Ketamine pharmacometrics

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Stereoselective ketamine effect on cardiac output: *A population pharmacokinetic-pharmacodynamic modeling study in healthy volunteers*

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Ketamine exhibits a plethora of significant adverse effects, including those on the cardiovascular system.[1] While ketamine has a direct negative inotropic effect, activation of the sympathetic system causes the release of catecholamines, vagal inhibition, noradrenaline release from sympathetic ganglia and inhibition of noradrenaline reuptake at neuronal and non-neuronal tissue (including the myocardium).[2-4] As a consequence, ketamine will induce cardiodepression when noradrenaline stores are depleted or cardiovascular excitation after administration of anesthetic doses of ketamine (often a short period of cardio-depression precedes excitation) and after low or subanesthetic doses of ketamine, used in the treatment of acute and chronic pain. Cardiovascular excitation is characterized by systemic and pulmonary hypertension, tachycardia and increases in cardiac output, all combined with an increase in myocardial oxygen consumption. Cardiodepression may be partially explained by a decrease in intracellular Ca^{2+} levels, due to the ketamine-induced inhibition of Ca^{2+}-release from intracellular stores and inhibition of the L-type voltage gated Ca^{2+}-channels.[5,6] The exact mechanism of ketamine-induced sympathoexcitation is not known but may be related to sodium channel blockade in parasympathetic centers in the brainstem and in spinal cord neurons.[7] Additionally, the reduction of intracellular nitric oxide concentrations has been proposed as mechanisms of sympathicoexcitation.[8]

In the current study, we examined the effect of racemic- (containing both *R*- and *S*-ketamine) and separately *S*-ketamine and their most relevant metabolites norketamine (NK), dehydronorketamine (DHNK) and hydroxynorketamine (HNK) on cardiac output, in a population of healthy volunteers. We analyzed the data using a population pharmacokinetic/pharmacodynamic modeling approach to separate the effects of *S*- and *R*-ketamine (and metabolites) on cardiac output. This study is part of a larger project in which the effect of nitric oxide donor sodium nitroprusside (SNP) on racemic (*RS*)- and *S*-ketamine-related adverse effects is studied. We previously reported that SNP reduces ketamine-induced schizotypal adverse effects following *RS*-ketamine but not following *S*-ketamine, suggestive of an SNP effect on a pathway activated by the *R*-ketamine isomer.[9] More recently, we published a pharmacokinetic model of ketamine and its metabolites and concluded that the SNP effects were not induced by changes in ketamine pharmacokinetics.[10] Our current analysis is aimed at determining the separate effects of *S*- and *R*-ketamine isomers and related metabolites on cardiac output and determine whether SNP has a mitigating effect of ketamine-induced cardiovascular excitatory effects.

METHODS

Ethics and subjects

This study is part of a large project on the ability of SNP to reduce *RS*- and *S*-ketamine ketamine-induced side effects. Apart from the primary analysis,[9] three separate secondary analyses were pre-planned: (1) development of a population pharmacokinetic model of *RS*- and *S*-ketamine and metabolites;[10] (2) development of a pharmacodynamic model of the analgesic and schizotypal side effects of *RS*- and *S*-ketamine; and finally, (3) development of a population pharmacodynamic model that describes the changes induced by *RS*- and *S*-ketamine on cardiac output and effect of SNP. Here, we report the results of the last analysis. The medical ethic committees of the Leiden University Medical Center (Medisch Ethische Toetsingscommissie Leiden, Den Haag, Delft) approved the study protocol, that was registered at the trial registry of the Dutch Cochrane Center (www.trialregister.nl) under registration number 5359. All study procedures followed the latest version of the Good Clinical Practice guidelines and the Declaration of Helsinki. The subject selection process can be found in Ref. 9. In brief, inclusion criteria were healthy male subjects, aged 18-35 years and body mass index of 19-30 kg/m^2. They were all screened and only after their history and physical examination (incl. negative drug tests) did not yield any abnormalities, the subjects were enrolled in the study. Subjects were not allowed to consume caffeinated food or drinks or consume any grapefruit containing products in the day and week, respectively, before dosing.

