Respiratory Depression by Tramadol in the Cat

Involvement of Opioid Receptors

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Background: Tramadol hydrochloride (tramadol) is a synthetic opioid analgesic with a relatively weak affinity at opioid receptors. At analgesic doses, tramadol seems to cause little or no respiratory depression in humans, although there are some conflicting data. The aim of this study was to examine whether tramadol causes dose-dependent inhibitory effects on the ventilatory carbon dioxide response curve and whether these are reversible or can be prevented by naloxone.

Methods: Experiments were performed in cats under α-chloralose–urethane anesthesia. The effects of tramadol and naloxone were studied by applying square-wave changes in end-tidal pressure of carbon dioxide ($P_{ET}CO_2$; 7.5–11 mmHg) and by analyzing the dynamic ventilatory responses using a two-compartment model with a fast peripheral and a slow central component, characterized by a time constant, carbon dioxide sensitivity, time delay, and a single offset (apneic threshold).

Results: In five animals 1, 2, and 4 mg/kg tramadol (intravenous) increased the apneic threshold (control: 28.3 ± 4.8 mmHg [mean ± SD]; after 4 mg/kg: 36.7 ± 7.1 mmHg; $P < 0.05$) and decreased the total carbon dioxide sensitivity (control: 109.3 ± 41.3 ml · min^{-1} · mmHg^{-1}) by 31, 59, and 68%, respectively, caused by proportional equal reductions in sensitivities of the peripheral and central chemoreflex loops. Naloxone (0.1 mg/kg, intravenous) completely reversed these effects. In five other cats, 4 mg/kg tramadol caused an approximately 70% ventilatory depression at a fixed $P_{ET}CO_2$ of 45 mmHg that was already achieved after 15 min. A third group of five animals received the same dose of tramadol after pretreatment with naloxone. At a fixed $P_{ET}CO_2$ of 45 mmHg, naloxone prevented more than 50% of the expected ventilatory depression in these animals.

Conclusions: Because naloxone completely reversed the inhibiting effects of tramadol on ventilatory control and it prevented more than 50% of the respiratory depression after a single dose of tramadol, the authors conclude that this analgesic causes respiratory depression that is mainly mediated by opioid receptors.

A MAJOR adverse effect of opioid analgesics is respiratory depression that is probably mediated by an effect on μ-opioid receptors.[1–3] The analgesic effect of the centrally acting synthetic opioid tramadol is thought to be mediated through both an action on μ-opioid receptors and the inhibition of the reuptake of monoamines and/or stimulation of their release.[4–7] The affinity, however, of tramadol at μ-opioid receptors is much lower ($> 6{,}000$ times) than that of morphine,[6–8] and this makes it a potentially interesting analgesic with minimal respira-

tory depression. Several clinical studies have reported the absence of a significant respiratory depression by an analgesic dose of tramadol.[9–16] Some other studies, however, indicate that under some circumstances, tramadol may cause respiratory depression.[17,18]

A frequently used method to assess the effects of agents on breathing is to measure respiratory frequency, tidal volume, and/or oxygen saturation. A more sensitive method, however, to asses ventilatory control is the ventilatory carbon dioxide response curve because by measuring carbon dioxide sensitivity and the apneic threshold (extrapolated x-intercept of the response curve), it is possible to anticipate a patient's ability to respond to sudden hypercapnic or hypoxic loads, *e.g.*, following an obstructive apnea. Few studies have used the carbon dioxide response to assess tramadol's effect on breathing. In patients without cardiorespiratory disease, Seitz *et al.*[19] found a dose-dependent decrease in carbon dioxide sensitivity and mouth occlusion pressure response after intravenous doses of 1 and 1.5 mg/kg, respectively. Using the technique of end-tidal carbon dioxide forcing, we recently found that in healthy volunteers, 100 mg oral tramadol reduced the carbon dioxide sensitivity of the peripheral and central chemoreflex loops by approximately 30%, an effect that is similar to that of an approximately equal analgesic dose of morphine.[20]

Thus, it seems that tramadol, at clinical doses, may be able to cause respiratory depression. Whether this depressant effect is mediated by opioid and/or monoaminergic mechanisms is unknown. The aim of the current study was to examine whether tramadol can cause a dose-dependent respiratory depression in the anesthetized cat. Furthermore, to investigate a possible opioid mechanism of action, we investigated whether naloxone could reverse and prevent a possible respiratory depression by tramadol.

