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Predictive performance of the Domino, Hijazi, and Clements models during low-dose target-controlled ketamine infusions in healthy volunteers

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Background. Healthy volunteers received low-dose target-controlled infusions (TCI) of ketamine controlled by the Domino model while cognitive function tests and functional neuroimaging were performed. The aim of the current study was to assess the predictive performance of the Domino model during these studies, and compare it with that of three other ketamine models.

Methods. Fifty-eight volunteers received ketamine administered by a TCI device on one or more occasions at target concentrations of either 50, 100, or 200 ng ml^{-1}. At each target concentration, two or three venous blood samples were withdrawn during infusion, with a further sample after the infusion ended. Ketamine assays were performed by gas chromatography. The plasma concentration time courses predicted by the Hijazi, Clements 125, and Clements 250 models were calculated retrospectively, and the predictive performance of each of the models was assessed using Varvel methodology.

Results. For the Domino model, bias, inaccuracy, wobble, and divergence were −2.7%, 33.9%, 24.2%, and 0.1463 % h^{-1}, respectively. There was a systematic increase in performance error over time. The Clements 250 model performed best by all criteria, whereas the Hijazi model performed least well by all criteria except for bias.

Conclusions. Performance of the Domino model during control of low-dose ketamine infusions was sub-optimal. The Clements 250 model may be a better model for controlling low-dose TCI ketamine administration

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In recent years, there has been renewed interest in ketamine, because of growing evidence that surgical patients may benefit from low-dose intraoperative infusions. Potential benefits include neuroprotection,[1] pre-emptive analgesia, and attenuation of postoperative hyperalgesia.[2] The influence of low-dose ketamine on postoperative analgesia was the subject of a recent Cochrane review.[3] Target-controlled infusion (TCI) technology has been employed for ketamine administration in several settings, including critical care,[4 5] the operating theatre,[6–8] and neuroscience studies.[9 10]

In our institution, ketamine infusions are being used to investigate the glutaminergic hypofunction theory of schizophrenia. Four studies have been performed, seeking to compare ketamine-induced cognitive changes in healthy volunteers with those observed in schizophrenic patients and also to examine the correlation between performance in different cognitive tasks/tests with the patterns of neural activation detected by functional magnetic resonance imaging (fMRI).[11–17]

The cognitive function tests used in these psychiatric studies vary in duration between tests, and also between

subjects. During all the tests, and particularly during tests examining memory and learning processes, stable blood and effect-site drug concentrations are desirable for pharmacodynamic analyses. Access to the subject is not possible during tests and, with a large number of tests being performed during each scanning session, it was impractical to obtain blood samples before and after each test. TCI technology provides a convenient and user-friendly means of administering stable blood concentrations.[18–20] Volunteers in our studies thus received TCI ketamine, implemented using the Domino model,[21] chosen because it is commonly used for low-dose TCI administration of ketamine in the experimental setting.[8–10 22]

Our group has funding to perform two further series of investigations of the influence of ketamine on cognitive function. We plan to continue using TCIs, but first wanted to determine if the Domino model is fit for this purpose. Thus, the aim of the current study was to assess the predictive performance of the Domino model during the four cognitive studies we have conducted so far. We were particularly interested in determining how well steady-state concentrations were maintained at constant target concentrations, and whether performance was similar across the different studies. A secondary goal was to compare the predictions of the Domino model with those of other published models, in order to identify or exclude possible candidate models for future studies. We chose for comparison three bicompartmental models (see Methods for rationale): a model derived by Clements using data from five healthy volunteers who received a single 125 μg kg^{-1} i.v. bolus (hereafter referred to as the 'Clements 125' model),[23] a model derived by Clements using data from the same five volunteers after receiving a 250 μg kg^{-1} i.v. bolus (hereafter referred to as the 'Clements 250' model),[23] and the Hijazi model (derived from data from a group of 12 critically ill patients who received a 2 mg kg^{-1} bolus followed by a 2 mg kg^{-1} h^{-1} infusion).[5] The model parameters for these models are summarized in Table 1.

Methods

Fifty-eight paid volunteers participating in four different studies underwent cognitive function tests and functional imaging while receiving either saline or racemic ketamine. Although each study involved different subjects, it was considered appropriate to include data from all the studies and subjects to increase the sample size and attenuate the impact of stochastic and inter-individual pharmacokinetic variations on the overall conclusions. To be included, subjects had to be ASA status I or II and right-handed. Exclusion criteria were history of psychiatric or physical illness, head injury, obesity, alcohol or drug dependence, and smoking. Subjects with a family history of psychiatric illness or alcohol abuse were also excluded. The studies were approved by the Cambridge Local Ethics Committee and were performed in accordance with the Declaration of Helsinki. Written informed consent was given by all subjects.