Study design

The study had a double-blind, randomized, 4-way crossover design. All subjects received escalating intravenous doses of intravenous *RS*-ketamine (Ketalar, Pfizer Pharma, Berlin, Germany) on visits A and B and escalating doses of *S*-ketamine (Ketanest, Eurocept BV, Ankeveen, the Netherlands) on visits C and D. On visits A and C, SNP was infused at a dose of 0.5 mg/kg per min, while placebo (NaCl 0.9%) was infused on visits B and D. *RS*-/*S*-ketamine and SNP/placebo were administered *via* two sperate infusion lines placed on opposing arms. The order of visits was randomized using a computer-generated, randomization list based on a four-block design (www.randomization.com). Blinding procedures, allocation and dispensing are described elsewhere. The researchers were unblinded after all experiments were concluded (August 24, 2017).

RS-ketamine and S-ketamine were dosed as follows: *RS*-ketamine 60 min 0.28 mg.kg^{-1}.h^{-1}; 60-120 min 0.57 mg.kg^{-1}.h^{-1} and 120-180 min: 1.14 mg.kg^{-1}.h^{-1}; *S*-ketamine was 0-60 min: 0.14 mg.kg^{-1}.h^{-1}, 60-120 min: 0.28 mg.kg^{-1}.h^{-1} and 120-180 min: 0.57 mg.kg^{-1}.h^{-1}. These doses were considered equipotent in terms of analgesic effect.[9] Arterial blood samples were obtained from an arterial line at the following times relative to the start of drug infusion (t = 0): t = 2, 6, 30, 59, 62, 66, 100, 119, 122, 126, 150, 179,

182, 186, 195 , 210 and 300 min. Plasma samples were analyzed in the laboratory of dr. Evan Kharasch as described by Rao et al.[11] Following *RS*-ketamine administration, the plasma concentration of *S*- *and R*-ketamine , *S*- *and R*-norketamine and *S*- *and R*-dehydronorketamine (DHNK), and total (*S* + *R*) hydroxynorketamine (HNK) were measured. Cardiac output was measured from the arterial pressure wave (obtained from the arterial cannula) using the FloTrac sensor and Vogileo. Cardiac output values were averaged over 1-minute intervals for further analysis.

Population pharmacokinetic-pharmacodynamic analysis

NONMEM version 7.4.4 (ICON Development Solution, Hanover, Maryland) was used for the data analyses. The plasma concentration – cardiac output data were analyzed by a two-step pharmacokinetic-pharmacodynamic approach. First a pharmacokinetic model was developed as described previously.[10] In brief, a seven-compartment PK model was constructed to describe the pharmacokinetics of ketamine, norketamine, DHNK enantiomers and total HNK. The central compartment of a two-compartmental ketamine model was linked *via* 2 metabolic (or delay) compartments to the central compartment of a two compartmental norketamine model. Since norketamine is further metabolized to either DHNK and HNK, the central norketamine compartment was linked to the DHNK disposition compartment *via* one metabolic (or delay) compartment; HNK was modeled with a two compartmental model, of which the central compartment was linked to the central norketamine compartment without a delay compartment. See also Figure 2 of Ref. 10.

In the second step, the empirical Bayesian estimates obtained from the pharmacokinetic analysis were used as input for the (cardiac output) pharmacodynamic model. Random effects were included in the model to account for interindividual variability and inter-occasions variability (IOV), as follows: $\theta_i = \theta \times \exp(\eta_i + \eta_{iov})$, where θ_i is the parameter for individual i, θ the population parameter, η_i is the random difference between the population and individual parameter and η_{iov} the difference between θ_i and θ due to inter-occasion variability.

To test the potential effect of each compound, we started with a base pharmacodynamic model that just included *S*-ketamine, which was sequentially expanded by adding its metabolites, and next *R*-ketamine and its metabolites. The total effect on cardiac output was defined as the sum of effects calculated for each compound. Compounds were only included in the pharmacodynamic model, when addition gave a significant ($p < 0.01$) improvement of the objective function value as calculated by NONMEM. To evaluate a potential hysteresis between ketamine and metabolite plasma concentrations and observed effects, postulated effect compartments were tested for each individual included compound (*i.e.* we tested whether effect equilibration compartments improved the objective function value). It was assumed that the effect compartment

equilibrates with the central plasma compartment with rate constant ke0 with effect half-time $t_{1/2} = \ln(2)/k_{e0}$.