Materials and Methods

The experiments were performed after approval of the protocol by the Ethical Committee for Animal Experiments of the Leiden University Medical Center (Leiden, The Netherlands). Fifteen cats of either sex (body weight, 2.6–5.0 kg) were sedated with 10 mg/kg ketamine hydrochloride (intramuscular). The animals were anesthetized with gas containing 0.7–1.4% sevoflurane and 30% O_2 in N_2. The right femoral vein and artery were cannulated, 20-mg/kg α-chloralose and 100 mg/kg ure-

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thane were slowly administered intravenously, and the volatile anesthetic was withdrawn. Approximately 1 h later, an infusion of an α-chloralose–urethane solution was started at a rate of 1.0–1.5 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} α-chloralose and 5.0–7.5 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} urethane. This regimen leads to conditions in which the level of anaesthesia is sufficient to suppress pain withdrawal reflexes but light enough to preserve the corneal reflex. The stability of the ventilatory parameters was studied on a previous occasion, and they were found to be similar to those in awake animals, as indicated by the fact that they were stable over a period of at least 6 h.[21-23]

To measure inspiratory and expiratory flow, the trachea was cannulated and connected *via* a Fleisch No. 0 transducer (Fleisch, Lausanne, Switzerland), which was connected to a differential pressure transducer (Statham PM197, Los Angeles, CA). With the aid of three computer-steered mass flow controllers (Hi-Tec, Veenendaal, The Netherlands), a prescribed composition of the inspirate from pure oxygen, carbon dioxide, and nitrogen could be obtained. The inspiratory and expiratory fractions of oxygen and carbon dioxide were measured with a Datex Multicap gas monitor (Datex-Engstrom, Helsinki, Finland). Rectal temperature was controlled within 1°C in each cat and ranged between cats from 36.5 to 38.5°C. Femoral arterial pressure was measured with a strain gauge transducer (Statham P23aC). All signals were recorded on polygraphs, converted to digital values (sample frequency = 100 Hz), and processed by a PC. All signals were stored on a breath-by-breath basis.

Study Design

Two protocols were performed in 15 animals altogether. In protocol I, the dose dependency of the tramadol effect and its reversibility by naloxone were studied in five animals (group 1). Two consecutive doses of 1 mg/kg followed by a final dose of 2 mg/kg were administered. The time interval between doses was approximately 50 min. After each dose, 2 or 3 dynamic end-tidal forcing (DEF) runs were performed at 15, 30, and 45 min after the bolus to analyze the effects on respiratory control (see data analysis). Finally, 0.1 mg/kg naloxone was given, after which two further DEF runs were performed.

Protocol II included two groups of five animals each. In a reversal group (group 2), we assessed the remaining effect of tramadol after opioid receptor block with naloxone. In this group, 35 min after an initial treatment with 0.1 mg/kg naloxone, a single dose of 4 mg/kg tramadol was infused as a bolus. In the five animals of a treatment group (group 3), the same tramadol dose was applied, but without any pretreatment with naloxone. In both groups, respiratory effects during 2 h following drug administration were analyzed by performing DEF runs every 15 min.

Dynamic End-Tidal Forcing

The ventilatory response to carbon dioxide was studied with the DEF technique. We applied the DEF technique by imposing stepwise changes in the end-tidal carbon dioxide tensions at a constant normoxic background (end-tidal pressure of oxygen [P_{ETO_2}] of approximately 105 mmHg). Each DEF run started with a steady state period of approximately 2 min, during which the end-tidal partial pressure of carbon dioxide (P_{CO_2}) was maintained approximately 4 mmHg above the resting value. Thereafter, the end-tidal pressure of carbon dioxide (P_{ETCO_2}) was elevated by approximately 7.5–11 mmHg within one or two breaths, maintained at a constant level for approximately 7 min, and then lowered to the previous value and kept constant for a further 7 min. Generally, within animals, DEF runs were not performed at the same baseline P_{CO_2}. To avoid irregular breathing at P_{CO_2} values close to the apneic threshold, we adjusted the baseline P_{CO_2} at a level approximately 5–7 mmHg higher than the apneic threshold during a given experimental condition (*i.e.*, control and after each drug infusion). Thus, because tramadol appeared to cause increases in the apneic threshold, it was necessary to increase the baseline P_{CO_2} in the course of individual experiments (see for example fig. 1, in which the baseline P_{CO_2} was increased after both tramadol infusions but decreased after naloxone, which induced a large decrease in apneic threshold).

Data Analysis

The steady state relation between inspiratory ventilation $\dot{V}_I$ and P_{ETCO_2} at constant P_{ETO_2} can be described by the following[24,25]:

$$\dot{V}_I = (G_P + G_c)(P_{ETCO_2} - B)$$

where G_P is the carbon dioxide sensitivity of the peripheral chemoreflex loop, G_c is the carbon dioxide sensitivity of the central chemoreflex loop, and B is the apneic threshold or extrapolated P_{ETCO_2} at zero $\dot{V}_I$. The sum of G_P and G_c is the overall carbon dioxide sensitivity.