Table 1 Model parameters for the Domino, Clements 125, Clements 250, and Hijazi models. *V*1, central compartment volume; k_{10}, metabolic clearance rate constant; k_{12}, k_{21}, rate constants for rapid distribution clearance (from compartment 1 to 2 and *vice versa*); k_{13}, k_{31}, rate constants for slow distribution clearance (from compartment 1 to 3 and *vice versa*)

	Domino	Clements 125	Clements 250	Hijazi
*V*1 (ml kg^{-1})	63.0	1245.5	1752.2	1080.0
k_{10} (min^{-1})	0.4381	0.0131	0.0109	0.0333
k_{12} (min^{-1})	0.5921	0.0219	0.0186	0.0088
k_{13} (min^{-1})	0.5900			
k_{21} (min^{-1})	0.2470	0.0132	0.0137	0.0030
k_{31} (min^{-1})	0.0146			

Ketamine administration and blood samples

Two 20 G i.v. cannulae were inserted on opposite hands or forearms: one for ketamine/saline administration and the other for blood sampling. Ketamine (1 mg ml^{-1}) and saline were delivered by a TCI device. The TCI device was a Graseby 3500 infusion pump that had been reprogrammed with the Domino model and sold to us by Anaesthesia Technology Ltd (Wetherby, UK). Throughout each of the studies, an experienced anaesthetist (consultant or senior trainee) was present, controlled the TCI device, and managed blood sampling, separation, and storage. The anaesthetist also prepared the study drug—either saline or ketamine (10 mg ml^{-1}, Pfizer, Surrey, UK) diluted to 1 mg ml^{-1} in saline—and was the only person not blinded to drug and target concentration allocations. The planned durations of infusion, target concentrations, and venous blood sample timings are summarized in Table 2.

As can be seen, depending on the study, volunteers were investigated on either two or three different occasions, during which they received either saline or ketamine at the different target concentrations shown in Table 2. The order of the visits (placebo *vs* drug) was randomized, and consecutive visits were at least a week apart. When saline was administered, the anaesthetist maintained blinding by withdrawing blood samples and using the TCI device in the same manner when saline was administered as when ketamine was administered (same size, labelled syringe in the TCI device, same target concentrations entered, etc).

For studies 1–3, only one target ketamine concentration was used at each visit. The second sample at each target concentration was obtained just before the infusion was stopped, and the third sample was obtained after the infusion was switched off. For the fourth study, the target concentration was initially 100 ng ml^{-1} and then finally 200 ng ml^{-1}; and all volunteers received an i.v. infusion of 500 ml of compound sodium lactate solution during the first hour of the study. For this study, the first three samples were obtained with the infusion pump running at a target ketamine concentration of 100 ng ml^{-1}. Immediately after the third sample was obtained, the target

Table 2 Summary of target concentrations, planned infusion duration, and timing of blood samples (for studies 1–3 the order of visits was randomized)

Study	Subjects (*n*)	Visits	Target concentration	Infusion duration (min)	Timing of blood samples (min after infusion onset)
1	14	3	Placebo	120	15, 120, 210
			50 ng ml^{-1}	120	15, 120, 210
			100 ng ml^{-1}	120	15, 120, 210
2	12	3	Placebo	70	15, 70, 130
			50 ng ml^{-1}	70	15, 70, 130
			100 ng ml^{-1}	70	15, 70, 130
3	15	2	Placebo	140	30, 140
			100 ng ml^{-1}	140	30, 140
4	17	2	Placebo	210	20, 60, 105, 130, 210, 225
			100 ng ml^{-1} for 105 min, then 0 for 5 min, finally 200 ng ml^{-1} for 100 min	210	20, 60, 105, 130, 210, 225

ketamine concentration was temporarily set to zero, causing the drug infusion to stop, so that the drug administration set could be disconnected while the volunteer was allowed a 5 min toilet break. During this time, the TCI device continued to estimate the decreasing blood concentrations. At the end of the break, the TCI administration set was reconnected, and the target concentration was set at 200 ng ml^{-1}. The fourth sample was obtained 20 min later, the fifth sample was obtained just before the infusion was finally stopped, and the sixth sample was obtained 'off infusion' a further 15 min later.