A linear pharmacodynamic model was initially developed to describe the plasma concentration-cardiac output data (*i.e.* the base model): YF = BLN * (1 + YE_{SUM}) + ε, where YF is the cardiac output value predicted by the model, BLN is the baseline cardiac output, YE_{SUM} the sum of the effects on the cardiac output caused by ketamine and its metabolites (*i.e.* $YE_{SUM} = YE_{X1} + \ldots\ldots + YE_{X7}$) and ε the residual error. The individual effect of each compound on cardiac output was defined by $YE_{Xn} = 0.25 \cdot (C_{Xn} / C_{25Xn})^{\gamma}$, where YE_{Xn} is the effect of compound Xn on cardiac output, γ the Hill coefficient, C_{Xn} the drug concentration, C_{25Xn} is the effect-site concentration of compound Xn that leads to a 25% change of cardiac output relative to baseline (25% is in the midst of the observed changes) of compound Xn contributing to changes in total cardiac output, where Xn ranges from X1 to X7 with X1 *S*-ketamine, X2 *R*-ketamine, X3 *S*-NK, X4 *R*-NK, X5 *S*-DHNK, X6 *R*-DHNK and X7 total HNK. Note that C_{Xn} could be either the drug concentration in the central volume of distribution, or in the effect compartment, depending on the compound.

Since an undershoot was observed in the cardiac output data following termination of ketamine infusion, a control mechanism was added to the model: YF = BLN * (1 + YE_{SUM} – YC) and τ dYC/dt = (YE_{SUM} – YC), where YC is the output of the controller that counteracts YE_{SUM} with time constant τ. In addition, since in some subjects the residuals of the data fits were correlated, a parallel process noise component (*i.e.* Kalman filter) was added to the model: $dYC = (YE_{SUM} - YC)/\tau \cdot dt + \sigma\nu \cdot dw$, where $\sigma\nu$ is the standard deviation of the noise component (with units $L \cdot min^{-1} \cdot min^{-0.5}$) and dw a stochastic (Wiener process), with units for w $min^{0.5}$. Finally, a trend parameter (TRD) was added to the model, because a clear increasing trend, irrespective of ketamine or metabolite concentrations, was observed: YF = BLN * (1 + YE_{SUM} – YC + TRD * t/300), where t is the time from the start of the experiment in minutes.

Model selection was based on significant improvements in the objective function value (-2LogLikelihood with $p < 0.01$ following a χ^2-distribution) and by assessment of individual model fits and goodness of fit plots (population predicted *versus* observed, individual predicted *versus* observed, conditional weighted residuals *versus* time and conditional weighted residuals *versus* population predicted plots) and the visual predictive checks. Additionally, auto- and cross-correlation plots were assessed to evaluate model goodness of fit. The correlation between two residuals shifted in time can be described by an auto-correlation function, in which residuals are uncorrelated (so called *white* residuals) when the auto-correlation function is equal to zero, with the exception when t = 0. In addition, the correlation between the residuals and input (*i.e.* the model output, before being inputted in the Kalman filter) shifted in time, can be described by the cross-correlation function. Similar to the auto-correlation function, if the

cross-correlation function equals zero, this indicates that the residuals are completely random, and the model therefore explains the data completely.[12]

Since a large number of combinations could be tested due to the potential effects of seven different compounds and the incorporation of the TRD parameter, Controller and Kalman filter in the model, we here only describe the most important model combinations. Sequential testing with ketamine and metabolites was performed for five models:

Model 1: base model with just the Kalman filter (no trend parameter or controller); note that when $YE_{SUM} = 0$ the controller is deactivated;
Model 2: model 1 + trend parameter;
Model 3: model 1 + controller;
Model 4: model 1 + trend parameter + controller; and
Model 5: model 2 without the Kalman filter.

The controller relates the undershoot in cardiac output after ketamine infusion ended, the trend term relates to a slow increase in cardiac output over time, and the Kalman filter to the noise in the data.