For the analysis of the dynamic response of ventilation to a stepwise change in P_{ETCO_2}, we used a two-compartment model[25]:

$$\dot{V}_p(t) + \tau_p \, d/dt \, \dot{V}_p(t) = G_P(P_{ETCO_2}[t - T_P] - B)$$

$$\dot{V}_c(t) + \tau_c \, d/dt \, \dot{V}_c(t) = G_c(P_{ETCO_2}[t - T_c] - B)$$

where τ_P and τ_c are the time constants of the peripheral and central chemoreflex loops, respectively; $\dot{V}_p(t)$ and $\dot{V}_C(t)$ are the outputs of the peripheral and central chemoreflex loops, respectively; P_{ETCO_2} [$t - T_P$] is the stimulus to the peripheral chemoreflex loop delayed by the peripheral transport delay time (T_P); and P_{ETCO_2} [$t - T_c$] is the stimulus to the central chemoreflex loop delayed by the central transport delay time (T_C).
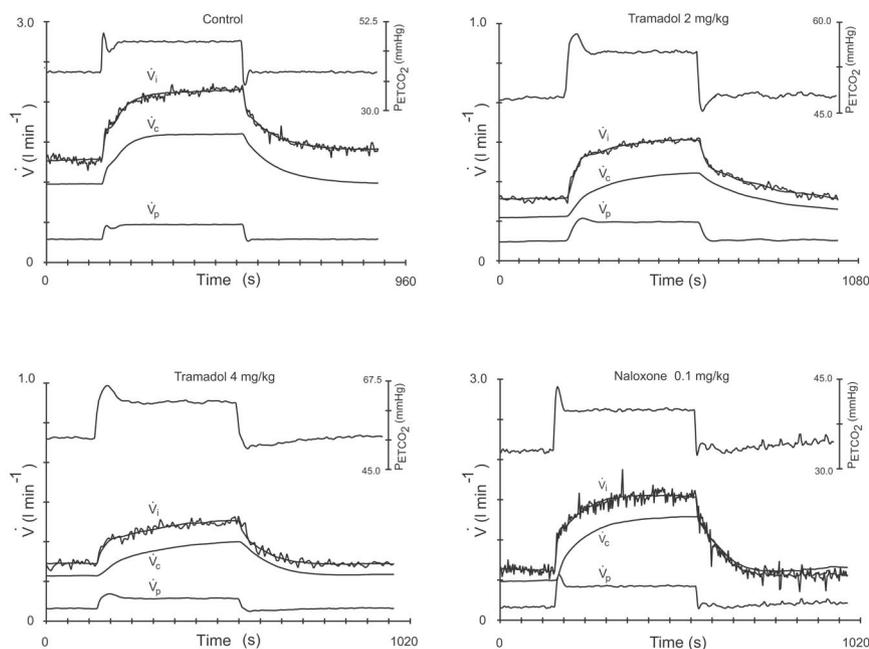
Fig. 1. Examples of dynamic end-tidal forcing (DEF) runs in one animal from group 1 showing the effects of 2 and 4 mg/kg tramadol and the total reversal of tramadol's effect by the infusion of 0.1 mg/kg naloxone. The top diagram in each panel is the end-tidal pressure of carbon dioxide (P_{ETCO_2}) input function. The line through the $\dot{V}_I$ (= total inspiratory minute ventilation) data is the sum of $\dot{V}_P$, $\dot{V}_C$, and a trend term. The $\dot{V}_P$ and $\dot{V}_C$ are the estimated outputs of the central and peripheral chemoreflex loops, respectively.

To allow the time constant of the ventilatory on transient to be different from that of the off transient, τ_c is written as:

$$\tau_c = x\tau_{on} + (1 - x)\tau_{off}$$

where τ_{on} is the time constant of the ventilatory on transient, τ_{off} is the time constant of the off transient, and $x = 1$ when P_{ETCO_2} is high, while $x = 0$ when P_{ETCO_2} is low.

It is our experience that in some animals, a small drift in ventilation may be present. We therefore included a trend term (Ct) in our model. The total ventilatory response $\dot{V}_I(t)$ is made up of the contributions of the central and peripheral chemoreflex loops and Ct:

$$\dot{V}_I(t) = \dot{V}_p(t) + \dot{V}_c(t) + Ct$$

The parameters of the model were estimated by fitting the model to the breath-by-breath data with a least-squares method. To obtain optimal time delays, a grid search was applied, and all combinations of T_P and T_c, with increments of 1 s and with $T_c \geq T_p$ were tried until a minimum in the residual sum of squares was obtained. The minimum time delay was chosen, arbitrarily, to be 1 s; the τ_P was constrained to be at least 0.3 s.