Ketamine assays

All blood samples were stored on ice until the end of the study session, when placebo samples were discarded. Ketamine-containing samples were cold-centrifuged, and plasma was removed and frozen (at -80°C). Plasma samples were later thawed in batches, and assayed for ketamine concentration by gas chromatography–mass spectrometry using published methods.[24] All samples were analysed within 6 months. The limit of detection was 1 ng ml^{-1} and the assay was linear across the range 10–400 ng ml^{-1}. Intra-day and inter-day coefficients of variability were $<15\%$.

Analysis of predictive performance

Standard Varvel criteria[25] were used to assess the predictive performance of the Domino model. This two-stage process involves first calculating the performance error (PE) for each blood sample. For the *j*th ketamine measurement in the *i*th volunteer, where $C_{\text{meas } ij}$ and $C_{\text{pred } ij}$ are the measured and predicted plasma ketamine concentrations, respectively, PE is calculated as follows:

$$\text{PE}_{ij} = \frac{(C_{\text{meas } ij} - C_{\text{pred } ij})}{C_{\text{pred } ij}} \times 100$$

In the second stage, the PEs are used to calculate for each volunteer, across sessions where appropriate, the median PE (MDPE), median absolute PE (MDAPE), wobble, and divergence. For the *i*th volunteer for whom N_i ketamine samples were assayed MDPE, MDAPE, wobble, and divergence are calculated as follows:

$\text{MDPE}_i = \text{median}\{\text{PE}_{ij}, j = 1, \ldots, N_i\}$

$\text{MDAPE}_i = \text{median}\{|\text{PE}_{ij}|, j = 1, \ldots, N_i\}$

$\text{Wobble}_i = \text{median}\{|\text{PE}_{ij} - \text{MDPE}_i|, j = 1, \ldots, N_i\}$

Divergence_i = slope of the regression curve of *absolute PE* over time.

MDPE is a signed value, which provides a measure of bias. It indicates the direction of the bias, whereas the MDAPE disregards the direction of the error and instead reflects the precision of the system. The MDAPE is sometimes referred to as the 'inaccuracy'—a larger value indicates greater inaccuracy. Wobble is a measure of intra-subject variation in PE. Divergence is an indication of time-related fluctuations in precision.

Divergence shows whether the spread of the errors increases or decreases with time, but may not detect a systematic trend in blood concentration over time, particularly if the number of samples is small or the duration of the study is short. During the cognitive tests performed as part of the four studies, stability of plasma concentrations while target concentrations remained unchanged was desirable. To assess stability further, the slope of the regression curve of *PE* over time was also calculated. Samples withdrawn after the infusions stopped were not included in the divergence/slope calculations, because PEs during infusion can often be quite different to PEs after infusion,[26–28] and in the current study performance during infusion was of particular interest.

For each study, these parameters were summarized by calculating the means across subjects. The mean values across all subjects involved in all the studies were also calculated.

Choice of models for comparison

A preliminary Varvel analysis of the Domino model performance during study 4 showed that the model tended to significantly overestimate the early blood samples (15–20 min after infusion onset) whereas it tended to

underestimate samples obtained after 2 h or more. We used TIVATrainer software (F. Engbers, Leiden, The Netherlands) to simulate the infusion profile for study 4, and by a process of trial and error found that we were able to produce a predicted concentration profile similar to the mean measured concentrations by increasing by several multiples the central compartment volume ($V1$), and by decreasing the metabolic clearance rate constant (k_{10}) by ~10%.

We thus sought to identify models that would cause a TCI system to administer more drug soon after starting an infusion, and less later on, and models that have larger values for $V1$ and smaller values for k_{10} than the Domino model. A literature search identified several possible published comparator models for ketamine.[5 6 23 29–33] For the Domino model and each comparator model, a simple simulation was performed [by Dr J. Glen, using PK-SIM (Bayer Technology Services GmbH, Germany)] to determine the infusion rates and cumulative doses the model would have caused to be administered, had it been used to control the infusion for the exact duration and at the same target concentration as shown in Table 2 for a 70 kg volunteer in study 4. The Wieber,[29] Kloos,[34] and M. White[6] models were excluded from further analysis on the basis that they would have administered a similar dose by 15 min when compared with the Domino model (10.5, 4.1, 5.5, and 9.8 *vs* 7.9 mg, respectively). Although the Idvall,[32] Geisslinger,[33] and P. White[31] models all would have administered more drug by 15 min, they were excluded—the Idvall[32] and P. White[31] models because they were derived from old studies involving large boluses and infusion rates and the Geisslinger models because they were derived from a study that involved only a single bolus and were all enantiomer-specific.[33] The M. White model is also enantiomer-specific.[6]

The remaining models were the Clements[23] and Hijazi[5] models. These models are bicompartmental and may have been considered unsuitable—the Clements models because they were derived from an old study involving a small number of volunteers receiving only bolus doses and the Hijazi because it was derived from a study of critically ill patients receiving larger doses than our volunteers. Nonetheless, as the Clements and Hijazi models have larger central compartment volumes and smaller metabolic clearance rates than the Domino model, it was likely that they would outperform the Domino model and so they were chosen for further comparison.

