

# Effect of Rifampicin on S-ketamine and S-norketamine Plasma Concentrations in Healthy Volunteers after Intravenous S-ketamine Administration

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## ABSTRACT

**Background:** Low-dose ketamine is used as analgesic for acute and chronic pain. It is metabolized in the liver to norketamine *via* cytochrome P450 (CYP) enzymes. There are few human data on the involvement of CYP enzymes on the elimination of norketamine and its possible contribution to analgesic effect. The aim of this study was to investigate the effect of CYP enzyme induction by rifampicin on the pharmacokinetics of S-ketamine and its major metabolite, S-norketamine, in healthy volunteers.

**Methods:** Twenty healthy male subjects received 20 mg/70 kg/h ( $n = 10$ ) or 40 mg/70 kg/h ( $n = 10$ ) intravenous S-ketamine for 2 h after either 5 days oral rifampicin (once daily 600 mg) or placebo treatment. During and 3 h after drug infusion, arterial plasma concentrations of S-ketamine and S-norketamine were obtained at regular intervals. The data were analyzed with a compartmental pharmacokinetic model consisting of three compartments for S-ketamine, three sequential metabolism compartments, and two S-norketamine compartments using the statistical package NONMEM® 7 (ICON Development Solutions, Ellicott City, MD).

**Results:** Rifampicin caused a 10% and 50% reduction in the area-under-the-curve of the plasma concentrations of

## What We Already Know about This Topic

- Ketamine is metabolized by cytochrome P450 enzymes primarily to norketamine, and these enzymes are induced by rifampicin
- The contribution of norketamine to antinociception after ketamine administration is unknown

## What This Article Tells Us That Is New

- In a randomized, placebo-controlled, crossover study of 20 male volunteers, rifampicin decreased S-ketamine plasma concentrations 10% because of a 13% increase in elimination and decreased S-norketamine concentrations 50% because of a 200% increase in elimination
- Simulations suggest a minimal contribution of norketamine to either acute or chronic ketamine antinociception

S-ketamine and S-norketamine, respectively. The compartmental analysis indicated a 13% and 200% increase in S-ketamine and S-norketamine elimination from their respective central compartments by rifampicin.

**Conclusions:** A novel observation is the large effect of rifampicin on S-norketamine concentrations and indicates that rifampicin induces the elimination of S-ketamine's metabolite, S-norketamine, probably *via* induction of the CYP3A4 and/or CYP2B6 enzymes.

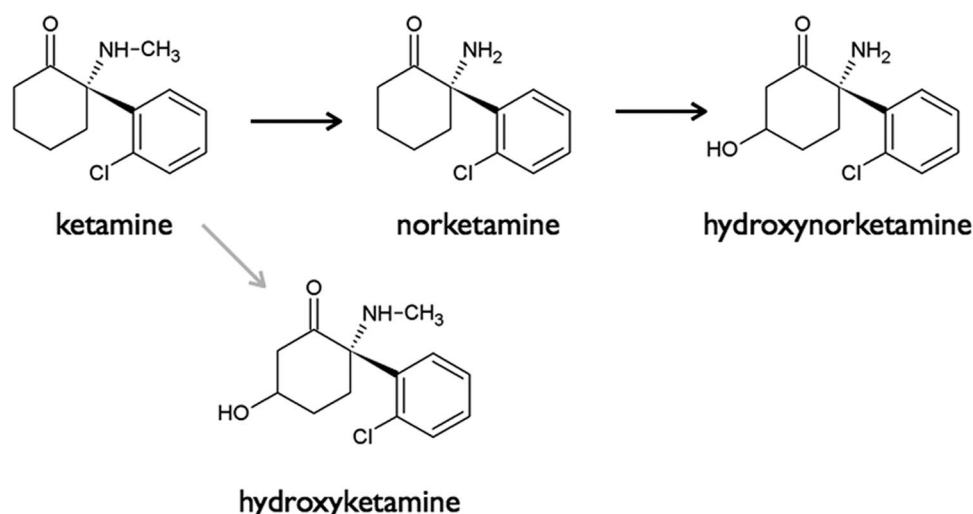
**K**ETAMINE is an arylcycloalkylamine structurally related to phencyclidine and first synthesized in 1963.<sup>1</sup> At relatively high dose, ketamine produces anesthesia, whereas at low, subanesthetic dose, it is a potent analgesic. Ketamine analgesia is thought to result from noncompetitive antagonism at the ionotropic glutamatergic *N*-methyl-D-aspartate (NMDA) receptor.<sup>2</sup> NMDA receptors are excitatory and involved in enhanced nociceptive processing at spinal and supraspinal sites.<sup>3</sup> By blocking the NMDA receptor, ketamine effectively reduces signal propagation in the pain circuitry from the spinal cord to the cortex and consequently produces analgesia. Ketamine-induced acute pain relief is driven by its pharmacokinetics; that is, upon termination of infusion (causing a brisk decrease in plasma concentration),

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**Fig. 1.** Metabolic pathways of ketamine. The *black arrows* indicate the major pathway, the *gray arrow* the minor pathway.

acute pain relief ends rapidly,<sup>4,5</sup> whereas in patients with chronic pain, the relief of spontaneous pain outlasts the treatment period by weeks to months.<sup>6–9</sup>

Ketamine undergoes extensive metabolism by hepatic cytochrome P450 (CYP). In rat liver microsomes, norketamine, hydroxynorketamine, and hydroxyketamine account for 80%, 15% and 5%, respectively, of ketamine metabolism (fig. 1).<sup>10</sup> *In vivo*, rabbits convert 68% of ketamine to norketamine.<sup>11</sup> In humans, *N*-demethylation to norketamine is the major route of metabolism, which can undergo further metabolism *via* cyclohexanone ring hydroxylation to form 4-, 5-, and 6-hydroxynorketamine. Ketamine itself can be hydroxylated, forming 4-hydroxyketamine, although this is considered quantitatively insignificant.<sup>10,12</sup> Other minor metabolites have recently been reported.<sup>13</sup> Finally, norketamine and the hydroxy metabolic products are subsequently glucuronidated and eliminated *via* the kidney and bile.<sup>14</sup> Just 10–15% of ketamine is eliminated unchanged. Like ketamine, norketamine is a noncompetitive antagonist at the NMDA receptor.<sup>15,16</sup> Nonhuman data indicate that norketamine passes the blood–brain barrier, has approximately one fifth to one third the potency of ketamine, and is thought to contribute up to 30% of ketamine analgesia and, albeit to a lesser extent, to the development of psychomimetic side effects.<sup>15,17,18</sup> No pharmacologic activity is attributed to the hydroxynorketamines.<sup>17</sup>

The major human hepatic CYPs that catalyze ketamine *N*-demethylation *in vitro* are CYP2B6 and CYP3A4, although there is ambiguity as to their comparative contributions to clinical ketamine metabolism.<sup>19,20</sup> Rifampicin is an effective and nonselective inducer of multiple CYPs, including those (CYP2B6 and CYP3A4) that catalyze ketamine *N*-demethylation.<sup>21</sup>

