Interaction of extradural morphine and lignocaine on ventilatory response

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Summary

We have evaluated the effects of lumbar extradural morphine and lignocaine on the ventilatory response to carbon dioxide. Twenty-four female patients were allocated randomly to receive extradural morphine 2 mg (group M), 2 % lignocaine 10 ml (group L) or a combination of morphine 2 mg and 2 % lignocaine 10 ml (group ML). On the day before surgery, resting ventilatory values including minute volume (VE) and tidal volume. (VT), and ventilatory response to progressive hyperoxic hypercapnia (VE/PECO2) were measured. On the day of surgery, the same measurements were repeated 30 min after extradural injection. Ventilatory values at rest were not altered after extradural injection. Mean (VE/PECO2) decreased significantly after extradural morphine (P = 0.002) and increased (P = 0.011) after extradural lignocaine. Mean VE 7.3 (Ve at PECO2, 7.3 kPa) decreased significantly after extradural morphine (P < 0.001) and increased after extradural lignocaine (P = 0.047). Extradural morphine and lignocaine did not significantly alter mean VE/PECO2 and mean Ve 7.3: 14.6 (95 % confidence intervals 12.1–17.1) to 15.3 (13.1–17.6) litre min−1 kPa−1 and 22.8 (18.1–27.5) to 22.8 (17.3–28.3) litre min−1, respectively. We conclude that extradural co-administration of morphine and lignocaine did not increase the risk of respiratory depression associated with morphine. (Br. J. Anaesth. 1995; 75: 394–398)

Key words

Extradural co-administration of opioids and local anaesthetics is a popular method for control of pain [1–3]. The objective is potentiation of analgesia and reduction of side effects. A synergistic antinociceptive interaction of extradurally and intrathecally administered opioids and local anaesthetics has been demonstrated clearly in animal experiments [4, 5]. However, there is little information on the influence of the interaction on side effects during co-administration of opioids and local anaesthetics. Respiratory depression after extradural opioids is of great concern for clinicians, although the incidence of apparent respiratory depression is low [6]. The usual ventilatory variables such as arterial carbon dioxide tension and ventilatory frequency are not sensitive enough to detect minor respiratory depression. There is some change in ventilatory response, even if it is not detectable by clinical observations [7, 8]. The absence of a normal ventilatory response to hypercapnia during extradural opioids may increase the likelihood of hypoxic episodes.

The ventilatory response to carbon dioxide increases after extradural injection of local anaesthetics [9, 10] and might be expected to counteract the response to extradural opioids when opioids and local anaesthetics are co-administered.

The purpose of the present study was to evaluate the interaction of extradurally co-administered morphine and lignocaine on the ventilatory response to carbon dioxide compared with that of extradural lignocaine or morphine alone.

Patients and methods

The study was approved by the Ethics Committee of Shimane Medical University and written informed consent was obtained from each patient. We studied 24 female patients, ASA I or II, undergoing abdominal surgery. Patients were allocated randomly to one of three groups. Group M (n = 8) received morphine 2 mg diluted in 10 ml of normal saline; group L (n = 8) received 2 % lignocaine 10 ml; and group ML (n = 8) received a combination of morphine 2 mg and 2 % lignocaine 10 ml.

All respiratory studies were performed in a quiet room in the operating department of Shimane Medical University Hospital. Each patient was examined on two separate days before and after extradural injection of drug.

On the day before surgery, ventilatory values were measured while the patients were at rest or given a carbon dioxide challenge after they had become familiar with the equipment and had rested for 20 min. After baseline measurements, an extradural catheter was inserted through a Tuohy needle at the L1–2 or L2–3 intervertebral space using the hanging drop technique. A test dose of 2 % lignocaine 2 ml was injected into the catheter to exclude intravascular injection or subarachnoid block.

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Extradural analgesia and ventilatory response

Patients did not receive premedication. Arterial pressure and heart rate were monitored continuously with an automatic sphygmomanometer (BP-1001, Nippon Colin, Komaki, Japan) and an electrocardiograph (2F21, Sanei, Tokyo, Japan) throughout the study. Ringer’s lactate solution was infused at a rate of 10 ml kg\(^{-1}\) h\(^{-1}\). Respiratory measurements were repeated 30 min after extradural injection of one of the three solutions. The level of analgesia was assessed by pinprick before measurement of ventilatory response. Systolic arterial pressure was maintained within 20 % of its control value with ephedrine 5 mg i.v. Three patients who were given ephedrine before the measurements were excluded.