Comparisons between models

An assessment of the predictive performance of the Clements 125 and Clements 250 models,[23] and the Hijazi model[5] in our volunteers was performed using the plasma concentrations retrospectively estimated for each model. For each volunteer Stanpump software [available free of charge from Dr S. Shafer MD on http://anesthesia.stanford.edu/pkpd/ (accessed November 27, 2006)] was used to estimate the ketamine infusion rate profile administered by the pump to achieve the recorded target concentration profile. This was necessary for each volunteer because of variability in the duration of infusion and timing of blood sample withdrawal. During the course of the fourth study, the total cumulative ketamine dose, immediately before each blood sample was obtained, was recorded manually. The mean absolute difference between the recorded total dose and that estimated by Stanpump was 0.48 mg, whereas the mean proportional error in predicted dose was 0.5%. The range of errors was −3.3 to 5.2 mg (absolute percentage error <7.5% in all cases). On this basis, we concluded that the Stanpump-generated infusion profiles were a reasonably accurate prediction of the actual dose received during study 4, and thus we assumed that the Stanpump predictions were likely to have similar accuracy for the other three studies.

Macro routines (written by T.D.S.) were then used to read the output files generated by Stanpump (containing the individualized infusion rate profile for each volunteer) and import these data into Excel spreadsheets programmed to estimate blood concentrations predicted by a pharmacokinetic data set based on a specified infusion profile. [Similar spreadsheets can be freely downloaded from http://www.demed.be/downloads.htm (accessed November 27, 2006).] The predicted concentrations were compared with measured values and subjected to the above-mentioned two-stage Varvel analysis, enabling a comparison of the predictive accuracy of the three different models with the Domino model.

Results

Fifty-eight paid volunteers were enrolled in the studies. A total of 254 samples were obtained from 53 volunteers (30 males and 23 females). In five volunteers, no samples were obtained and in a further seven at least one sampling attempt failed because of inability to withdraw blood through the second i.v. cannula (the total number of missing samples was 34). Of the 53 volunteers from whom one or more samples were obtained, the mean (range) age was 32 (18–64) yr, mean (range) weight 72 (55–102) kg, and mean (range) height 173 (145–190) cm.

Two samples were excluded from all further analyses because they were obtained from a volunteer before it was realized that the ketamine administration cannula was extravascular. The remaining 252 measured ketamine concentrations are shown in Figure 1. Variability in the timing of the blood samples occurred because volunteers were allowed to complete some of the cognitive tasks at their own pace.

Varvel criteria for the Domino model were approximately normally distributed. Mean values for the four different studies are shown in Table 3. PEs tended to increase over time. For early samples, they were typically negative (measured concentration < predicted), whereas