In the current study, we performed a compartmental pharmacokinetic analysis to quantify the effect of CYP induction on the elimination of S(+)-ketamine (S-ketamine)

and formation and elimination of S(+)-norketamine (S-norketamine). We took this approach (*i.e.*, CYP induction) because norketamine is unavailable for testing in humans. Next, using a sigmoid  $E_{MAX}$  model equation with S-ketamine and S-norketamine contributions, we simulated the effect of rifampicin on analgesia to obtain an indication of the importance of variations in S-norketamine concentration on analgesic effect. We tested the effect of the S(+)-enantiomer of ketamine because it is the only ketamine product registered for human use in The Netherlands. S-ketamine has greater analgesic potency than either the R(–) variant or the racemic mixture, with possibly fewer side effects than the racemic mixture.<sup>16,22</sup>

## Materials and Methods

### Subjects

Twenty healthy male volunteers (age 19–29 yr, body mass index less than 30 kg/m<sup>2</sup>) were recruited to participate in the study after approval of the protocol by the local Human Ethics Committee (Commissie Medische Ethiek, Leiden University Medical Center, Leiden, The Netherlands). Written informed consent was obtained before inclusion in the study according to the Declaration of Helsinki. All subjects were instructed not to eat or drink for at least 8 h before the study. Alcohol, coffee, and chocolate were not allowed for 24 h, and grapefruit or grapefruit juice was not allowed 6 days before the study day. The study was registered under number NTR1328.\*\*

### Study Design: S-ketamine Infusion and Blood Sampling

The study design was randomized single-blind, placebo-controlled, and crossover. Subjects received 600 mg oral rifampicin daily (Sandoz BV, Almere, The Netherlands) (session 1) or placebo (session 2; cellulose tablets produced by the local pharmacy) in the 5 days preceding the experimental testing (five 600-mg doses were given). Rifampicin/placebo was taken at bedtime. The time interval between the last dose and

\*\* Available at: [www.trialregister.nl](http://www.trialregister.nl). Accessed January 21, 2011.

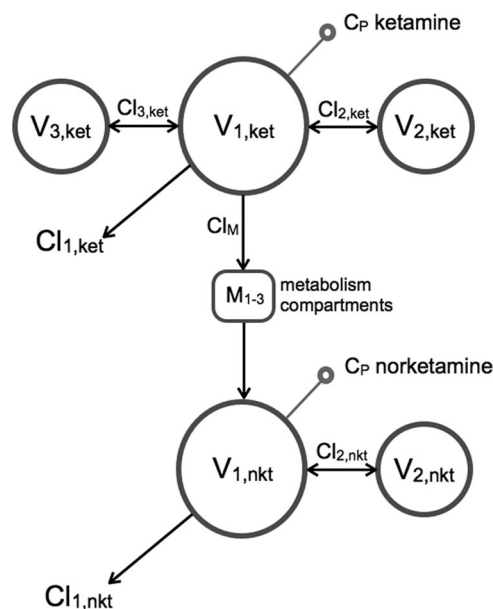
the ketamine administration was 10–12 h. The order of the sessions was random, with at least 3 weeks between sessions. On the study day, the subjects had an arterial line placed in the radial artery of the nondominant hand for blood sampling and a venous line placed in the contralateral arm for drug infusion. Total study duration was 5 h, of which S-ketamine (Ketanest S, Pfizer BV, Capelle aan de IJssel, The Netherlands) was administered during the first 2 h. The subjects were randomly allocated to receive a 20 mg/70 kg/h or 40 mg/70 kg/h S-ketamine infusion. The ketamine infusions were similar for sessions 1 and 2. Randomization was done by the pharmacy using computer-generated randomization lists.

Arterial blood sampling was performed at times  $t = 0$  (predrug baseline) and 5, 10, 15, 30, 45, 60, 75, 90, 105, 120, 125, 130, 135, 150, 180, 210, 240, 270, and 300 min after the start of the infusion. Five milliliters blood was collected per sample. The analysis has been described previously.<sup>4</sup> In brief, the samples were centrifuged at a speed of 3,000 rpm for 10 min; 2–3 ml plasma was separated within 15 min of blood collection and stored at  $-25^{\circ}\text{C}$  until analysis. For the construction of S-ketamine and S-norketamine calibration lines, solid substances were obtained from Parke-Davis (Dallas, TX) and Tocris (St. Louis, MO), respectively. After extraction from the specific sample, S(+)-ketamine and S(+)-norketamine were determined by HPLC on a Gemini C18 column (Phenomenex, Utrecht, The Netherlands) at  $40^{\circ}\text{C}$ . Monitoring of the eluent was performed at 195 nm with a photodiode array detector (PDA 100, Dionex, Amsterdam, The Netherlands). The lower limit of quantitation was 10 ng/ml, and the lower limit of detection was 3 ng/ml for both drugs. All samples with concentrations more than 3 ng/ml were included in the analysis. None of the samples had ketamine concentrations of less than 3 ng/ml, whereas the initial two norketamine samples of all subjects had concentrations lower than the detection limit.

### Pharmacokinetic Analysis

A  $t$  test was performed to compare the maximum plasma concentration of S-ketamine and S-norketamine ( $C_{\text{MAX}}$ ), their time of occurrence, and the area under the plasma concentration curve (AUC) divided by the duration of the experiment ( $\text{AUC}_{0 \rightarrow 300}$ ) of the placebo *versus* ketamine treatment. The analysis was performed in SPSS for Windows version 16.0 (SPSS Inc., Chicago, IL). Significance was  $P < 0.05$ . Values reported are mean  $\pm$  SD.

The compartmental model used for pharmacokinetic analysis was identical to a previously published model.<sup>4</sup> The analysis was performed in two steps. Initially, only the ketamine data were analyzed. Subsequently, the combined ketamine and norketamine data were analyzed. The model consisted of three ketamine compartments connected to two norketamine compartments (see fig. 2). Because we had found that norketamine's formation and elimination (and intercompartmental distribution) rates were not simultaneously estimable,<sup>4</sup> the norketamine formation rate was set



**Fig. 2.** Schematic representation of the pharmacokinetic model used to analyze the combined S-ketamine and S-norketamine data.  $V_{1,\text{ket}}$ ,  $V_{2,\text{ket}}$ , and  $V_{3,\text{ket}}$  are the three ketamine (ket) compartments and  $V_{1,\text{nkt}}$  and  $V_{2,\text{nkt}}$  the two norketamine (nket) compartments.  $M_{1-3}$  represents three sequential metabolism compartments.  $Cl_{1,\text{ket}}$  is the clearance from compartment  $V_{1,\text{ket}}$ ,  $Cl_{2,\text{ket}}$  the clearance from compartment  $V_{2,\text{ket}}$ ,  $Cl_{3,\text{ket}}$  the clearance from compartment  $V_{3,\text{ket}}$ ,  $Cl_{1,\text{nkt}}$  the clearance from compartment  $V_{1,\text{nkt}}$ , and  $Cl_{2,\text{nkt}}$  the clearance from compartment  $V_{2,\text{nkt}}$ .  $Cl_M$  is the S-ketamine clearance responsible for the S-norketamine formation.

equal to the ketamine elimination rate. Volumes were scaled *via*  $\text{WT}/70$  and clearances *via*  $(\text{WT}/70)^{0.75}$ , where WT is body weight in kilograms.<sup>23</sup> To test for a significant rifampicin effect on clearances, we introduced factor F as follows:

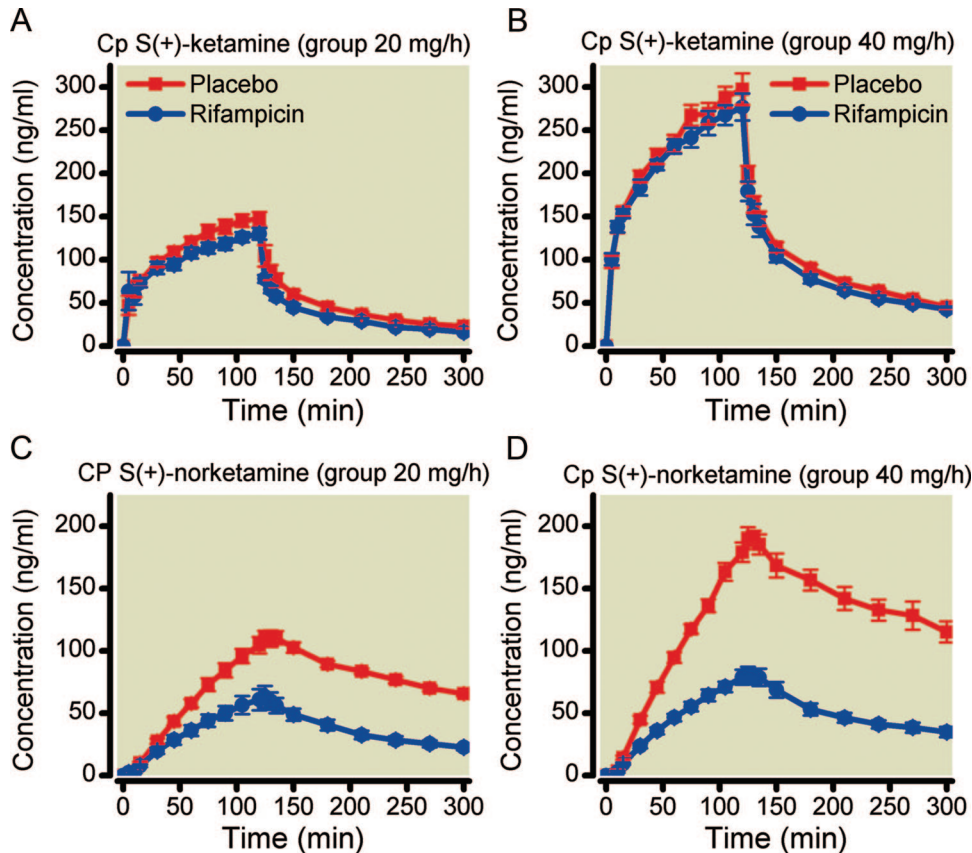
$$\text{Parameter}_{\text{RIFAMPICIN}} = \text{Parameter}_{\text{PLACEBO}} \cdot (1 + F). \quad (1)$$

For example, an F value of 2 indicates that the parameter increased by 200% after rifampicin treatment. Significance of factors was tested using forward selection. Because experiments were performed on two separate days, we estimated both interindividual ( $\omega^2$ ) and interoccasion ( $\nu^2$ ) variances. Exponential error models were used for inter- and intraindividual variability.

The compartmental analysis was performed with the statistical package NONMEM® 7 (ICON Development Solutions, Ellicott City, MD) with first-order conditional estimation with interaction method.<sup>24</sup> Data presented are median and 95% CI. A bootstrap analysis was used to check the final model and to obtain 95% CI for the model parameters (from 1,000 successful runs).

### Side Effects

Drug high and sedation were scored using an 11-point numerical rating scale ranging from 0 (no effect) to 10 (maximum possible effect) at regular intervals during and after ketamine infusion.



**Fig. 3.** Effect of rifampicin treatment on plasma concentrations of S-ketamine (A and B) and S-norketamine (C and D) during and 3 h after a 2-h S-(+)-ketamine infusion of 20 mg/h (A and C) and 40 mg/h (B and D). Values are mean  $\pm$  SEM. S-ketamine was infused from  $t = 0$  to  $t = 120$  min.

### Simulation Study

Simulation studies enable the systematic exploration of inferences made in our study with respect to anticipated norketamine effect size. Here we performed simulations to estimate the effect of the large change in norketamine concentration and relatively modest change in ketamine concentration that we observed after rifampicin treatment on pain relief. Two sets of simulation were performed, one set on pain relief induced by short-term ketamine infusion and another set on pain relief induced by chronic ketamine administration. To that end, we made *a priori* assumptions with respect to the norketamine contributions to ketamine effect: simulations with 0, 10, and 25% norketamine contribution were made. The difference in effect observed in the simulated pain relief with and without rifampicin treatment will give an indication of the norketamine contribution to effect.

**Acute Antinociception Paradigm.** Using the pharmacokinetic model parameters, the effect of rifampicin treatment on acute antinociception was simulated for different norketamine contributions to effect. To that end, analgesic effect during and after a 2-h S-ketamine infusion of 40 mg/h was simulated using the current pharmacokinetic data set linked to pharmacodynamic data previously obtained and modeled in a similar subject population in our

laboratory.<sup>4</sup> Analgesia was simulated using a sigmoid  $E_{MAX}$  model assuming an additive effect of S-ketamine and S-norketamine as follows:

$$VAS(t) = \frac{BLN}{1 + \left( \frac{C_{ket}(t)}{C_{50,ket}} + \frac{C_{nkt}(t)}{C_{50,nkt}} \right)^\gamma} \quad (2)$$

where VAS is visual analog score (ranging from 0 cm = no pain to 10 cm = severe pain), BLN is baseline (or predrug) VAS,  $\gamma$  a shape parameter,  $C_{ket}$  and  $C_{nkt}$  the plasma concentrations of S-ketamine and S-norketamine, respectively;  $C_{50,ket}$  the plasma concentration S-norketamine causing 50% effect, and  $C_{50,nkt}$  the concentration S-norketamine causing 50% effect. The following model parameters (from Sigtermans *et al.*<sup>4</sup>) were used: BLN = 6.7 cm,  $\gamma = 2.5$ , and  $C_{50,ket} = 375$  ng/ml. The  $C_{50,nkt}$  was varied in such a way that it contributed 0, 10, and 25% to total analgesic effect. We assumed no delay between blood concentration and acute antinociceptive effect (*i.e.*, pain relief in response to an experimental heat pain stimulus) for both S-ketamine and S-norketamine.<sup>4,5</sup>