Finally, potential covariates were tested on the best model, by an automated stepwise covariate screening algorithm (Stepwise Covariate Model building module from Pearl speaks NONMEM).[13] Tested covariates were: (i) *S*- or *RS*-ketamine administration and (ii) placebo or SNP administration. First a forward search was performed, adding covariates to the model that caused a significant drop ($p < 0.01$) of the objective function value. Potential covariates were added to the model parameters in a linear relation, described as: $\theta_i = \theta_{ref} \times (1 + \theta_{COV})$, where θ_{ref} is the typical parameter value for a subject belonging to the reference category of the covariate and θ_{COV} the effect of belonging to the non-reference category. Once covariates caused no further drop in objective function value, the backward search was started. In this step, covariates were sequentially removed from the model. When removal caused a significant reduction of the objective function value ($p < 0.001$), the covariate was retained in the model. This process was continued until all covariates were excluded or until no more covariates were left to exclude. To limit the risk of including irrelevant covariates, the backward search was performed with a more stringent selection criterion.

RESULTS

All twenty subjects successfully completed the study without serious adverse effects. Mean ± SD (range) subject age was 23 ± 2(19-28) years, height 186 ± 6 (175-193) cm, body weight 83 ± 9 (60-98) kg and body mass index 24 ± 2.1 (19.5-28.4) kg/m^2. Cardiac

output data were obtained from all subjects, except from subject 19. We did not collect cardiac output data on one occasion due to failure of insertion of the arterial line. Mean cardiac output *versus* time curves are shown in Figure 1.

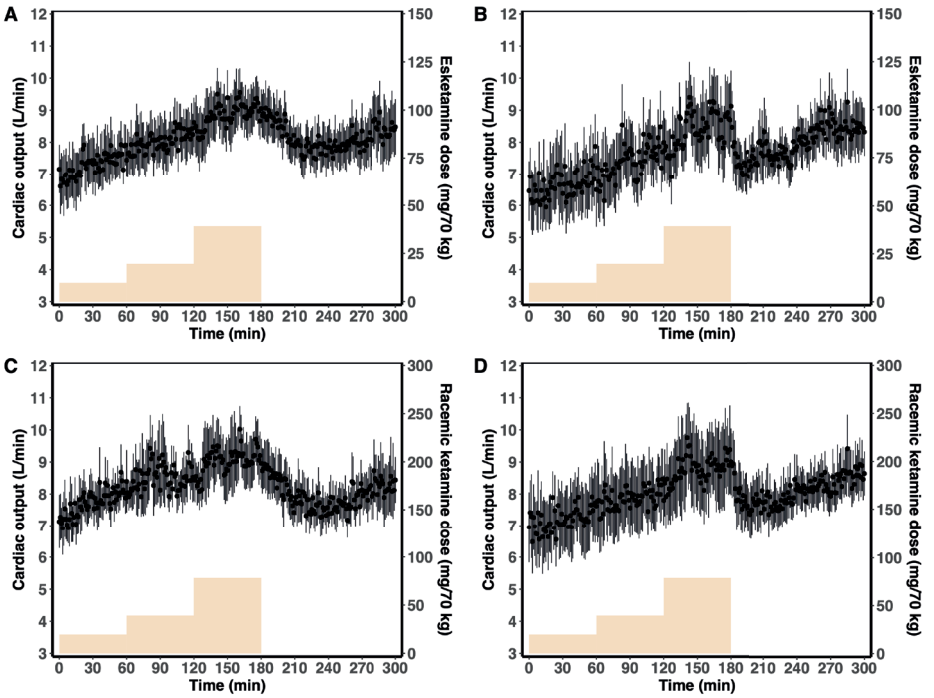

Figure 1. Mean time-cardiac output curves after *S*-ketamine with either placebo or sodium nitroprusside (SNP) co-administration (**A, B**) and after *RS*-ketamine with either placebo or SNP co-administration (**C, D**). Data are mean ± SD. Ketamine doses are given in yellow (right y-axis).