Statistical Analysis

Results are presented as mean of the means per cat ± SD. Differences between the obtained parameters in the control condition and after the three different doses of tramadol and after naloxone, respectively (group 1), were analyzed by performing a two-way analysis of variance using a fixed model. The level of significance was set at 0.013 (Bonferroni correction). Control and naloxone data in group 2 and control and tramadol data in group 3 were compared with paired *t* tests with the level of significance set at 0.05.

Results

Examples of individual DEF runs in one animal from group 1 are shown in figure 1. In this example, 2 and 4 mg/kg tramadol reduced the carbon dioxide sensitivities of the peripheral and central chemoreflex loops and increased the apneic threshold, indicating depressant effects on ventilatory output. The last panel in figure 1 shows that after infusion of 0.1 mg/kg naloxone, these inhibiting effects were completely reversed. The results in all animals from group 1 are summarized in table 1. The total (= peripheral + central) carbon dioxide sensitivity in these animals (control value: 89.3 ± 36.0 ml · min^{-1} · mmHg^{-1}) was reduced by 31, 59, and 68% by 1, 2, and 4 mg/kg tramadol, respectively, and these effects were caused by proportionally equal reductions in sensitivities of the peripheral and central chemoreflex loops (see unchanged G_p/G_c ratios in table 1). Also in a dose-dependent way, the apneic threshold increased from 28.3 ± 4.8 mmHg in the control situation to 36.7 ± 7.1 mmHg after the highest dose (*P* values in legends of table 1). The lung-to-chemoreceptor time delays and time constants were not influenced by both agents (data not shown). After each tramadol dose, we calculated the minute ventilation at a fixed end-tidal P_{CO_2} of 45 mmHg using the values for the slope (G_{tot}) and intercept (B) of the ventilatory carbon dioxide response curve obtained from the optimal curve fittings using the formula: $\dot{V}_I = (G_p + G_c)(P_{ETCO_2} - B)$. Figure 2 displays the dose-dependent ventilatory depression, calculated as $V_{I,TRAMADOL}/V_{I,CONTROL}$ at this P_{CO_2} level in the animals of group 1. The

Table 1. Dose-dependent Respiratory Effects of Tramadol and Reversal by Naloxone

	Control	1 mg/kg Tramadol	2 mg/kg Tramadol	4 mg/kg Tramadol	0.1 mg/kg Naloxone
Number of DEF runs	26	15	14	14	10
G_c, $ml \cdot min^{-1} \cdot mmHg^{-1}$	89.3 ± 36.0	60.0 ± 32.0	37.3 ± 22.7	28.0 ± 17.3	92.0 ± 17.3*
G_p, $ml \cdot min^{-1} \cdot mmHg^{-1}$	20.0 ± 5.0	14.6 ± 6.7*	6.7 ± 4.0	6.7 ± 4.0	24.0 ± 10.6*
G_{total}, $ml \cdot min^{-1} \cdot mmHg^{-1}$	109.3 ± 41.3	74.7 ± 38.7	45.3 ± 26.6	36.0 ± 21.3	114.7 ± 24.0*
G_p/G_c	0.27 ± 0.10	0.27 ± 0.06*	0.21 ± 0.07*	0.28 ± 0.10*	0.26 ± 0.09*
B, mmHg	28.3 ± 4.8	30.8 ± 6.56	32.3 ± 5.7	36.7 ± 7.1	25.8 ± 6.1*
ABP, mmHg	134.3 ± 18.0	136.5 ± 12.8*	131.3 ± 12.8*	125.3 ± 14.3*	129.8 ± 30.8*
V_I 45 mmHg, l/min	1.83 ± 0.95	1.05 ± 0.72	0.54 ± 0.42	0.36 ± 0.38	2.16 ± 0.64*

Respiratory variables from five cats (group 1) obtained from the optimal model fits in the control conditions after three cumulative intravenous doses of tramadol and after naloxone; 15, 30, and 45 min after each bolus, dynamic end-tidal forcing (DEF) runs were performed, and the obtained data were averaged. After naloxone, DEF runs were performed 15 and 30 min after administration. Displayed data are mean ± SD, obtained by averaging the mean values of the individual animals.

* Not significantly different from the control value. All other values are significantly different from control ($P < 0.013$).

ABP = arterial blood pressure; B = apneic threshold; G_c = central carbon dioxide sensitivity; G_p = peripheral carbon dioxide sensitivity; $G_{total} = G_p + G_c$; V_I 45 mmHg = calculated minute ventilation at a fixed end-tidal P_{CO_2} of 45 mmHg.

depression by tramadol ranged from approximately 45% after 1 mg/kg (mean $V_{I,TRAMADOL}/V_{I,CONTROL} = 0.55 ± 0.16$) to approximately 84% after the total dose of 4 mg/kg (mean $V_{I,TRAMADOL}/V_{I,CONTROL} = 0.16 ± 0.12$). The last column in table 1 shows the mean results of two DEF runs recorded 15 and 30 min, respectively, after a final administration of 0.1 mg/kg naloxone to the animals of group 1. Control and naloxone parameter values did not differ from each other, indicating a complete reversal by naloxone of the depressant effects induced by tramadol. Neither tramadol nor naloxone caused significant changes in blood pressure (table 1).