**Chronic Analgesia Paradigm.** Using pharmacokinetic model parameters (from a study on the effect of ketamine on spontaneous chronic pain relief in patients with complex



regional pain syndrome type 1<sup>6,7</sup>), the effect of rifampicin treatment on chronic analgesia was simulated for different norketamine contributions to effect (0, 10, and 25%). To that end, analgesic effect during and after a 4-day S-ketamine infusion of 5 mg/h on day 1, 10 mg/h on day 2, 15 mg/h on day 3, and 20 mg/h on day 4 was simulated.<sup>6,7</sup> Before the simulations were performed, the pharmacokinetic data obtained in the healthy volunteer population and patients with chronic pain were compared. The differences were sufficiently small (data not shown) to allow the application of a rifampicin effect as observed in our current study to the kinetic data obtained in patients with chronic pain. The pharmacodynamic model was as given above with model parameters: BLN = 7 cm,  $\gamma = 1.9$ , and  $C_{50, \text{ket}} = 10$  ng/ml. The  $C_{50, \text{nkt}}$  was varied in such a way that it contributed 0, 10, and 25% to total analgesic effect. We previously observed that in our group of patients with chronic pain, the effect of ketamine on spontaneous pain relief lasted beyond the duration of treatment.<sup>6,7</sup> In a subgroup of these patients (*i.e.*, those with response to therapy), we estimated an effect half-life ( $t_{1/2k}$ ) of approximately 11 days and used this value in the chronic pain simulations.<sup>7</sup>

## Results

### Subjects

All subjects completed the protocol without unexpected side effects. One subject (in the 20-mg/h ketamine group) failed to return, for unknown reasons, for his second experimental session. The subjects' ages ranged from 20 to 29 yr (mean age, 22.0 yr); body mass index range was from 19 to 28 kg/m<sup>2</sup> (mean, 22.2 kg/m<sup>2</sup>). There were no differences in age or body mass index between treatment groups.

### Descriptive Pharmacokinetic Analysis

In figure 3, the mean S-ketamine and S-norketamine concentrations in plasma after rifampicin and placebo are plotted. Rifampicin decreased S-ketamine concentrations, although the effects were modest in magnitude. The effect of rifampicin was most prominent in the lower S-ketamine infusion group: during the 20-mg/h infusion, rifampicin caused a 17% decrease in  $C_{\text{MAX}}$  ( $P < 0.001$ ) and a 14% decrease in  $\text{AUC}_{0 \rightarrow 300}$  ( $P < 0.001$ ). At double the ketamine infusion dose, rifampicin decreased  $C_{\text{MAX}}$  by 6% (not significant) and  $\text{AUC}_{0 \rightarrow 300}$  by 7% ( $P = 0.02$ ; table 1). S-ketamine time-of-occurrence values remained unaffected by rifampicin (table 1). In contrast, the effects of rifampicin on S-ketamine's metabolite S-norketamine concentrations in plasma were large, with a 44% and 58% decrease in  $C_{\text{MAX}}$  for the infusion of 20 mg/h ( $P = 0.001$ ) and 40 mg/h ( $P < 0.001$ ), respectively, and a 53% and 62% decrease in  $\text{AUC}_{0 \rightarrow 300}$  for the 20-mg/h and 40-mg/h infusions ( $P < 0.001$ ), respectively (table 1, fig. 3). S(+)-norketamine time-of-occurrence values remained unaffected by rifampicin (table 1). The metabolite-to-parent drug  $\text{AUC}_{0 \rightarrow 300}$  ratios

**Table 1.** Effect of Rifampicin on S-ketamine and Norketamine Concentrations:  $C_{\text{MAX}}$ ,  $T_{\text{MAX}}$ , and Area-Under-the-Curve (AUC) Values

	Placebo	Rifampicin	P Value
[S-ketamine] <sub>20</sub> *			
$C_{\text{MAX}}$ (ng/ml)	150.4 ± 3.9	132.6 ± 7.1	< 0.001
$T_{\text{MAX}}$ (min)	114 ± 3	113 ± 4	0.72
$\text{AUC}_{0 \rightarrow 300}$ (ng/ml)	71.5 ± 5.4	60.8 ± 5.1	< 0.001
[S-norketamine] <sub>20</sub> *			
$C_{\text{MAX}}$ (ng/ml)	113.8 ± 5.9	64.5 ± 8.7	0.001
$T_{\text{MAX}}$ (min)	129 ± 2	125 ± 1	0.06
$\text{AUC}_{0 \rightarrow 300}$ (ng/ml)	73.3 ± 8.4	35.5 ± 11.7	< 0.001
$\text{AUC}_M/\text{AUC}_P$	1.03 ± 0.19	0.58 ± 0.19	< 0.001
[S-ketamine] <sub>40</sub> *			
$C_{\text{MAX}}$ (ng/ml)	304.7 ± 17.5	285.6 ± 14	0.27
$T_{\text{MAX}}$ (min)	110 ± 5	113 ± 3	0.51
$\text{AUC}_{0 \rightarrow 300}$ (ng/ml)	142 ± 15.8	132.0 ± 17.4	0.02
[S-norketamine] <sub>40</sub> *			
$C_{\text{MAX}}$ (ng/ml)	198.3 ± 8.1	83.6 ± 6.2	< 0.001
$T_{\text{MAX}}$ (min)	132 ± 2	128 ± 2	0.17
$\text{AUC}_{0 \rightarrow 300}$ (ng/ml)	124.8 ± 18.5	47.9 ± 11.6	< 0.001
$\text{AUC}_M/\text{AUC}_P$	0.90 ± 0.12	0.36 ± 0.10	< 0.001

Values are mean ± SD.

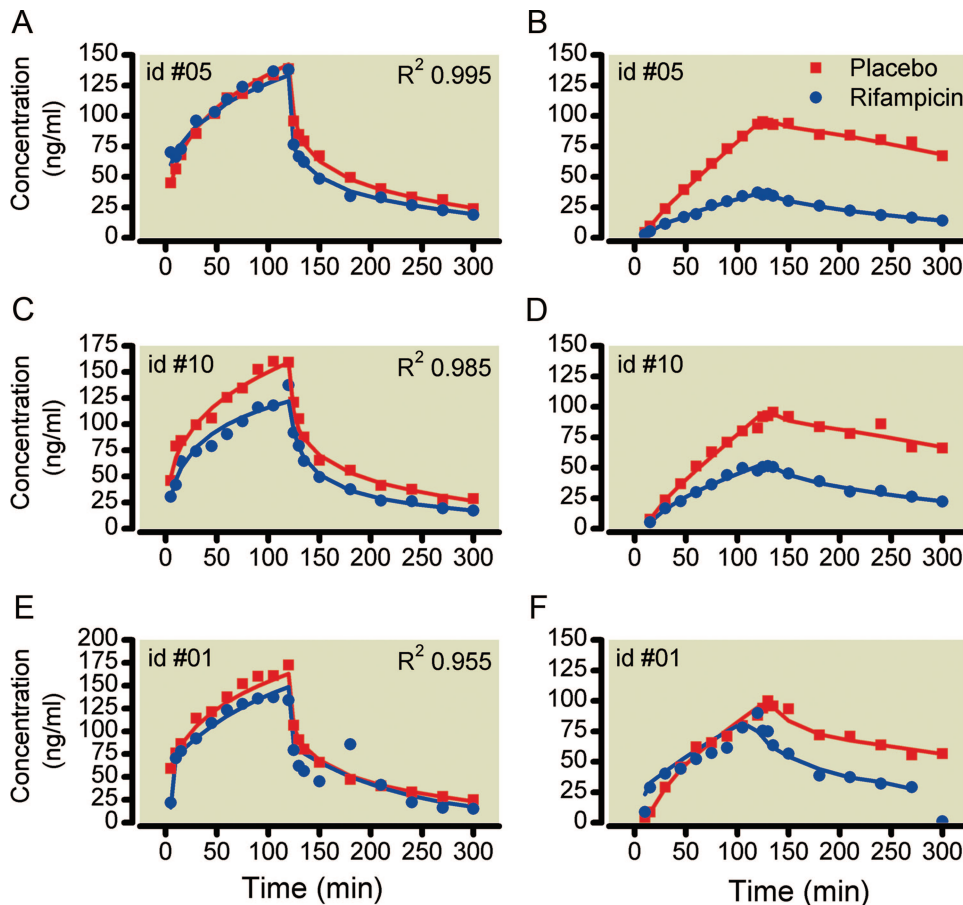
\*<sub>20</sub> and <sub>40</sub> denote data obtained during and after the 2-h infusion of 20 mg/h and 40 mg/h S-ketamine (both per 70 kg), respectively.