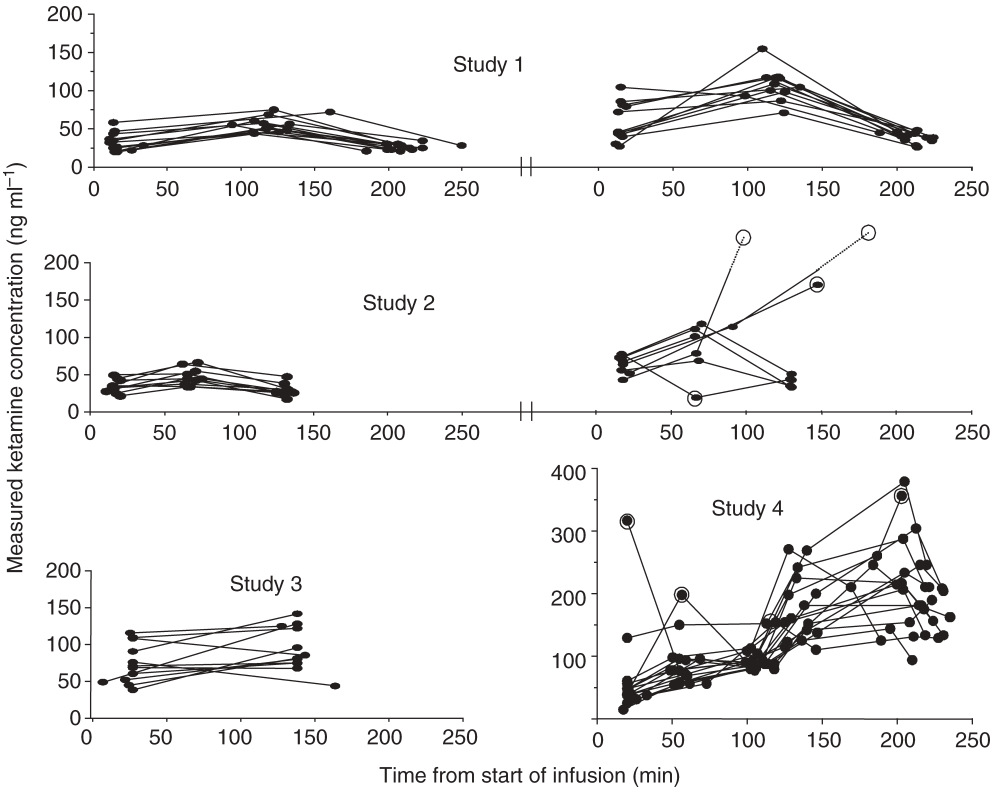

Fig 1 Measured ketamine concentrations (ng ml^{-1}). Each filled circle represents one data point. Lines linking data points indicate which samples came from the same subject, and do not indicate estimated or extrapolated concentrations between samples.

for samples obtained >2 h after infusion onset, particularly samples obtained after the end of the infusion, PEs were typically positive (measured concentration > predicted). This systematic trend was generally laterally symmetrical over the time course of the studies and is thus not reflected in the bias (MDPE), which had an overall mean value close to zero (−4.6%). The systematic trend is better shown by the high overall values for inaccuracy/MDAPE (34.7%), wobble (23.5%), and divergence (0.3855% h^{-1}).

Fourteen samples were excluded from the simulation exercise and model comparisons. Six samples from study 3 were excluded because the time at which the sample was obtained was not recorded, making it impossible to calculate predicted concentrations for other models. A further eight samples were excluded because the measured ketamine concentration was at least two standard deviations above or below the mean for that sampling point, and appeared to be anomalous for one of the following reasons: for samples obtained during infusion, the measured concentration was much higher than a subsequent sample or much lower than a previous sample; for samples obtained 'off infusion', the measured concentration was much higher than the previous sample obtained just before the end of the infusion. For each of these samples, the assay was repeated and, in each case, the repeat assay produced an almost identical result to the first. The most likely explanation is that the anomalous results were caused by sampling errors (e.g. blood withdrawn into contaminated syringes). These eight anomalous samples are indicated in Figure 1 by open circles. Exclusion of these 14 samples from the Varvel analysis for the Domino model results in a modest improvement in all performance parameters except wobble (the 'Overall' column in Table 3 shows the results with these samples included, whereas the 'Domino' column in Table 4 shows the results with these samples excluded).

The Varvel criteria calculated from the 238 remaining measured concentrations, and predicted concentrations calculated by simulation for the Hijazi and Clements models, are summarized in Table 4. Mean values for slope of PEs over time are also shown in Table 4. The Clements 250

Table 3 Summary of the Varvel predictive performance parameters of the Domino model. Numbers in the 'volunteers' row indicate the number of volunteers from whom at least one blood sample was obtained (total samples included in analysis 252). MDPE, median performance error; MDAPE, median absolute performance error; Div APE, divergence in absolute performance error; slope of PEs, slope of performance errors

	Study 1	Study 2	Study 3	Study 4	Overall
Samples analysed	79	53	24	96	252
Volunteers	14	11	12	16	53
MDPE (%)	5.0	1.2	−16.5	−8.3	−4.6
MDAPE (%)	37.3	43.2	29.0	30.8	34.7
Wobble (%)	33.7	35.8	14.6	21.3	23.5
Div APE (% h^{-1})	0.0920	1.4791	−0.0790	0.0647	0.3855
Slope of PEs (% h^{-1})	0.5031	2.1068	0.1883	0.4837	0.8316

Table 4 Comparison of overall Varvel parameters for the Domino, Clements 125, Clements 250, and Hijazi models (total samples included in analysis: 238). MDPE, median performance error; MDAPE, median absolute performance error; slope of PEs, slope of performance errors