Pharmacodynamic models

Starting with model 1 (base model with Kalman filter, absolute objective function value 24,517), adding the trend term resulted in a ΔOFV of -74 points (model 2). No significant improvement was observed when the controller was added to model 1 (model 3). Since the structure of model 2 best described the data, we limit the description of the sequential compound testing to model 2. The effect of *S*-ketamine on cardiac output was best modeled by adding an effect compartment (ΔOFV of -9.41 points). Sequential expansion of the model with metabolites only showed a significant effect of *S*-norketamine (ΔOFV of -18 points), but, in contrast to *S*-ketamine, reducing cardiac output. Adding *R*-ketamine or its metabolites did not cause a significant improvement of the model and these were therefore not incorporated. Finally, adding an S-norketamine effect compartment improved the model (ΔOFV of -11 points). In agreement with these findings,

sequential compound testing of models 1, 3-5 failed to show significant metabolite effects, indicating that the trend term and controller did not obfuscate potential metabolite effects on cardiac output. Removal of the Kalman filter from the final model 2 resulted in an increase in objective function value by 5986 points and rather large ω^2 values, indicating that the Kalman filter significantly improved the model.

Pharmacodynamic parameters of the final model (model 2) are given in Table 1 with best, median and worst data fits in Figure 2. The *S*-ketamine concentration causing an increase in cardiac output by 25% was 1.68 ± 0.45 nmol/mL. The *S*-ketamine blood-effect-site equilibration half-life ($t½k_{e0}$) was 2.28 ± 0.64 min, the time constant of the noise component was 31.4 ± 7.9 min and the value of the trend term 0.38 ± 0.08 L/300 min (*i.e.* a 380 ml/min increase in ventilation over the course of the study). In addition, the *S*-norketamine concentration causing a 25% reduction of cardiac output, was 0.67 ± 0.22 nmol/mL, with an equilibration half-life of 29.3 ± 16.4 min.

Table 1. Pharmacodynamic parameters estimates of model 2

	Typical parameter value (SEE) [%CV]	**Inter-individual variability % (SEE) [%CV]**	**Inter-occasion variability % (SEE) [%CV]**
Baseline cardiac output (L/min)	6.8 (0.2) [3]	11.3 (3.4) [29]	9.7 (1.5) [15]
γ	1 FIX	-	26.4 (8.7) [33]
Trend term (L/min^2)	0.384 (0.081) [21]	17.1 (3.4) [20]	-
C_{25} *S*-ketamine (nmol/ml)	1.68 (0.45) [27]	93.8 (20.6) [22]	-
C_{25} *S*-norketamine (nmol/ml)	0.673 (0.215) [32]	-	
S-ketamine $t_{1/2}k_{e0}$ (min)	2.28 (0.64) [28]	-	-
S-norketamine $t_{1/2}k_{e0}$ (min)	29.3 (16.4) [56]		
τ of the noise component (min)	31.4 (7.9) [25]	-	-
$\sigma\nu$ (L · min^{-1} · min $^{-0.5}$)	0.89 (0.05) [6]	22.9 (2.7) [12]	25.4 (3.6) [14]
$\sigma\in$ (L/min)	0.037 (0.004) [10]	-	35.9 (4.3) [12]

γ is a shape parameter, TRD is a trend term; C_{25} *S*-ketamine is the *S*-ketamine plasma concentration that causes an 25% increase in cardiac output; C_{25} S-norketamine is the *S*-norketamine plasma concentration that causes 25% of the maximum (100%) counteracting effect on the S-ketamine effect; $t_{1/2}k_{e0}$ is the plasma effect compartment equilibrium half-life; τ is the time constant of the noise compartment; $\sigma\nu$ and $\sigma\in$ are the standard deviations of the process and measurement noise components respectively. SEE is the standard error of the estimate and CV the coefficient of variation.

Goodness of fit plots and the visual predictive check for model 2 are given in Figures 3 and 4. Auto-correlation function plots for models 2 and 5 are shown in Fig. 5. The visual predictive check revealed a slight undershoot of the simulated 5th percentile data

