Influence of oral tramadol on the dynamic ventilatory response to carbon dioxide in healthy volunteers

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We tested the effect of tramadol on ventilatory control by quantifying its effect on the steady-state ventilatory carbon dioxide response and by locating its site of respiratory action within the ventilatory control system. We imposed square-wave changes in end-tidal carbon dioxide (~1 kPa; end-tidal oxygen concentration kept constant at resting levels) in 10 healthy volunteers (six men, four women) before and after oral ingestion of 100 mg tramadol, and measured the ventilatory responses. Each hypercapnic response was separated into a fast, peripheral and a slow, central component. Two control and two tramadol carbon dioxide studies were performed in each subject. Tramadol reduced the total ventilatory carbon dioxide sensitivity by ~30% from 12.8 (6.1) [lower (25%) and upper (75%) quartiles 7.4 and 16.6 litre min⁻¹ kPa⁻¹] to 9.1 (5.3) (5.3–14.1) litre min⁻¹ kPa⁻¹ (P<0.001). The fast and slow response gains were reduced by 23 (46) (3–54)% (P<0.05) and 30 (22) (15–54)% (P<0.01) respectively. The ratio of these carbon dioxide sensitivities and the apnoeic threshold were not significantly changed by tramadol. We suggest that tramadol affects the ventilatory control system by acting at the μ-opioid receptors in the respiratory integrating centres within the brainstem.

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Tramadol is an analgesic with putative opioid and non-opioid modes of action. The respiratory effects of tramadol are not clear: some clinical studies indicate little or no respiratory depression but others find significant respiratory effects. Several case reports suggest that the respiratory depressant effect of tramadol is usually underestimated. These differences could be caused by the different methods used to test ventilatory control, the state of arousal of the subjects or the doses and routes of administration.

We set out to quantify the effect of oral tramadol on ventilatory control in healthy volunteers and to locate its site of action within the ventilatory control system. In order to do so, we used the dynamic end-tidal forcing technique. This technique measures the steady-state ventilatory carbon dioxide sensitivity and also estimates the relative contributions of the peripheral and central chemoreflex gains.

We applied square-wave changes in end-tidal carbon dioxide concentration and divided the ventilatory response (measured on a breath-to-breath basis) into a fast, peripheral dynamic component and a slow, central component, using an empirical two-compartment model of the ventilatory controller. This mathematical model has been validated in cats. It has been used in humans to assess the effect of opioids, anaesthetics and catecholamines on ventilatory control.

Methods

Twelve volunteers (aged 22–56 yr; seven men) participated in the study after approval had been obtained from the local human ethics committee. The subjects were healthy and did not smoke tobacco. Subjects were asked not to take caffeine-containing drinks for 8 h beforehand, and fasted for at least 4 h before the studies. They were studied in a semirecumbent position in a well-lit room and listened to music via headphones.
On the study day, after arrival at the laboratory, electrodes for ECG (Hewlett-Packard 78351A) and EEG electrodes (BisSensor; Aspect Medical Systems, Newton, MA, USA) were placed on the thorax and head respectively. Next, the subjects rested for 10–20 min. The subjects breathed through a facemask (Vital Signs, Totowa, NJ, USA). Expiratory gas flows were measured with a pneumotachograph (Fleisch no. 2) and a pressure transducer (Furness Micromanometer), and the signal was integrated electronically to obtain volume. The inspired gas mixture was set using mass-flow controllers (Bronkhorst High-Tec, Veenendaal, The Netherlands) controlled by a personal computer (Elonex PT-5120/1). This allows the forcing of end-tidal $P_{O_2}$ ($P_{E'O_2}$) and end-tidal $P_{CO_2}$ ($P_{E'CO_2}$) according to a specified pattern in time. The inspired and expired oxygen and carbon dioxide concentrations were measured near the mouth with a mass spectrometer (VG Spectralab M, Winsford, UK) and the arterial haemoglobin oxygen saturation ($S_{PO_2}$) with a pulse oximeter (Ohmeda Biox 3700, Ohmeda, Helsinki, Finland) set to give a rapid response. End-tidal oxygen and carbon dioxide partial pressures, tidal volume, inspiratory time ($Ti$), expiratory time ($Te$), breathing frequency ($f=60/[Ti+Te]$), expired minute ventilation ($V_{e}=f\times VT$) and $S_{PO_2}$ were collected and stored on disk for further analysis.