	Domino	Clements 125	Clements 250	Hijazi
MDPE (%)	−2.7	−20.4	−1.8	12.9
MDAPE (%)	33.9	26.0	23.7	38.6
Wobble (%)	24.2	22.4	15.7	33.9
Divergence (% h^{-1})	0.1463	−0.0539	−0.1013	1.4577
Slope of PEs (% h^{-1})	0.6113	0.0321	−0.0555	1.7753

model performed best for all four Varvel criteria (i.e. small values for bias, inaccuracy, and wobble; and small, negative values for divergence and slope of PEs). ANOVA reveals significant differences among models for all variables ($P \leq 0.0001$ for each variable). *Post hoc* testing (Dunn) reveals that values for MDAPE, wobble, and slope of PEs are significantly lower for the Clements 250 model than for the Domino model ($P < 0.002$, $P < 0.0001$, and $P < 0.0001$, respectively).

Figure 2 shows the mean (standard deviation) of the measured concentrations at the different sampling points, depicted at the average time interval (after start of infusion) for each sampling point. To give an overall visual impression of prediction accuracy, Figure 2 has superimposed on it the predicted blood ketamine concentration profiles for each of the models and studies, assuming that the duration of infusion was the average duration for each study. In this figure, it can be seen that the concentration profiles predicted by the Clements models match the measured concentrations more closely than the other models. The Clements 250 model is the only model for which the predicted concentrations all fall within 2 standard deviations of the measured concentration. Further detailed analysis of these data is not valid because the predicted concentration for individual samples of individual volunteers is very sensitive to the timing of the sample, particularly when the gradient in predicted concentration over time is steep (as occurs with samples obtained off infusion).

Discussion

Authorities such as Swinhoe and colleagues[28] and Schuttler and colleagues[30] have stated that predictive performance is acceptable if the MDPE is <10–20% and MDAPE is <20–40%. By these criteria, the predictive performance of the Domino model in our studies was acceptable. Indeed, by these criteria, the performance of the Domino model in our study compared favourably with the performance of other commonly used models for other drugs. For example, when Barvais and colleagues[35] studied the performance of the Gepts model[36] for sufentanil, the MDPE was −22.9% and the MDAPE 29.0%, and when Swinhoe and colleagues[28] studied the performance of the Marsh model for propofol, the MDPE was 16.2% and the MDAPE 24.1%.[37]

There are two main problems with reliance on these two criteria to assess performance. The first is that these criteria may not be sensitive to systematic trends in PEs, and the second is that if PEs do change systematically over time, then the final values for bias (MDPE) and inaccuracy (MDAPE) will depend on the duration of infusion, and

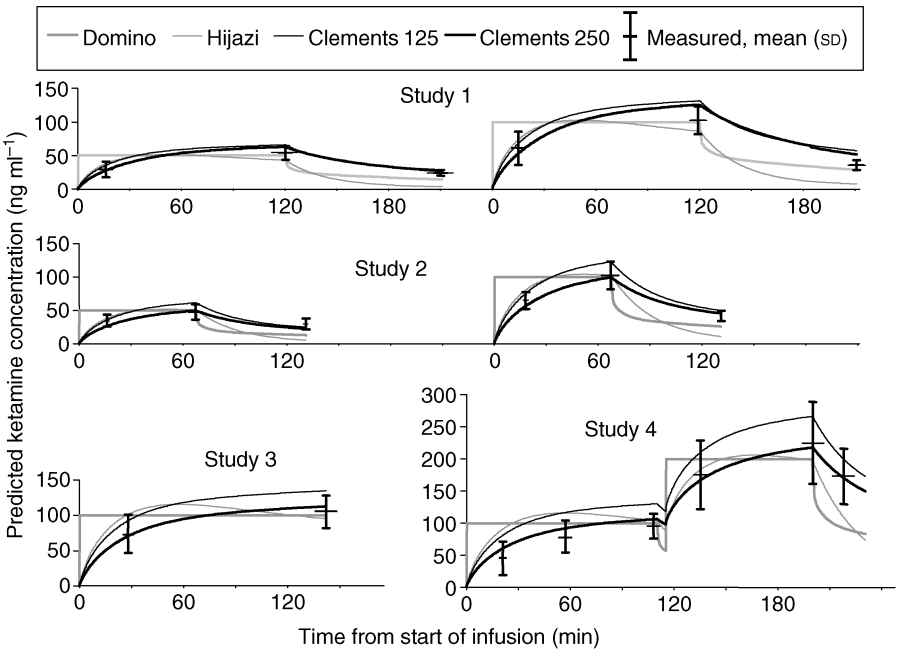

Fig 2 Measured and predicted ketamine concentrations over time. Vertical bars represent the mean (SD) measured ketamine concentrations, but depicted at the average time (from the start of the infusions) at which the samples were obtained. Horizontal bars in the middle of the vertical bars represent the SD of the time interval at which the samples were obtained.