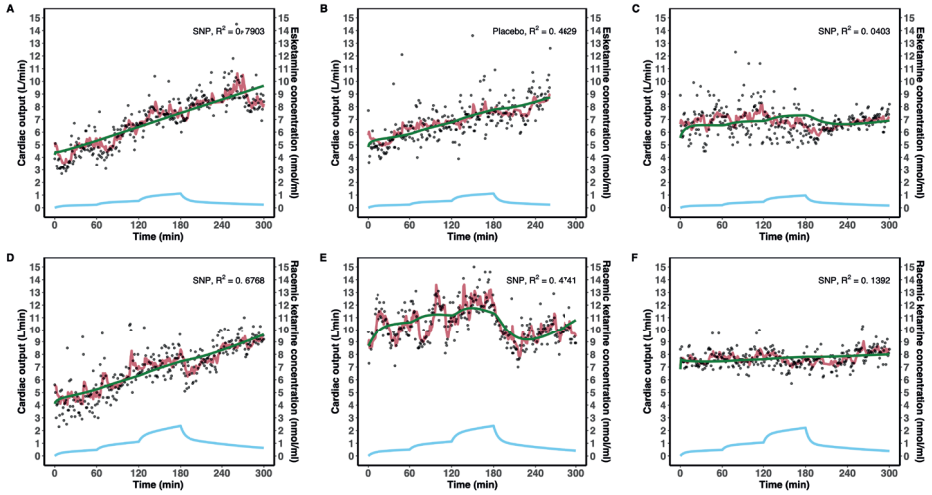

Figure 2. Pharmacodynamic model fits. Best (**A**), median (**B**) and worst (**C**) cardiac output model fits after esketamine administration and best (**D**), median (**E**) and worst (**F**) cardiac output model fits after racemic ketamine administration. The dots are the measured data, the red and green lines the output of models 2 (with Kalman filter) and 5 (without Kalman filter), respectively. The blue lines are the simulated *S*-ketamine concentrations (right y-axis), based on the empirical Bayesian estimates obtained from Kamp et al.[10]

compared to that of the 5th percentile of the true data (lower black line and shaded area). Adding the Kalman filter improved the model fits and resulted in substantially improved goodness-of-fit plots, visual predictive checks (data not shown) and auto- and cross-validation values. This indicates that model 2 has uncorrelated residuals and is to be preferred over model 5. Finally, screening model 2 for covariates failed to show significant effects of either ketamine administration form (*e.g. S*-ketamine *versus RS*-ketamine administration) or placebo *versus* SNP administration.

DISCUSSION

We observed a stereoselective effect of ketamine on cardiac output. While *S*-ketamine increased cardiac output in a concentration-dependent manner, no effect of *R*-ketamine on cardiac output was detected in our data set. Additionally, we observed that, in contrast to *S*-ketamine, its active metabolite *S*-norketamine reduced cardiac output. There was no effect of the nitric oxide donor sodium nitroprusside on the effect of either *S*- or *RS*-ketamine.

Two earlier pharmacokinetic-pharmacodynamic studies on the effect of ketamine on cardiac output were published. Sigtermans et al. administered increasing doses of *S*-ketamine to healthy volunteers and modelled the effect of *S*-ketamine and *S*-norket-