The EEG was recorded using an A-2000 EEG monitor (Aspect Medical Systems; software version 3.3). The monitor computed the bispectral index (BIS) over 5-s epochs. We averaged the BIS values over 1-min intervals.

Oxygen consumption (litre min$^{-1}$ standard temperature and pressure, dry (STPD) and carbon dioxide output (litre min$^{-1}$ STPD) were measured from collections of mixed expired gas made over a 2-min period, and the gas exchange ratio was calculated. Concentrations of oxygen and carbon dioxide were measured using a Servomex oxygen analyser (model 570A, Servomex, Norwood, MA, USA) calibrated with air and 100% nitrogen, and carbon dioxide with a Datex analyser (Normocap 200, Datex, Helsinki, Finland) calibrated with four calibration gas mixtures.

The experiments consisted of normoxic steps into and out of hypercapnia. After a period of steady-state breathing (assessed by stable ventilation) with $P_{E'CO_2}$ raised 0.1–0.2 kPa above resting values, $P_{E'CO_2}$ was increased by ~1 kPa in a stepwise fashion and kept constant for 7 min. Subsequently, $P_{E'CO_2}$ was returned to its original value and kept constant for another 7 min. During the experiment, $P_{E'O_2}$ was kept constant at resting values. In each subject, two control studies and two tramadol studies were performed. Control runs preceded the drug runs. The drug runs were started 30 min after the subject had taken 100 mg tramadol as two 50 mg tablets (Zydol; Searle). Females were studied within the first 10 days of a normal menses to ensure

![Fig 1](image-url) Control (left) and tramadol (right) ventilatory responses to carbon dioxide of one subject. The $P_{E'CO_2}$ input function is shown in the top panel. In the middle panel, each circle represents one breath. The thick line through the breaths is the model output, which is the sum of the outputs of the peripheral ($V_P$) and central ($V_C$) chemoreflex loops and a trend term (not shown). Estimated control values are $B=4.1$ kPa, $G_P=2.1$ litre min$^{-1}$ kPa$^{-1}$ and $G_C=11.1$ litre min$^{-1}$ kPa$^{-1}$. Estimated tramadol parameter values are $B=4.0$ kPa, $G_P=1.6$ litre min$^{-1}$ kPa$^{-1}$ and $G_C=8.0$ litre min$^{-1}$ kPa$^{-1}$. 
that they were not pregnant and to avoid any effect of progesterone on ventilation.

The data were analysed by fitting the breath-by-breath ventilatory responses to a two-compartment model, as described previously. In short, the steady-state relationship of \( V_E \) to \( P_{E'CO_2} \) at constant \( P_{E'O_2} \) is described by the expression

\[
\hat{V}_E = (G_P + G_C) \left[ P_{E'CO_2} - B \right]
\]

where \( \hat{V}_E \) is minute ventilation, \( G_P \) 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 apnoeic threshold or extrapolated \( P_{E'CO_2} \) of the steady-state ventilatory response to carbon dioxide at zero \( \hat{V}_E \). The sum of \( G_P \) and \( G_C \) is the total carbon dioxide sensitivity (GTOT). To describe the delay in effect and dynamics of the peripheral and central ventilatory responses to carbon dioxide, time delays and time constants are incorporated in the model. The deterministic model parameters are \( B \), \( G_C \), \( G_P \), the time constant of the peripheral chemoreflex loop, the time constant of the central chemoreflex loop and a linear trend term. The noise corrupting the data was modelled through an external pathway with first-order dynamics. The parameters were estimated with a one-step prediction error method.

The estimated parameters of control and tramadol experiments were tested by two-way analysis of variance. \( P \)-values <0.05 were considered significant. All values are given as mean (SD) and the lower (25%) and upper (75%) quartiles.

**Results**

Control of the \( P_{E'CO_2} \) was within 0.18 kPa (i.e. the SD of the breath-by-breath \( P_{E'CO_2} \) of single periods was 0.18 kPa or less). \( P_{E'O_2} \) was controlled within 0.26 kPa. Data from two subjects were discarded because of consistently irregular breathing, which made estimates of the model parameters impossible.

Mean age of the remaining subjects was 33 (7) (29–37) yr, weight 72 (14) (65–78.75) kg and height 170 (11) (160.0–180.75) cm. All subjects finished the measurements without side-effects.