$\text{AUC}_M$  = metabolite  $\text{AUC}_{0 \rightarrow 300}$  (S-norketamine);  $\text{AUC}_{0 \rightarrow 300}$  = area-under-the-curve determined for the 300-min study period divided by 300 min;  $\text{AUC}_P$  = parent  $\text{AUC}_{0 \rightarrow 300}$  (S-ketamine);  $C_{\text{MAX}}$  = peak concentration;  $T_{\text{MAX}}$  = time of occurrence of  $C_{\text{MAX}}$ .

( $\text{AUC}_M/\text{AUC}_P$  in table 1) were decreased by approximately 50% by rifampicin compared with placebo, irrespective of the S-ketamine infusion dose.

### Compartmental Pharmacokinetic Analysis

The pharmacokinetic model is given in figure 2. In agreement with a previous observation,<sup>4</sup> extending the three-compartmental model (in which only the ketamine data were modeled) with a part describing the norketamine data did not cause any change in S-ketamine pharmacokinetic parameter values (data not shown). This indicates that adding the metabolism compartments ( $M_{1-3}$  in fig. 2) and the two norketamine compartments did not affect the analysis of ketamine. As judged by the eye, the model adequately described the data. Best, median, and worst data fits, as determined by the coefficient of determination ( $R^2$ ) for the combined S-ketamine/S-norketamine data fits, are given in figure 4; goodness-of-fit plots are given in figure 5 (individual predicted *vs.* measured concentration). Model parameter estimates, together with their 95% CIs, are given in table 2. The pharmacokinetic model parameters were in agreement with previous findings.<sup>4,25-27</sup> Rifampicin affected S-ketamine



**Fig. 4.** Pharmacokinetic data fits of the combined S-ketamine–S-norketamine model. Best S-ketamine and S-norketamine fits of subject 5 (A and B). Median S-ketamine and S-norketamine data fits of subject 10 (C and D). Worst S-ketamine and S-norketamine data fits of subject 1 (E and F). Red symbols and red lines are the placebo data; blue symbols and blue lines are the rifampicin data. Goodness of fit was determined by the coefficient of determination ( $R^2$ ).

elimination (and consequently S-norketamine formation) modestly: clearance from the central compartment ( $V_{1, \text{ket}}$ ) increased by 13% ( $F \text{ Cl}_{1, \text{ket}} = 0.13$  in table 2). In contrast, rifampicin had a much greater effect on S-norketamine elimination: S-norketamine clearance from its central compartment ( $V_{1, \text{nkt}}$ ) increased by approximately 200% ( $F \text{ Cl}_{1, \text{nkt}} = 2.02$  in table 2).

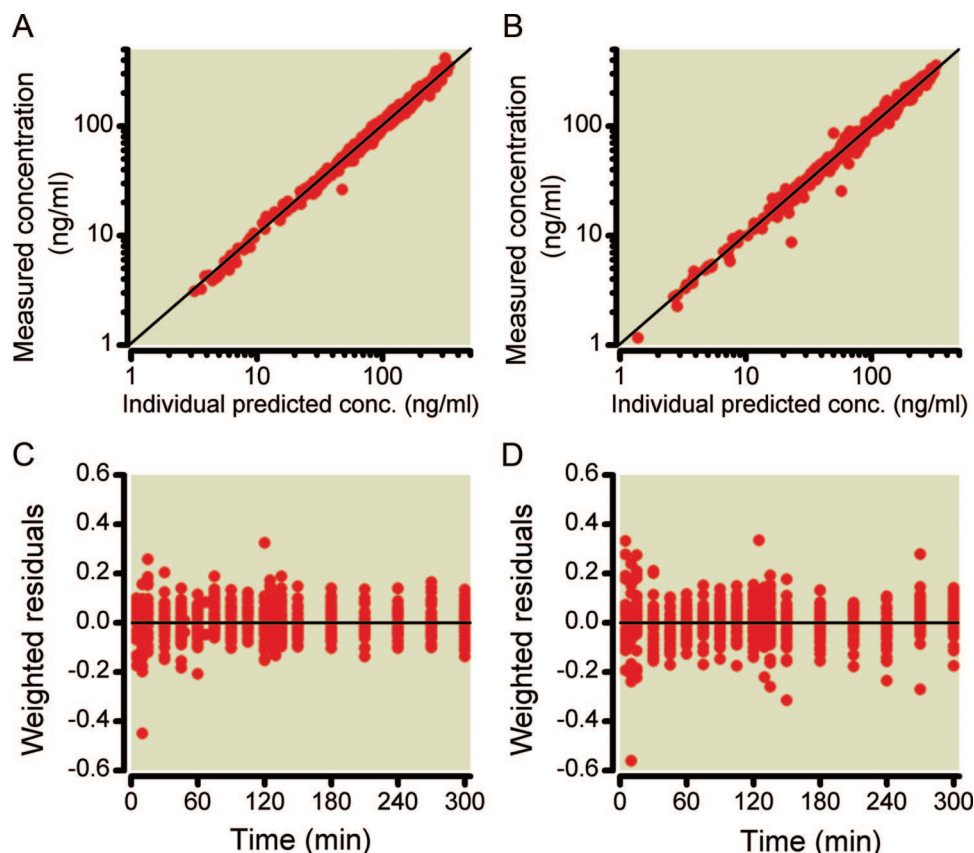
### Side Effects

Side effects were present during ketamine infusion and resolved promptly upon termination of infusion. The highest scores measured during ketamine infusion all occurred at the end of the infusion period and were for drug high:  $6.5 \pm 2.3$  (placebo, low-dose ketamine) versus  $5.5 \pm 3.0$  (rifampicin, low-dose ketamine;  $P > 0.05$ ),  $8.1 \pm 2.0$  (placebo, high-dose ketamine) versus  $7.8 \pm 2.6$  (rifampicin, high-dose ketamine;  $P > 0.05$ ); and for sedation  $3.8 \pm 3.6$  (placebo, low-dose ketamine) versus  $3.8 \pm 2.6$  (rifampicin, low-dose ketamine;  $P > 0.05$ ), and  $5.1 \pm 3.6$  (placebo, high-dose ketamine) versus  $4.5 \pm 3.8$  (rifampicin, high-dose ketamine;  $P > 0.05$ ).