Administration of naloxone in the animals of group 2 resulted in modest stimulatory effects on respiratory control. With the exception of the apneic threshold, these effects did not reach significance (table 2—the large standard deviations after naloxone are caused by the fact that naloxone had little effect in three animals but considerable effects in the remaining two cats). Subsequent administration (*i.e.*, 35 min after the initial naloxone infusion) of 4 mg/kg tramadol caused an *immediate* respiratory depression in all five animals, which, 50 min after the naloxone pretreatment, was only approximately 50% of the depression seen in animals that received no naloxone treatment (open and closed symbols in fig. 3). As can be seen in figure 3, the full depressant effect of tramadol developed much more slowly in naloxone-pretreated than in untreated animals. In the latter group of animals (group 3), the full depressant effect (expressed as the ratio $V_{I,TRAMADOL}/V_{I,PRETRAMADOL}$) had already developed 15 min after tramadol administration. In these animals, the bolus infusion of 4 mg/kg caused a depression (calculated at a fixed end-tidal P_{CO_2} of 45 mmHg) by approximately 70% (closed symbols in fig. 3). However, 15 min after tramadol infusion in the naloxone-pretreated animals, ventilation was only depressed by somewhat less than 40% (open symbols in fig. 3). Ventilatory depression in these animals was calculated as $V_{I,TRAMADOL}/V_{I,PRETRAMADOL}$, where $V_{I,PRETRAMADOL}$ rep-
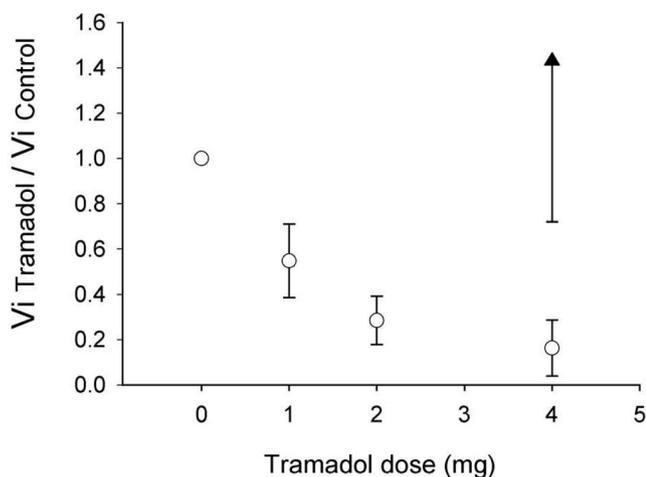
Fig. 2. The dose-dependent decrease in carbon dioxide response under tramadol relative to control extrapolated for the end-tidal carbon dioxide tension of 45 mmHg in five animals (group 1). The triangle depicts the effect of 0.1 mg/kg naloxone given after 4 mg/kg tramadol.

Table 2. Respiratory Effects of Naloxone

	Control	0.1 mg/kg Naloxone
Number of DEF runs	22	10
G_c, $ml \cdot min^{-1} \cdot mmHg^{-1}$	54.7 ± 16.0	76.0 ± 58.0
G_p, $ml \cdot min^{-1} \cdot mmHg^{-1}$	12.0 ± 6.7	13.3 ± 8.0
G_{total}, $ml \cdot min^{-1} \cdot mmHg^{-1}$	66.7 ± 22.7	89.3 ± 65.3
G_p/G_c	0.20 ± 0.08	0.20 ± 0.12
B, mmHg	31.58 ± 3.8	27.2 ± 5.6*
V_I 45 mmHg, l/min	0.94 ± 0.51	1.66 ± 1.37

Effects of 0.1 mg/kg naloxone (intravenous) on mean (± SD) respiratory variables in five cats (group 2). Parameter values after naloxone are the means of two dynamic end-tidal forcing (DEF) runs performed 15 and 30 min after administration, respectively. Displayed data are mean ± SD, obtained by averaging the mean values of the individual animals.

* Significantly different from control ($P < 0.05$).