may be difficult to interpret. If the PEs cross zero approximately half-way through the infusion, bias will be close to zero. Otherwise bias may be positive or negative depending on when during the study the errors crossed zero. Similar problems apply to MDAPE, which only takes into account the absolute value of the PE. When PEs change systematically over time, magnitude of MDAPE will again depend on when, and if, the PEs cross zero, being larger if the zero crossing point is not half-way through the study. For our data, omission from the analysis of the 'off infusion' blood sample at each concentration causes the MDPE and MDAPE for the Domino model to change from −4.6% and 34.7% to −18.7% and 28.5%, respectively.

The Varvel parameter divergence can only show if the absolute value of the PEs is increasing or decreasing over time. Where there is a systematic change in PE, the divergence statistic is also dependent on the duration of infusion/sampling relative to when the PEs cross zero. If there are few samples and the absolute PEs are laterally symmetrical about the zero crossing point then divergence will be close to zero. Figure 3 shows the trend in the mean PE for each sampling point for the different studies and for different models. For each study, at each target concentration, the mean PE for the Domino model (heavy grey lines) is negative at the first sample, close to zero for the second, and positive for any later samples. Off infusion PEs are large positive values, and the positive values for divergence for the Domino model mostly result from the latter values. In contrast, the PEs for the Clements 250 model (heavy black lines) remain remarkably constant over time.

During our cognitive studies,[11–16] stable blood concentrations were desirable, because in cognitive function analyses the confounds arising from instability of the measured concentrations are more serious than the confounds arising from bias. The wobble statistic measures the intra-individual variability in PEs over time (see formula above), and in the context of our studies is probably the most useful Varvel statistic for comparing among different models the changes in PE over time. As stable plasma concentrations are crucial, we further assessed the stability of prediction error over time by calculating the average slope of the regression curve for PE *vs* time for each subject. For the latter statistic, and for wobble, the Domino model performed poorly when compared with the Clements 250 predictions.

Any pharmacokinetic model is likely to perform best if it is used in a similar population group to that in which it was derived. From this perspective, it is unsurprising that the Clements 250 model performed best by all the criteria used. However, given that it was derived from a study involving single boluses administered to only five subjects,[23] the accuracy of the predictions it generates is remarkable. There were large differences in predictive performance between the Domino and Clements 250 models 15–20 min after the start of an infusion and 15–20 min after the end of an infusion (Fig. 1). Soon after the start of an infusion, predictive performance depends largely upon appropriate values for $V1$ and rapid re-distribution, whereas later it also depends on appropriate values for metabolic clearance and slow re-distribution clearance. After an infusion stops, the concentrations predicted by a model depend on several factors that include the parameters of the model, the duration of infusion (which determines the residual concentration gradients between compartments), and the target concentration profile during the infusion. As can be seen from Table 1, there are many differences between the two models, the most significant being that the Domino model has three compartments, whereas the Clements 250 model has two compartments, of which $V1$ is several orders of magnitude greater in size than $V1$ (and of $V1 + V2$) of the Domino model. To determine the contributions of the different parameters to the differences in

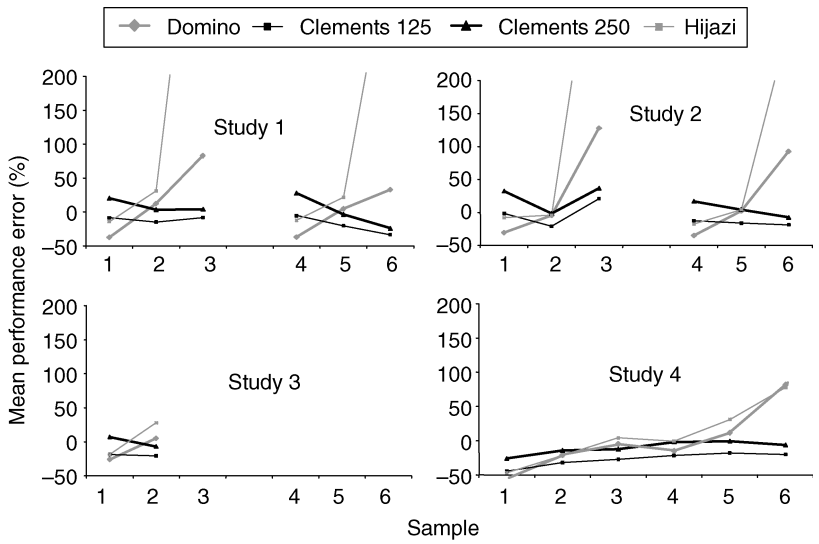

Fig 3 Trends in mean performance errors for each of the models during the different studies.

performance between the models, extra blood samples at different times are required.