### Simulation Study

**Acute Analgesia Paradigm.** The simulation study was based on the current pharmacokinetic model parameters (table 2) linked to a pharmacodynamic model in which both S-ketamine and S-norketamine contribute to effect. The results of the simulations are shown in figure 6. At increasing norketamine contributions to analgesic effect, peak VAS is reduced by a maximum of 0.7 cm at 25% contribution. At 0, 10, and 25% norketamine contribution, rifampicin treatment causes an increase in peak VAS of 0.3 (5% of peak VAS), 0.4 (10%), and 0.7 cm (21%), respectively (fig. 6).

**Chronic Pain Paradigm.** The study was based on the application of the rifampicin effect to pharmacokinetic and pharmacodynamic data obtained in patients with chronic pain. Thus, the effect of S-ketamine infusion mimics the effect observed in such patients (fig. 7).<sup>19</sup> The effect of rifampicin was relatively small, with maximum increases in VAS of 0.4 (0% norketamine contribution), 0.8 (10%) and 1.3 cm (25%, fig. 7). A biphasic effect of rifampicin on analgesia was observed with an initial peak during infusion (peak on day 2) and a second peak between days 20 and 30, irrespective of the magnitude of the norketamine contribution.



**Fig. 5.** Goodness-of-fits plots: individual predicted data versus measured data for S-ketamine (A) and S-norketamine (B). Weighted residuals ( $(Y_{\text{measured}} - Y_{\text{predicted}})/Y_{\text{predicted}}$ ) versus time for S-ketamine concentrations (C) and S-norketamine concentrations (D).

## Discussion

Rifampicin caused a 10% reduction in S-ketamine plasma concentrations coupled to a 50% reduction in plasma concentrations of ketamine's metabolite S-norketamine. We relate these changes to the induction of S-ketamine and S-norketamine elimination. The compartmental pharmacokinetic analysis indicated a 13% increase in S-ketamine elimination and a 200% increase in S-norketamine elimination.

The significant reduction in norketamine plasma concentrations in rifampin-treated subjects was an unexpected finding. Both norketamine  $C_{\text{MAX}}$  and  $\text{AUC}_{\text{norketamine}}/\text{AUC}_{\text{ketamine}}$  ratio were diminished. Several explanations, not necessarily mutually exclusive, are possible. The first is a diminished rate of norketamine formation. This seems unlikely. CYP2B6 and CYP3A4 are the major human hepatic CYPs catalyzing ketamine *N*-demethylation *in vitro*, although their relative contributions *in vivo* remain unknown.<sup>19,20</sup> At therapeutic substrate concentrations, both the rate and intrinsic clearance of *N*-demethylation to norketamine by CYP2B6 were found to be more than 10-fold greater than by CYP3A4 in two different studies.<sup>19,20</sup> Based on this observation, using individual S(+) and R(−) ketamine enantiomers, Yanagihara *et al.*<sup>19</sup> concluded that CYP2B6 mainly mediates ketamine *N*-demethylation. In contrast, Hijazi *et al.*<sup>20</sup> concluded that CYP3A4 is the pre-

dominant CYP responsible for ketamine *N*-demethylation, which is based in part on the greater hepatic expression of CYP3A4 than CYP2B6. At clinical ketamine concentrations (less than 5  $\mu\text{M}$ ) there is no evidence for the involvement of other important CYPs. At supraclinical ketamine concentrations (50  $\mu\text{M}$ ), other CYP involvement has been described,<sup>28</sup> although CYP2B6 and CYP3A4 are the enzymes with the highest activity at those ketamine concentrations. The clinical involvement of CYP3A4 was supported by the effect of the CYP3A4 inhibitor clarithromycin, which caused a 3.6-fold increase in S-ketamine  $C_{\text{MAX}}$ , whereas norketamine  $C_{\text{MAX}}$  was reduced by 54%.<sup>29</sup> Regardless of the relative contributions of CYP2B6 and CYP3A4 to ketamine *N*-demethylation, because rifampicin (600 mg daily for 5 days) induces the hepatic expression and catalytic activity of CYP2B6 and CYP3A4 several-fold, as well as the clinical metabolism of numerous CYP2B6 and CYP3A4 substrates,<sup>21</sup> induction of ketamine metabolism by rifampicin is expected. Patients treated with long-term barbiturate (another inducer of hepatic CYP enzymes) regimens have lower plasma ketamine concentrations.<sup>30</sup> Together these findings do not suggest that rifampicin inhibits ketamine *N*-demethylation *in vivo*.

Another possible explanation for reduced norketamine concentrations is increased ketamine metabolism *via* an alternate

**Table 2.** Pharmacokinetic Model Parameters of the Combined Ketamine-Norketamine Model

	Estimate	SEM	$\omega^2$	SEM	$\nu^2$	SEM
<b>S(+)-ketamine</b>						
$V_{1, \text{ket}}$ (L)	17.0	1.91	—	—	0.148	0.048
95% CI	13.6–21.0				0.06–0.25	
$V_{2, \text{ket}}$ (L)	28.3	2.97	—	—	—	—
95% CI	23.3–34.1					
$V_{3, \text{ket}}$ (L)	147	10.2	0.065	0.019	0.029	0.020
95% CI	129–172		0.03–0.10		0.00001–0.08	
$Cl_{1, \text{ket}}$ (L/h)	93.5	2.70	0.007	0.004	0.006	0.002
95% CI	87.6–98.8		0.001–0.02		0.002–0.01	
F $Cl_{1, \text{ket}}$ *	0.13	0.03				
95% CI	0.07–0.20					
$Cl_{2, \text{ket}}$ (L/h)	127	12.3	—	—	—	—
95% CI	107–148		—		—	
$Cl_{3, \text{ket}}$ (L/h)	91.9	5.10	0.02	0.006	—	—
95% CI	82–101		0.01–0.03		—	
$\sigma^2$	0.008	0.002				
<b>S(+)-norketamine</b>						
MTT (h)	0.25	0.02	0.05†	0.03†	0.02	0.01
95% CI	0.21–0.28		0.01–0.14		0.004–0.05	
$V_{2, \text{nkt}}$ (L)	193	10.6	—	—	0.14	0.03
95% CI	173–217		—		0.09–0.19	
$Cl_{1, \text{nkt}}$ (L/h)	64.9	2.81	0.03	0.01	0.03	0.01
95% CI	58.5–70.8		0.01–0.06		0.01–0.05	
F $Cl_{1, \text{nkt}}$ *	2.02	0.19				
95% CI	1.67–2.41					
$Cl_{2, \text{nkt}}$ (L/h)	334	30.5	0.05†	0.03†	0.14	0.04
95% CI	285–411		0.01–0.14		0.07–0.22	
$\sigma^2$	0.007	0.001				

Units of the volumes are l/kg at 70 kg; units of the clearances are l/h at 70 kg. Factor F denotes the significant effect of rifampicin treatment on model parameters  $Cl_{1, \text{nkt}}$  and  $Cl_{2, \text{nkt}}$  ( $P < 0.01$ ).

\*  $P < 0.01$ . † One parameter was sufficient for the interindividual error of  $Cl_{2, \text{nkt}}$  and MTT.