Examples of a control and a tramadol hypercapnic experiment and model fits of one subject are given in Fig.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Estimated model parameters. Mean (SD). *Two-way analysis of variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>( B ) (kPa)</td>
<td>Control: 4.6 (0.8)</td>
</tr>
<tr>
<td>( G_C ) (litre min(^{-1}) kPa(^{-1}))</td>
<td>Control: 10.8 (5.0)</td>
</tr>
<tr>
<td>( G_P ) (litre min(^{-1}) kPa(^{-1}))</td>
<td>Control: 2.0 (1.1)</td>
</tr>
<tr>
<td>( G_{TOT} ) (litre min(^{-1}) kPa(^{-1}))</td>
<td>Control: 12.8 (5.7)</td>
</tr>
<tr>
<td>( G_P/G_C )</td>
<td>Control: 0.19 (0.09)</td>
</tr>
</tbody>
</table>

*Fig 2* Scatter diagrams of the mean values in each subject of the apnoeic threshold (B) (top left), central carbon dioxide sensitivity (\( G_C \)) (top right), peripheral carbon dioxide sensitivity (\( G_P \)) (bottom left) and the ratio \( G_P/G_C \) (bottom right) for control and tramadol experiments. Each subject is represented by the same symbol in all diagrams.
1, which shows decreases in the fast and slow components (Vp and Vc) after tramadol.

The estimated model parameters are collected in Table 1. Tramadol had no effect on the position of the VCO2 response curve relative to the x-axis (parameter B), but reduced the slope of the curve (i.e. the total carbon dioxide sensitivity) by 29 (20) (11–51)%. This was caused by a reduction in central and peripheral carbon dioxide sensitivities, by 30 (22) (15–54)% and 23 (46) (3–54)% respectively. Tramadol did not affect the ratio Gp/Gc. The trend term and the time constants and time delays of both chemoreflex loops were not affected (data not shown). In Fig. 2 the mean values of B, Gp, Gc and Gp/Gc of each subject for the control and tramadol experiments are shown in scatter diagrams.

Carbon dioxide output decreased significantly by a small amount [VCO2, control 0.19 (0.04) (0.15–0.22), tramadol 0.17 (0.04) (0.13–0.21) litre min⁻¹ (P<0.043)]. The oxygen consumption and gas exchange ratio remained unaffected by tramadol [VO2, control 0.22 (0.06) (015–0.26), tramadol 0.21 (0.04) (0.20–0.24) litre min⁻¹ (not significant); gas exchange ratio, control 0.89 (0.18) (0.93–1.03), tramadol 0.82 (0.11) (0.69–0.94) (not significant)].

Tramadol did not affect the arousal level of the subjects as judged by the BIS of the EEG [control 96.2 (0.6) (95.8–96.9), tramadol 94.7 (4.1) (91.3–97) (not significant)].

Two subjects reported side-effects several hours after taking tramadol. One reported dizziness, the other nausea and vomiting.

**Discussion**

We found that an analgesic dose of tramadol depresses respiration in healthy volunteers. Respiratory control was assessed by measuring the ventilatory response to carbon dioxide. The VE−CO2 response curve (i.e. its slope and its position relative to the x-axis) is a sensitive tool to assess the effects of pharmacological agents on ventilatory control and is superior to single measurements of VE, arterial, end-tidal or transcutaneous PCO2. Tramadol reduced the ventilatory carbon dioxide sensitivity by ~30%. This effect could be caused at various sites: the peripheral or central chemoreceptors, the integrating respiratory centres in the brainstem, the neuromechanical link between the brainstem and ventilation (i.e. motor neurone, neuromuscular junction, respiratory muscles and lung tissue) or sites involved in the control of behavioural state. Our approach of using the dynamic end-tidal forcing technique, which allows us to quantify the relative contributions of the peripheral and central chemoreflex loops to total ventilation, in combination with measurement of the bispectral index of the EEG (an objective measure of sedation/hypnosis) during the experiments enabled us to differentiate between these sites and give an approximate location of tramadol’s respiratory sites of actions. Tramadol did not materially affect VO2, VCO2 or BIS, suggesting that tramadol did not depress carbon dioxide sensitivity by a decrease in the metabolic or arousal state of the subjects. An effect at sites common to both chemoreflex loops seems most probable because the outputs of the peripheral and central chemoreflex loops were decreased by about 25–30%. Tramadol probably affected the ventilatory control system by acting at the respiratory integrating centres within the brainstem. In this respect, tramadol does not differ from other agents acting at μ-opioid receptors.