B = apneic threshold; G_c = central carbon dioxide sensitivity; G_p = peripheral carbon dioxide sensitivity; $G_{total} = G_p + G_c$; V_I 45 mmHg = calculated minute ventilation at a fixed end-tidal P_{CO_2} of 45 mmHg.
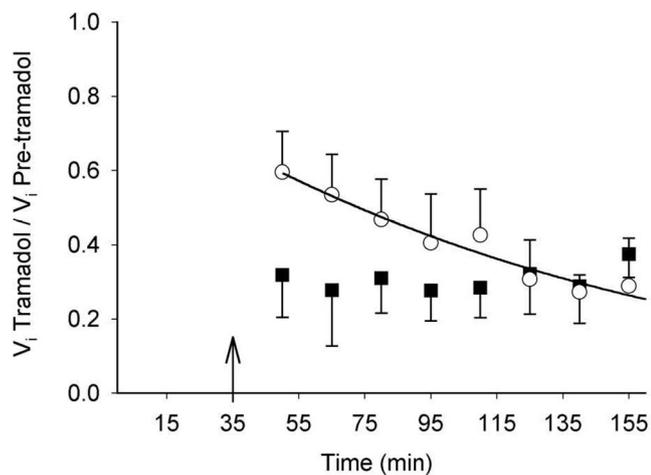
Fig. 3. Effect of naloxone pretreatment on respiratory depression by tramadol. For both curves, respiratory depression under tramadol was calculated as minute ventilation relative to pretramadol at a fixed end-tidal pressure of carbon dioxide ($P_{ET}CO_2$) of 45 mmHg. At the arrow, 4 mg/kg intravenous tramadol was given to animals that were pretreated with 0.1 mg/kg naloxone at time t = 0 (open symbols, group 2; n = 5) or that received no pretreatment at all (closed symbols, group 3; n = 5). The continuous line is an exponential function of time *versus* minute ventilation relative to pretramadol in animals pretreated with naloxone from t = 50 min on. At t = 35 min, the animals of group 2 (open symbols) were treated with tramadol. Mean ± SD values for V_I (in l/min) in these animals at the different time points were as follows: 1.06 ± 0.84 at t = 50 min; 0.78 ± 0.48 at t = 65 min; 0.67 ± 0.41 at t = 80 min; 0.55 ± 0.33 at t = 95 min; 0.37 ± 0.24 at t =110 min; 0.44 ± 0.34 at t = 125 min; 0.57 ± 0.30 at t = 140 min; and 0.56 ± 0.29 at t = 150 min. Mean values for group 3 animals are given in table 3.

resents the calculated minute ventilation between the naloxone and tramadol infusions. The pretramadol data in this time period are given in the naloxone column of table 2 and are the average results of two DEF runs performed 15 and 30 min after naloxone infusion, respectively (both these DEF runs yielded approximately equal results).

Discussion

The novel finding in this study in the anesthetized cat is that in the dose range of 1–4 mg/kg, tramadol caused a dose-dependent depressant effect on ventilatory control, consisting of a decrease in carbon dioxide sensitivity of the peripheral and central chemoreflex loops and an increase in the apneic threshold. In addition, at a dose of 0.1 mg/kg, naloxone completely reversed the depressant effect of a cumulative dose of 4 mg/kg tramadol and prevented more than 50% of the depressant effect of an equal acute tramadol dose, indicating that these depressant effects are largely mediated by an action on opioid receptors.

The reputation of tramadol as an analgesic lacking respiratory depression has contributed to its incremental clinical use in the intraoperative and postoperative periods.[26] The absence, however, of changes in end-tidal or

arterial P_{CO_2} and/or ventilation does not preclude possible depressant effect on ventilatory control. Single respiratory variables, such as respiratory frequency, tidal volume, P_{CO_2}, oxygen saturation, and others, do not represent the output of the respiratory controller and have no predictive value as to a patient's ability to adequately respond to hypercapnia and hypoxia.

Differences in methods and doses may explain why we find much greater depressant effects of tramadol than in most clinical studies. In the latter, effects are often studied in closed-loop conditions in which all feedback signals operate to set the level of minute ventilation and in which the ventilation determines the P_{CO_2}. When in a patient an agent has depressant effects by reducing carbon dioxide sensitivity, ventilation falls and P_{CO_2} rises. The extent, however, to which both parameters change depends on the patient's initial position on the metabolic hyperbola for carbon dioxide. If this position is within the relatively flat region of this hyperbola, any depressant effect is reflected in changes in P_{CO_2} rather than ventilation because changes in the latter parameter will be hardly measurable.[27] Conversely, if the patient's initial condition is on the relatively steep region, minute ventilation, rather than P_{CO_2}, is the predominant parameter that undergoes measurable changes. Thus, single observations on sometimes hardly measurable changes in one of these parameters could easily lead to an underestimation of the agent's respiratory effect, and no information as to possible changes in carbon dioxide sensitivity will be obtained. In an open-loop condition, however, minute ventilation is measured at two (or more) clamped levels of the end-tidal P_{CO_2}. Given the linear ventilatory carbon dioxide response between $P_{ET}CO_2$ values of 3.0 mmHg above the apneic threshold and approximately 75 mmHg, this method provides a means to assess ventilatory carbon dioxide sensitivity and to calculate the ventilation at any P_{CO_2} level (using the obtained values for the slope and intercept of the linear relation).