$Cl_{1, \text{ket}}$  = clearance from compartment 1, ket;  $Cl_{2, \text{ket}}$  = clearance from compartment 2, ket;  $Cl_{3, \text{ket}}$  = clearance from compartment 3, ket;  $Cl_{1, \text{nkt}}$  = clearance from compartment 1, nkt;  $Cl_{2, \text{nkt}}$  = clearance from compartment 2, nkt; F = factor F; ket = ketamine; MTT = mean transit time; nkt = norketamine;  $V_{1, \text{ket}}$  = volume of compartment 1, ket;  $V_{2, \text{ket}}$  = volume of compartment 2, ket;  $V_{3, \text{ket}}$  = volume of compartment 3, ket;  $V_{2, \text{nkt}}$  = volume of compartment 2, nkt;  $\nu^2$  = interoccasion variability (in the log-domain);  $\omega^2$  = intersubject variability (in the log-domain);  $\sigma^2$  = within-subject variability (in the log domain).

pathway and metabolic switching. Human liver microsomes form 4- and 5-hydroxyketamine.<sup>10</sup> Although ketamine hydroxylation is considered minor compared with *N*-demethylation, the enzymes responsible for ketamine hydroxylation and the effect of rifampin induction are unknown.

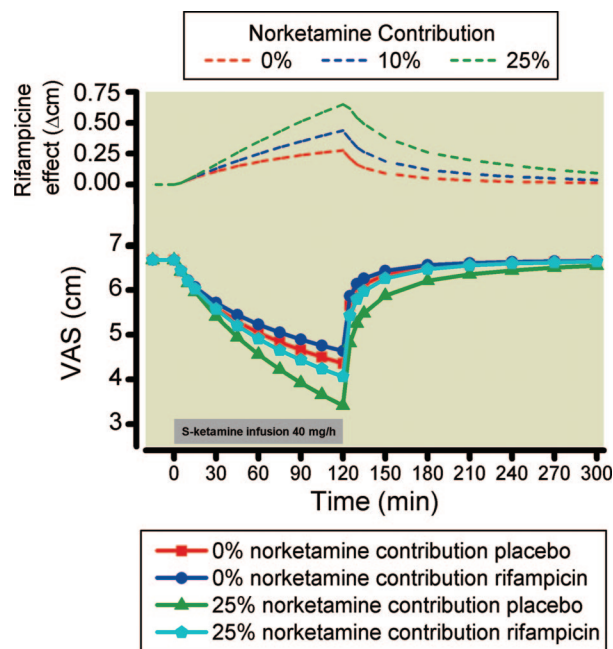
A third potential explanation for rifampicin reduction of plasma norketamine concentrations is increased secondary metabolism of norketamine. The major secondary metabolite is 6-hydroxynorketamine, with lesser formation of 4- and 5-hydroxynorketamine. At clinical ketamine concentrations, the enzymes responsible for norketamine hydroxylation and the effect of rifampin induction are unknown. A recent study performed at supraclinical concentrations (50  $\mu\text{M}$  norketamine) indicates involvement of CYP2B6 and CYP2A6.<sup>28</sup> Our compartmental analysis indicates that this possible mechanism is most likely. Norketamine formation may have increased by 13%, but its elimination was increased by more than 200% (table 2). Assuming that at clinical concentrations norketamine metabolism is predominantly regulated *via* CYP2B6 and CYP2A6 enzymes, it is highly probable that rifampicin caused induction of these enzymes and conse-

quently increased the elimination of S-norketamine and caused the 50% reduction in S-norketamine plasma concentrations we observed (figs. 3 and 4).

Finally, another potential explanation is an effect of hepatic and/or renal drug transporters on ketamine and/or norketamine disposition. In addition to induction of several CYP isoforms, rifampicin is an effective inducer of several drug transporters, including the efflux transporters P-glycoprotein, breast cancer resistance protein, and multidrug resistance proteins 1 and 2, and an inhibitor of the hepatic uptake transporter organic anion-transporting polypeptide.<sup>21,31</sup> Inhibition of hepatic ketamine uptake or induction of efflux might reduce intracellular concentrations and thus the extent of *N*-demethylation, despite an accelerated rate. No information is available on ketamine or norketamine and hepatic drug transport.

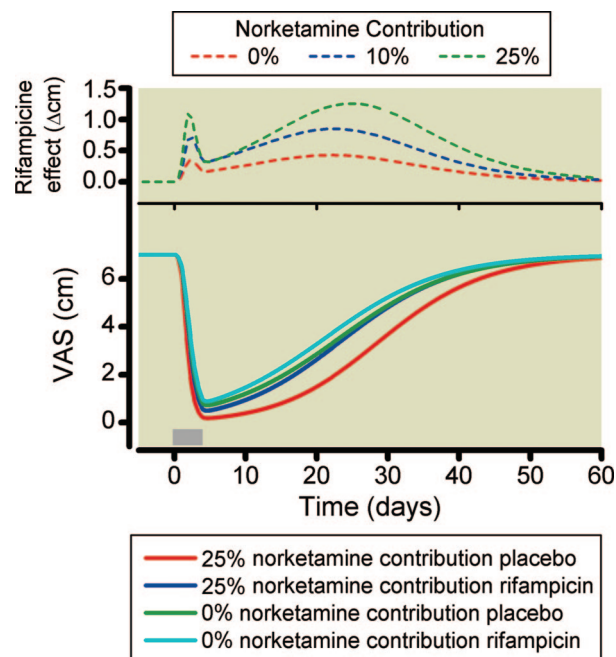
We previously modeled the contribution of norketamine-to-ketamine effect in a study on the effect of a ketamine infusion on acute antinociception using an experimental heat pain model.<sup>4</sup> In that study, we were unable to estimate a contribution of norketamine to ketamine antinociception,





**Fig. 6.** Simulation study for an acute pain paradigm. Simulation studies enable the systematic exploration of inferences made in our study with respect to anticipated norketamine effect size. We performed simulations to estimate the effect of the large change in norketamine concentration and relatively modest change in ketamine concentration that we observed after rifampicin treatment on acute pain relief induced by the 2-h, 40-mg/h ketamine infusion (gray bar). We made *a priori* assumptions with respect to the norketamine contributions to ketamine effect: simulations with 0, 10, and 25% norketamine contribution were made. The difference in effect observed in the simulated pain relief with and without rifampicin treatment will give an indication of the norketamine contribution to effect. The top diagram shows the difference in VAS between placebo and rifampicin data for the three norketamine contributions to effect: 0, 10, and 25%. VAS = visual analog score.

suggesting that, in humans, norketamine is not analgesic. However, because norketamine concentrations were not manipulated, there was considerable uncertainty in the estimation of norketamine contribution to effect. To get an indication of the pharmacodynamic effect of the variations in S-norketamine concentration, we performed a simulation study with acute analgesia as the end point. Animal data show that S-norketamine is a noncompetitive NMDA receptor antagonist in the spinal cord and cortex.<sup>15</sup> Its affinity to the NMDA receptor is weaker than that of S-ketamine, but there seems consensus that, at least in animals, norketamine contributes significantly to the antinociceptive properties of ketamine (up to 30%), irrespective of whether the S(+)-isomer or the racemic mixture is tested.<sup>14,15,17,18</sup> Extrapolating the animal data to our simulations, we assumed that S-norketamine contributed to overall analgesic effect in a range of from 0 to 25%. Our simulation indicates that rifampicin caused a reduction in acute pain responses, with a maximum in effect in VAS increase of less than 1 cm (fig. 6). Part