We performed control and drug experiments on one day. For each subject, the order of experiments was the same: first the control and then the tramadol experiment. There are several reasons for this approach. We did not want to perform control and drug experiments on separate days, because day-to-day variability of the ventilatory responses to hypercapnia is more significant than within-day variability. A randomized cross-over study on one day leads to excessively long sessions and discomfort of the subjects. Furthermore, because tramadol is not eliminated completely within a short time, an influence on subsequent control experiments cannot be excluded. Because the differences between treatments could have been small, we opted to use a protocol in which the run-to-run variability was minimal.

Previous studies on the effect of tramadol on ventilatory control give conflicting results, which we relate to the various methods used to measure ventilatory effect and/or to the complexity of protocols. For example, Tarkkila and colleagues and Vickers and colleagues compared the respiratory effects of tramadol with meperidine or morphine on ventilation in anaesthetized patients breathing 0.3–1% halothane in 70% nitrous oxide before elective surgery. While meperidine and morphine caused significant respiratory depression, as observed by an increase in end-tidal PCO2, and decreases in minute ventilation and respiratory rate, i.v. tramadol seemed devoid of respiratory effects or had only a minor effect on respiratory rate. Such studies are hard to interpret, taking into account the respiratory effects of halothane (depression of peripheral and central carbon dioxide responses) and nitrous oxide, which can stimulate ventilatory control, probably as a result of its sympathicomimetic properties. Interaction of these agents with the opioid and non-opioid actions of tramadol cannot be excluded.

Our observations support those of Seitz and colleagues, who found that the VE−CO2 response was depressed dose-dependently by 15–25% by tramadol 1 and 1.5 mg kg⁻¹ i.v. in healthy awake volunteers. Warren and colleagues tested the effect of oral tramadol on the ventilatory response to short-term (7 min) hypoxia against the background of mild isohypercapnia. Whereas hypercapnic ventilation was reduced, an observation in agreement with our findings, tramadol had no effect on the hypoxic VE response. This is surprising in view of our present observation of a depressant effect of tramadol on respiration, which is probably located in the respiratory integrating centres. The ventilatory
response to hypoxia is biphasic: an initial hyperventilatory response, originating in the carotid bodies, is followed after 3–5 min by a slow decline, which originates centrally (i.e. within the central nervous system).22 The mechanism of this respiratory effect of central hypoxia remains unknown but may involve various neurmodulators. Tramadol may have reduced central hypoxic depression by its non-opioid modes of action, such as central serotonin release (see below), and thus offset the depression of the acute hypoxic response.

Tramadol and the O-desmethyltramadol metabolite of its (+) enantiomer produce analgesia by an agonistic effect on the μ-opioid receptor.23 However, the antinociceptive effect of tramadol in the rat hotplate test is only partially antagonized by naloxone, and activation of opioid receptors appears to be responsible for only 50% of tramadol’s analgesic effect.1 The remainder of its analgesic action may be by inhibition of norepinephrine and serotonin reuptake and by facilitation of serotonin release in descending neural antinociceptive pathways.1,24 The molecular mechanisms of the respiratory effects of tramadol remain unknown. Whereas the activation of the μ-opioid receptor is associated with respiratory depression,25 the effects of monoamines on respiration are less evident.26–28 Central release of serotonin may depress as well as stimulate breathing, depending on the type of respiratory neurone and 5-HT receptor subtype involved.26 Most studies indicate that central release of norepinephrine causes respiratory depression.27 To determine the relative effect of the μ-opioid receptor in tramadol-induced respiratory depression, Teppema and colleagues determined the ability of naloxone to reverse the depression by tramadol of the V̇E–CO₂ response in an anaesthetized cat model.29 Respiratory depression by tramadol was reduced by 70–80% after naloxone pretreatment, suggesting that at least 70% of tramadol’s respiratory effect is related to its action at opioid receptors, while the remainder could be by inhibition of serotonin and norepinephrine reuptake.

Respiration in perioperative patients is related to the balance between stimulation from pain, stress and activated chemoreflexes and depression resulting from sedation and the direct effect of analgesics and anaesthetics on respiratory neurones.30 Our subjects were free of pain or surgical stress, which should be considered before extrapolating our findings to perioperative patients. The respiratory effects in the present study may have been overestimated. The effect observed in this study is equivalent to that found after morphine 0.13 mg kg⁻¹ i.v. in healthy volunteers without pain.12

In conclusion, tramadol reduces the hypercapnic ventilatory response. This depression probably acts through the respiratory integrating centres within the brainstem.

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