Our data confirm and extend previous data obtained from humans[20] and show a clear dose-dependent increase in the apneic threshold and decrease in carbon dioxide sensitivity by tramadol. We cannot rule out the possibility that synergism in respiratory effects between the background anesthesia and tramadol also contributed to the magnitude of the effects that we report here. In awake humans, however, we found previously that 100 mg oral tramadol caused an approximately 30% reduction in carbon dioxide sensitivity, an effect that is equal to the depression that we found after 0.1 mg/kg in our anesthetized preparation. Similar tramadol doses in awake humans and anesthetized cats may thus elicit respiratory depressant effects of similar magnitude.

Our finding that the respiratory depressant effect of tramadol could be completely reversed by naloxone contrasts with results obtained in clinical tests in which the opioid

Table 3. Respiratory Effects of a Bolus Infusion of Tramadol

	Control	4 mg/kg Tramadol
Number of DEF runs	22	37
G_c, $ml \cdot min^{-1} \cdot mmHg^{-1}$	78.7 ± 33.3	38.7 ± 14.7*
G_p, $ml \cdot min^{-1} \cdot mmHg^{-1}$	18.7 ± 9.3	6.67 ± 4.0
G_{total}, $ml \cdot min^{-1} \cdot mmHg^{-1}$	97.3 ± 3.3	45.3 ± 16.0*
G_p/G_c	0.27 ± 0.14	0.18 ± 0.13
B, mmHg	31.5 ± 2.8	35.8 ± 3.0*
V_I 45 mmHg, l/min	1.37 ± 0.69	0.42 ± 0.25

Effects of a single intravenous infusion of 4 mg/kg tramadol on respiratory variables in five cats (group 3). After tramadol, dynamic end-tidal forcing (DEF) runs were performed every 15 min during 2 h. Displayed data are mean ± SD, obtained by averaging the mean values of the individual animals.

* Significantly different from control ($P < 0.05$).

B = apneic threshold; G_c = central carbon dioxide sensitivity; G_p = peripheral carbon dioxide sensitivity; $G_{total} = G_p + G_c$; V_I 45 mmHg = calculated minute ventilation at a fixed end-tidal P_{CO_2} of 45 mmHg.

antagonist only partially inhibited tramadol's analgesic effect.[28] In humans, only approximately one third of the antinociceptive action of tramadol, for which the parent compound is probably responsible, can be reversed by naloxone.[29] The α_2-adrenergic antagonist yohimbine, however, greatly reduced the antinociceptive action of 100 mg oral tramadol in healthy volunteers.[29] In most animal tests, tramadol-induced antinociception was only partially reversed by naloxone.[6,30] In contrast, intravenous yohimbine appeared to inhibit the antinociceptive effect of spinally administered tramadol but not morphine on the tail-flick response in the rat.[6] These results led to the hypothesis that the analgesic effect of tramadol is produced both by opioid and nonopioid, *i.e.*, monoaminergic, mechanisms. The opioid effect may be mediated *via* μ receptors because tramadol's affinity at δ and κ receptors is even lower than at the μ receptor.[6,8] Tramadol is a racemic mixture of two enantiomers, and the opioid action is exerted by the (+)-enantiomer and its metabolite *O*-desmethyltramadol (M1), which has a greater affinity at the μ receptor than its parent compound.[6] The monoaminergic mode of action may consist of an inhibition of the reuptake of serotonin and/or noradrenaline. This is mainly caused by the (−)-enantiomer of tramadol and acts synergistically with the analgesic effect of the (+)-enantiomer.[4–8,30,31]

It is unknown whether respiratory depression by tramadol is also mediated *via* both opioid and monoaminergic mechanisms. Our finding that naloxone completely reversed tramadol's depressant effects indicates an important contribution of opioid—probably μ receptors—but does not necessarily imply that these effects were solely due to an opioid mechanism of action: We cannot exclude that part of the relief by naloxone from the tramadol-induced depression was caused by blockade of a tonic inhibitory influence of endogenous opioid peptides on ventilatory control in our animal preparation. For this reason, we tested the effect of naloxone in a separate group of animals (group 2) without any pretreatment with tramadol; subsequently, these animals were given tramadol to see whether a respiratory depression developed. The ventilatory effects seen in these animals were then compared with those seen in animals receiving the same acute dose of tramadol but without being subjected to a pretreatment with naloxone. The finding that naloxone caused a moderate stimulatory effect on ventilatory control (an insignificant increase in carbon dioxide sensitivity and a significant decrease in the apneic threshold of approximately 4.5 mmHg; table 2) indicates a tonic inhibitory influence of endogenous opioid peptides in our animal preparation, which, however, is much too small to account for the very large stimulation (*i.e.*, complete reversal of the large depression after the highest tramadol dose) that was seen in the animals in which the ventilation was greatly depressed by tramadol (table 1). Comparison of the respiratory behavior after tramadol administration between animals with and without naloxone pretreatment (fig. 3) clearly shows that naloxone prevented approximately 50% of tramadol's depressant effect as determined 15 min after the tramadol dose. Despite the naloxone pretreatment in the animals of group 2, tramadol exerted its depressant effect very rapidly in these cats: Respiratory depression was already seen immediately upon the bolus infusion and 15 min after it, the full depressant effect had already developed. We attribute the increasing respiratory depression over time in these naloxone-pretreated animals to a diminishing action of the opioid antagonist, which has a known half-time of approximately 90 min.