**Fig. 7.** Simulation study for a chronic pain paradigm. We performed simulations to estimate the effect of the large change in norketamine concentration and relatively modest change in ketamine concentration that we observed after rifampicin treatment on chronic pain relief. Induced by a 4-day intravenous ketamine infusion (gray bar: day 1 = 5 mg/h; day 2 = 10 mg/h; day 3 = 15 mg/h; and day 4 = 20 mg/h). Simulations with 0, 10, and 25% norketamine contribution were made. The difference in effect observed in the simulated pain relief with and without rifampicin treatment will give an estimate of the norketamine contribution to effect. The top diagram shows the difference in VAS between placebo and rifampicin data for the three norketamine contributions to effect: 0, 10, and 25%. VAS = visual analog score.

of this effect is attributed to changes in S-ketamine concentration (7%), whereas the remainder is related to the changes in the concentration of S-norketamine (up to 16%). In actual practice, such an effect is small and may not be clinically detectable or important. Thus, this suggests that the dose of ketamine for treatment of acute pain in patients receiving rifampicin needs little or no adjustment.

We infused S-ketamine for 2 h and observed an  $AUC_M/AUC_P$  ratio of approximately 1 after placebo treatment (table 1). Similar ratios are observed after long-term intravenous S-ketamine infusion in patients with chronic pain.<sup>6</sup> Our simulation study revealed only a relatively small effect of variations in norketamine concentration on analgesia in patients with chronic pain (maximum increase in VAS = 1.3 cm, fig. 7). However, a prolonged exposure to norketamine may cause a greater passage of the drug into the central nervous system than occurred during our short-term infusion, and this may then increase its contribution to ketamine's pharmacodynamics.<sup>18</sup> Thus, we may have underestimated the norketamine effect in our estimation of analgesia from S-ketamine in patients with chronic pain. In addition, the

route of administration may play a role in norketamine's contribution to effect. For example, after oral and sublingual ketamine administration, the concentration S-norketamine exceeds that of S-ketamine because of the first-pass effect in the liver and enterocytes.<sup>27</sup> These higher concentrations may increase norketamine's bioavailability to the brain compartment, with a corresponding increase in contribution to ketamine's analgesic effect. Additional studies are needed to assess the effect of the induction of CYP enzymes on norketamine's contribution to ketamine-induced analgesia.

The two simulation studies we performed used different values for effect half-life (no delay for acute pain and a  $t_{1/2k}$  of 11 days for chronic pain relief). The absence of a delay for acute pain is derived from various studies on the acute effects of ketamine (measuring ketamine-induced electroencephalographic changes, arousal, and recall during anesthesia and acute pain relief)<sup>4,5,32,33</sup> and suggests a rapid passage of ketamine across the blood–brain barrier. The equilibration half-life ( $t_{1/2k}$ ) of 11 days used in the chronic pain study is not a blood–effect site equilibration constant but rather a disease modulatory factor. Various studies indicate that ketamine produces long-term analgesic effects beyond the treatment period, with a half-life of many days.<sup>5–9</sup> We recently estimated a value for  $t_{1/2k}$  of approximately 11 days in patients with chronic pain associated with complex regional pain syndrome type 1.<sup>7</sup> Side effects in patients with chronic pain treated with ketamine still show a rapid onset and offset, suggesting that the drug rapidly crosses the blood–brain barrier and that the persistent analgesia observed is unrelated to the brain ketamine concentration.<sup>5,6</sup> We recently argued that ketamine initiates a cascade of events (of which NMDA receptor antagonism is a first step) resulting in persistent analgesia.<sup>34</sup>

In conclusion, using rifampicin as an inducer of specific CYP enzymes, we observed that rifampicin induces the elimination of S-ketamine's metabolite, S-norketamine, probably *via* induction of the CYP3A4, CYP2B6, and/or CYP2A6 enzymes.

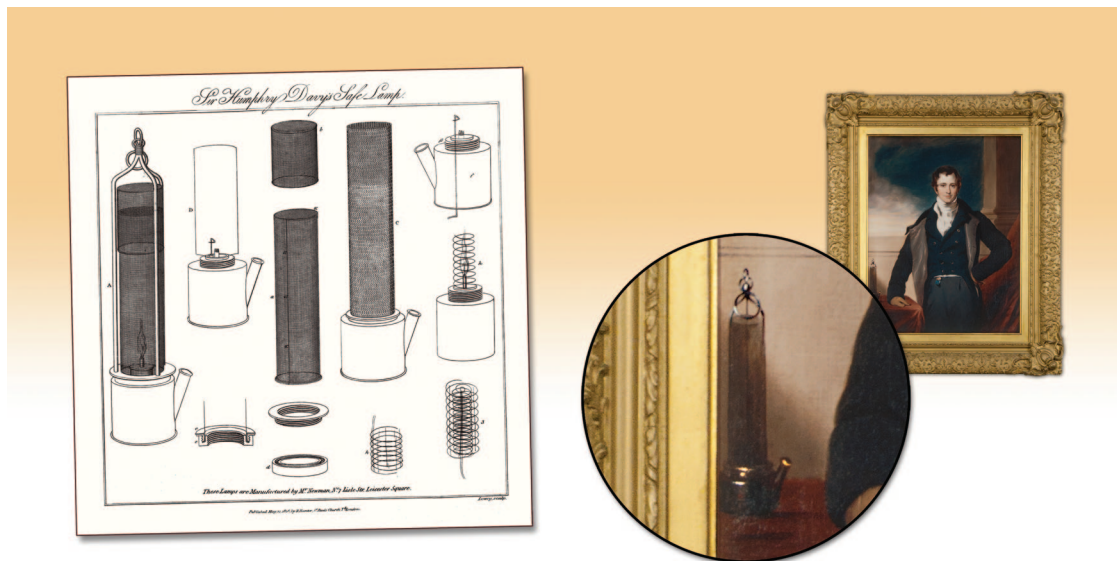
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## ANESTHESIOLOGY REFLECTIONS

### The Davy Safety Lamp and “Miner’s Lung”



Titled “Sir Humphry Davy’s Safe Lamp,” this diagram (*left*) was published on May 21, 1818, from St. Paul’s Church Yard, London by “R. Hunter.” A painted version of that lamp (*middle*) also appears in the lower left corner of this issue’s cover portrait of Sir Humphry Davy. These Davy safety lamps replaced miners’ canaries for detecting asphyxial and/or flammable gases in the mines—without igniting explosions of methane. Because of such safety lamps, miners were able to spend more years laboring underground. So, the safety of the Davy lamp contributed, ironically, to an increase in deaths from an occupational disease later known as “miner’s lung.” (Copyright © the American Society of Anesthesiologists, Inc. This image also appears in the *Anesthesiology Reflections* online collection available at [www.anesthesiology.org](http://www.anesthesiology.org).)

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