Unfortunately, there were practical considerations that limited the number of blood samples that were possible, and restricted the timing of blood samples to times that are not optimal for extended pharmacokinetic analysis. The fMRI scans were performed in the Woolfson Brain Imaging Centre, a busy research facility serving multiple research communities. Time in the scanner is very limited and expensive, and access to subjects is limited to the intervals between scans. To save time, the T1-weighted anatomical scans and 'shimming' procedures were performed immediately after the ketamine infusions were started. As these processes take approximately 15 min, it was not possible to obtain samples until after this. Thereafter, the timing of samples was determined by the durations of the cognitive tests and functional scans, and was the result of a pragmatic compromise between ethical considerations (limiting the total volume of blood sampled), the ideal timings for pharmacokinetic analysis, and the requirements for measured ketamine levels to enable pharmacodynamic analysis.

Our study suffers from a few other weaknesses. It should be emphasized that in the current studies, the Domino model was used to control the infusions and the Clements predictions were calculated retrospectively from *estimates* of the infusion rates and doses actually used. This limits the confidence with which we can draw conclusions about the likely predictive performance of the Clements model were it to be used to control a TCI. Given the close concordance between estimated and recorded dosing histories for study 4, it is unlikely that this potential source of error significantly altered our results. Although our results indicate that the Clements 250 model is likely to have been a better model for controlling low-dose ketamine infusions in our subjects, it is important to remember that this can only be definitively demonstrated by a prospective study of the predictive performance of the Clements 250 model during low-dose infusions in similar subjects.

Another weakness is the paucity of samples used to calculate divergence and the slope of the PEs. As for all parameters, the likelihood that stochastic errors will have an influence on the results is inversely related to the number of samples. For studies 1 and 2, volunteers received ketamine twice, and two blood samples were obtained during the infusion on each occasion. The slope for each of these volunteers was calculated as the average of the slopes obtained from each visit. Thus, for these studies the slope value for each volunteer was calculated from four samples, whereas in study 4 slopes were calculated from five samples, and for study 3 slopes were only calculated from two samples. These differences in sample sizes combined with the large degree of inder-individual pharmacokinetic variability probably explain the differences in Varvel parameters between studies. Our main concern was with the stability of concentrations and PEs over time, and overall it is unlikely that the paucity of samples per individual has caused a significant error in the slope calculations, since although there is variability between studies, there was a consistent trend with all four studies showing an increase in PE over time. Moreover, when the mean PE is calculated for each sample, and plotted over time, a similar pattern is detectable on visual inspection of the data (Fig. 3).

Finally, it is tempting to ascribe the poor performance of the Hijazi model to the fact that it was derived from a study involving critically ill patients,[5] in whom significant alterations in drug distribution and metabolism of other drugs such as midazolam have been found to result in greater than expected drug concentrations.[38 39] In our healthy volunteers, the Hijazi model significantly underpredicted the measured concentrations. It is possible that the different (greater) doses used in the Hijazi study are a more significant factor. There is a paucity of information on the effects of critical illness on the pharmacokinetics of ketamine, but its sympathomimetic effects are likely to cause dose-related changes (increases) in cardiac output and hepatic blood flow, so that at high doses metabolism is increased, resulting in lower blood levels.

In conclusion, we have prospectively tested the predictive performance of the Domino model for administration of low-dose TCIs of ketamine in healthy volunteers, using the Varvel criteria. Although we found that the bias and inaccuracy fell within accepted limits, performance was suboptimal because of a systematic increase in PE over time, revealed by moderately high wobble and a positive mean slope of the regression curves for the trend in PEs over time. Retrospective analysis of the predictive performance of the Hijazi and Clements models showed that the Hijazi model performed poorly, whereas the Clements 250 model performed best. For the purposes of future cognitive studies with ketamine in our institution, it is possible that nonlinear mixed effects analysis using the data from the four studies performed so far may generate a better model than both the Domino and Clements 250 models. Once we have generated a new model, we will validate it prospectively and compare its prospective predictive performance with that of the Domino and Clements models.

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