The experimental protocol did not include a continuous infusion of naloxone to achieve a complete and constant blockade of all opiate receptors after the infusion of tramadol. Note that approximately 35 min elapsed between the administrations of naloxone and tramadol. Because naloxone has a rather short duration of action, the dose of 0.1 mg/kg may have been too low to guarantee full opioid receptor antagonism that lasted long enough to prevent respiratory depression immediately upon infusion of tramadol. However, the applied dose of naloxone was much higher (approximately 10 times higher) than that usually needed to reverse the effect of high-dose morphine, which exerts its respiratory depressant effect *via* a μ receptor–mediated action.[1] Note also that after cumulative administration, 4 mg/kg tramadol had a larger steady state depressant effect (that was *fully* antagonized by naloxone) than in the animals (including those of group 2) in which the same dose was applied as a bolus (tables 1 and 3 and figs. 2 and 3). The finding that in the latter animals naloxone was unable to prevent an *immediate* ventilatory depression could thus be explained by a possible involvement of receptor systems other than opiate receptors. Altogether, however, while our data clearly indicate a major contribution of opioid receptors in the respiratory depressant effect of tramadol, they do not allow us to draw firm conclusions as to a (small, if any) quantitative involvement of other

receptors. Further studies, *e.g.*, utilizing the α_2-adrenoceptor antagonist yohimbine, are needed to investigate whether similar to its analgesic effect tramadol may also cause respiratory depression through a monoaminergic (α_2 adrenergic) mechanism *via* inhibition of the reuptake of noradrenaline. In the anesthetized cat, α_2-adrenoceptor stimulation by clonidine elicits respiratory depressant effects.[32,33] The effect of serotonin on ventilatory control is more complex and depends on the specific respiratory neuron and type of 5-HT receptor subtype involved.[34]

Because the effect of tramadol on carbon dioxide sensitivity was caused by proportionally equal reductions in the sensitivities of the peripheral and central chemoreflex loops (unchanged ratio G_p/G_c; table 1), we suggest that the agent acts at the respiratory integrating centers within the brain stem, and in this respect, tramadol does not differ from other agents acting at μ receptors. Tramadol, 1 mg/kg, reduces the carbon dioxide sensitivity by approximately 30%, which is approximately equal to the effect of 0.15 mg/kg morphine that we observed previously in the same animal preparation,[35] indicating that in the cat, morphine is 6 to 7 times more potent as a respiratory depressant than tramadol.

Clinical Relevance

Our results may be of clinical relevance, particularly in perioperative situations in which residual anesthetic and opiates (and possibly tramadol, if applicable) may act synergistically to reduce the ability of patients to respond adequately to hypoxic and hypercapnic loads. For example, particular care is required in the management of patients with sleep-disordered breathing, which has a high incidence in the general population. Although we are cautious to extrapolate our findings to men, the facts that in humans, tramadol possesses approximately one sixth to one tenth of the analgesic potency of morphine,[36] an analgesic oral dose of 100 mg in healthy volunteers reduced the carbon dioxide response by approximately 30%,[20] and intravenous doses of 1 and 1.5 mg/kg clearly caused a decrease in carbon dioxide sensitivity[19] indicate that in clinical doses, tramadol may have similar respiratory depressant effects as we report here. Since in humans tramadol is often used in doses higher than 1 mg/kg, it would be worthwhile to assess its possible depressant effect on the ventilatory carbon dioxide response curve and its reversibility by naloxone at these doses. Further studies are also needed to investigate whether anesthetics and tramadol may act synergistically to depress ventilatory output in perioperative situations, which, in that case, may put patients at increased risk during the occurrence of sleep apnea or other events resulting in abnormal blood gas tensions.

In summary, from our data, we conclude that tramadol has a dose-dependent depressant effect on the control of breathing in the anesthetized cat, which is largely, if not completely, mediated by an action on opioid receptors.

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