .

influence on the pharmacokinetics of clomethiazole, and this provided valuable information from a drug development perspective. For example, the absence of effect of creatinine clearance on the clearance of clomethiazole.

The covariates identified as important in the pharmacokinetics of clomethiazole, namely weight and concomitant medication with liver enzyme inducing drugs, were as expected. In a recent study the clearance of clomethiazole was increased by 30% after treatment with carbamazepine [26]. The present finding of an increase of 40% in patients taking enzyme inducing drugs is in the same range.

We used simulations to evaluate the relevance of the small trends seen in Figure 2. The final model was used to simulate a new dataset, to which the model was fitted. This procedure is similar to a posterior predictive check, and we concluded that it showed that the model adequately described the data. The remaining trend in the individual predictions is likely to be caused by shrinkage towards the mean, which in this case is likely to be pronounced with high residual variability and with few observations per individual.

Sedation was increased by clomethiazole treatment but it was not possible to define a plasma concentration-effect relationship. This was partly due to the study design, since the dosing regimen was designed to achieve

the same target concentration in all patients. A significant proportion of the patients had dose-interruptions according to the protocol when reaching a sedation score of 4 or greater which contributed further to the problems of finding a concentration-sedation relationship. The finding of two apparently different groups of patients, some sedation sensitive and some sedation insensitive to clomethiazole treatment has been observed previously after clomethiazole treatment [14]. However we show that this can also occur in placebo treated patients. Individuals developing oedema after a stroke are more likely to be sedated [5]. It is possible that the interindividual differences in sedation could be due partly to the presence of oedema. However reliable measures of oedema at admission to the study were not available to confirm this hypothesis.

Stroke severity and clomethiazole treatment were the most important covariates for sedation. Stroke severity at admission has been shown to correlate significantly with the acute lesion volume as assessed by diffusion-weighted magnetic resonance imaging [27]. This measure is likely to predict the potential for development of subsequent brain oedema and subsequent sedation. A nonlinear relation with stroke severity and sedation was noted, the latter being less apparent at severities exceeding a NIH score of 16. It is possible that the strategy of dose-interruption and dose-reduction to lessen sedation decreased the sensitivity of the model to detect sedation in patients with more severe stroke and who are thus most prone to sedation [28]. Age also influenced the probability of sedation occurring after stroke, with patients older than 74 years being at most risk.

Drug-induced sedation was not affected by stroke severity but increased with increasing body weight. This was surprising since a concentration-sedation relationship was not found and clomethiazole was administered according to body weight. This might indicate that even though the dosing algorithm gave the desired plasma concentrations, it may still have been suboptimal regarding sedation.

The model for the sedative effect of clomethiazole included a component for the natural occurrence of sedation after stroke. This part of the model is independent of drug treatment and can be used in other studies of neurotrauma patients where sedation is an important factor, especially as sedative drugs are commonly used in the treatment of this category of patients [29].

In conclusion, the pharmacokinetics of clomethiazole were characterized in acute stroke patients, and several possible covariates of interest in drug development were excluded. The time course of sedation after stroke was quantitatively described during the first 24 h following an acute stroke in the presence or absence of clomethiazole treatment. It was necessary to incorporate a model

for the natural course of sedation following stroke in the analysis, and this part of the model might be used in other studies where sedation is an important variable.

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