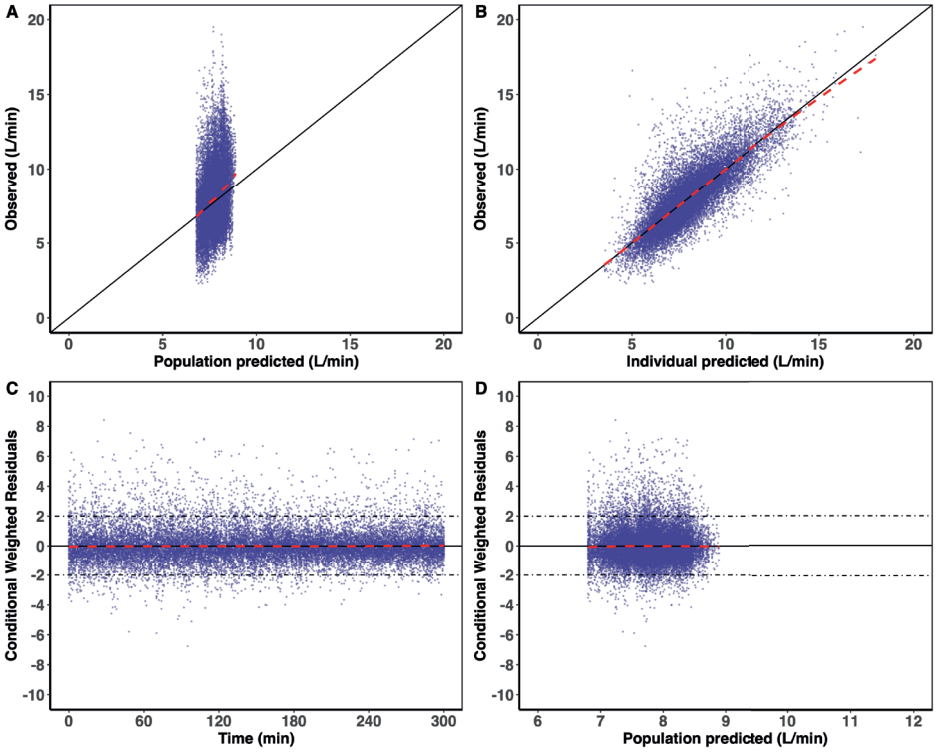

Figure 3. Goodness of fit plots. Observed *versus* population predicted cardiac output (**A**), observed *versus* individual predicted cardiac output (**B**), conditional weighted residuals *versus* time (**C**) and conditional weighted residuals *versus* population predicted cardiac output (**D**) for Model 2. Red lines show LOESS smoothers to identify potential trends.

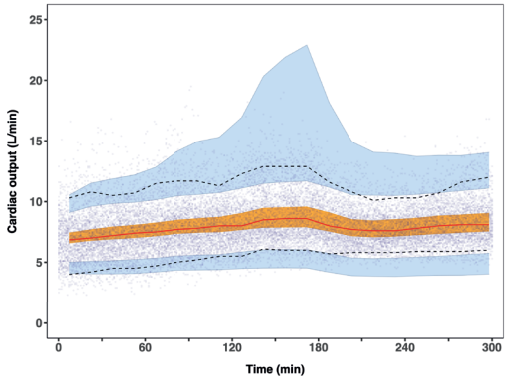

Figure 4. Visual predictive check based on the simulation of 1,000 datasets from model 2. The 50th, 5th and 95th percentiles of the true data are shown by the red and lower and upper black lines respectively. The orange and upper and lower blue shaded areas show the 95% confidence intervals of the simulated 50th (orange) 5th and 95th (blue) percentile data. The dots are the measured cardiac output data.

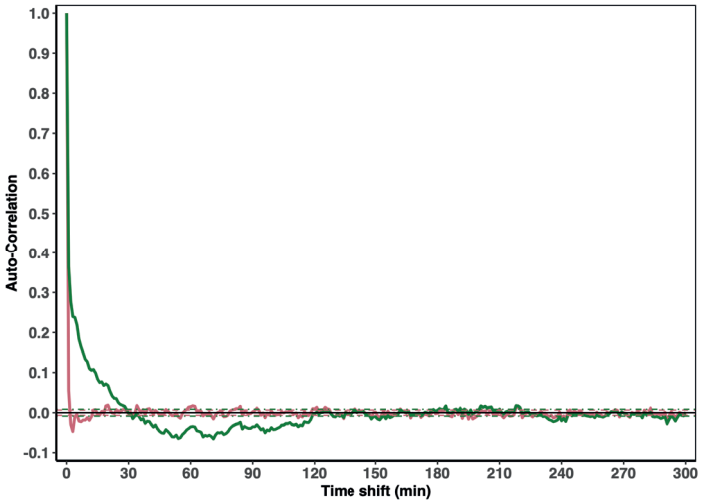

Figure 5. Auto-correlation function of the residuals of Model 2 (red line) and Model 5 (green line) for the total dataset.

amine on cardiac output using a base model with trend term but without controller or noise component.[14] In that study, the increase in cardiac output following infusion of *S*-ketamine was well described by the *S*-ketamine concentration in plasma without any effect from *S*-norketamine. Olofsen et al. administered increasing *S*-ketamine pulsatile doses to healthy volunteers and patients diagnosed with chronic regional pain syndrome type 1.[12] They modelled the effect of just *S*-ketamine on cardiac output using a pharmacodynamic model with controller and noise component. In the current pharmacodynamic analyses incorporation of a trend term and noise component (Kalman filter) contributed to the significant improvement of the description of the data (model 2), while adding a controller did not; the negative contribution of norketamine allowed for the characterization of the undershoot in the data.

The trend term described a slow change in effect over time, independent of the plasma ketamine concentration. Sigtermans et al. observed a positive trend term in their study on the effect of ketamine on antinociception.[14] Possibly, the change in cardiac output of +0.38 L/min in 300 min in the current study may be related to the slow increase in concentration of DHNK and HNK. In order to confirm this hypothesis, we performed sequential metabolite effect testing of the base model without and with a trend term but could not detect a significant contribution of either metabolite to the trend term. Other causes for the positive trend may be a slow increase in arterial carbon dioxide concentration due to the respiratory effects of ketamine, or anxiety-related due to the psychedelic effects of ketamine.

In agreement with Olofsen et al. we added a Kalman filter to the base model. The Kalman filter is a method to track the state of a system in the presence of random disturbances. These disturbances are to be distinguished from residual or measurement noise; here they might affect physiological processes related to homeostasis, and because of the inertia of such processes, the disturbances lead to correlated residual noise in addition to the measurement noise. In the current study, auto-correlation (correlation between residuals) and cross-correlation (correlation between residuals and pharmacodynamic input indicate absence of significant correlations in the model with Kalman filter (model 2), while the noise was correlated in the model without Kalman filter (model 5). This indicates a significant improvement in model performance with more reliable estimates of variability and deterministic model parameters. Additionally, data analyses without Kalman filter yielded much larger ω^2 values (data not shown). These findings agree with earlier studies exploring noisy respiratory data and transdermal opioid absorption.[15,16]

The absence of effect of *R*-ketamine on cardiac output agrees with earlier findings of a lesser potency of *R*-ketamine compared to *S*-ketamine on various endpoints. For example, Geisslinger et al. reported significant higher systolic and diastolic blood pressures following *S*-ketamine compared to *RS*-ketamine.[17] Their results suggest that *S*-ketamine is mostly responsible for the observed cardiovascular effects associated with ketamine administration. Hence, *R*- and *S*-enantiomers differentially engage sympathoexcitation, possibly related to differences in receptor activation. For example, *S*-ketamine is about twice as potent as *R*-ketamine in producing voltage and use dependent blockade of the *N*-methyl-D-aspartate receptor.[18] These data agree with observations that *S*-ketamine, at anesthetic doses, is more potent in reducing the electroencephalogram power spectrum compared to anesthetic doses of *R*-and *RS*-ketamine and the difference in analgesic potency between *S*- and *RS*-ketamine at subanesthetic doses.[9,19]

Covariate analysis revealed absence of effects from the administration form (racemic ketamine or the *S*-isomer) or from absence or presence of the nitric oxide donor SNP. This later observation contrasts a study in rabbits that shows that L-arginine, a substrate of nitric oxide formation, attenuated ketamine-induced increased in renal sympathetic nerve activity.[8] Possibly the SNP dose in our study was too low to reduce cardiac output (in contrast to the effect of SNP on psychedelic symptoms). Additionally, compensatory mechanisms may have prevented any effect of low-dose SNP in our healthy and young population of volunteers.

Finally, we observed a negative contribution of *S*-norketamine on cardiac output, an effect that could explain the undershoot following ketamine infusion. In fact, *S*-norketamine counteracted the effect of *S*-ketamine on cardio-excitation. This finding agrees with an earlier modeling study in which norketamine was anti-analgesic and counteracted the analgesic effects of ketamine.[20] The mechanism of this antagonist effect remains unknown, and may be related to a differential receptor activation profile of

norketamine *versus* ketamine.[20] However, as stated earlier, one needs to be rather careful in the interpretation of these finding from our complex modeling study.[20] Additional proof from either animal or human studies is needed before any defensive conclusions regarding the behavior of *S*-norketamine on cardiac output may be drawn.

CONCLUSIONS

In this chapter, we performed a pharmacodynamic modeling study that evaluated the effects of *R*- and *S*-ketamine and its most important metabolites on cardiac output in healthy male volunteers. Important findings were that, in contrast to *S*-ketamine, *R*-ketamine was devoid of effect on cardiac output, while *S*-norketamine counteracted the effect of *S*-ketamine by having a negative effect on cardiac output.

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