Each patient was placed in a supine, relaxed position and wearing a face mask (dead space volume 40 ml), which was connected to a hot-wire respiratory flowmeter (Respiromonitor RM-200, Minato Medical Science, Osaka, Japan). End-tidal fraction of carbon dioxide (\(P_{\text{ET}}\)\(CO_2\)) was measured with a capnograph (CD-300, Datex Instrumentarium, Helsinki, Finland) calibrated before and after each measurement. Ventilatory frequency (\(f\)), minute volume (\(V_E\)), tidal volume (\(V_T\)) and \(P_{\text{ET}}\)\(CO_2\) were recorded on a four-channel recorder (Rectigraph 8K, Sanei, Tokyo, Japan). Volumes were expressed as BTPS. End-tidal partial pressure of carbon dioxide \(P_{\text{ET}}\)\(CO_2\) was calculated from the measured \(P_{\text{ET}}\)\(CO_2\). Oxygen saturation (\(S_{\text{PO}_2}\)) was monitored continuously with a pulse oximeter (OLV-1200, Nihon Kohden, Tokyo, Japan).

After each measurement of resting ventilation, a carbon dioxide challenge was administered by a modified Read’s method [11]. Each patient rebreathed exhaled gas through a two-way valve attached to a 10-litre reservoir, filled initially with 7 % carbon dioxide in oxygen. Rebreathing was continued until \(P_{\text{ET}}\)\(CO_2\) reached 8 kPa. The carbon dioxide response was calculated from \(V_E\) and \(P_{\text{ET}}\)\(CO_2\) by means of least-squares linear regression analysis for each carbon dioxide challenge curve. All responses were linear, with a correlation coefficient \(r > 0.96.\) The results were expressed by the slope \((\Delta V_E/\Delta P_{\text{ET}}\)\(CO_2\)) and the value of \(V_E\) at 7.3 kPa (\(V_E\) 7.3).

For analysis of blood-gas tensions and measurements of plasma concentrations of lignocaine, arterial blood samples were obtained by direct puncture of the femoral artery before and 30 min after extradural injection. Plasma concentrations of lignocaine were measured by enzyme immunoassay (ACA Discrete Clinical analyser, Du Pont, Wilmington, DE, USA) in groups L and ML. The detection limit was 0.1 \(\mu g\) ml\(^{-1}\).

Repeated measure analysis of variance (ANOVA) followed by Student’s paired \(t\) test within groups for post hoc comparison was used to evaluate statistical significance. Differences were considered statistically significant at \(P < 0.05.\) Data were analysed using the Statview 4.02 statistical package (Abacus Concepts Inc., Berkeley, CA, USA) on a Power Macintosh 7100 (Apple Computer Inc., Cupertino, CA, USA).

Results

Patient data are summarized in table 1. There were no differences in age, body weight and body height between the three groups. The upper and lower sensory levels of extradural analgesia in group L did not differ significantly from those in group ML. The level assessed by pinprick was not clear in group M, although extradural morphine produced hypoalgesia.

Ventilatory values before and after extradural anaesthesia are presented in table 2. Before extradural anaesthesia there were no significant differences in resting \(f\), \(V_E\), \(V_T\), \(P_{\text{ET}}\)\(CO_2\) or \(P_{\text{ET}}\)\(CO_2\) between the three groups. \(f\), \(V_E\), \(V_T\), \(P_{\text{ET}}\)\(CO_2\) or \(P_{\text{ET}}\)\(CO_2\) at rest were not altered significantly by extradural administration of morphine or lignocaine alone, or by the combination of morphine and lignocaine.

Individually changes in \(V_E/\Delta P_{\text{ET}}\)\(CO_2\) are shown in figure 1. \(V_E/\Delta P_{\text{ET}}\)\(CO_2\) decreased in all patients given extradural morphine but did not change consistently in patients given extradural morphine and lignocaine. Mean \(V_E/\Delta P_{\text{ET}}\)\(CO_2\) decreased significantly.
from 16.8 (95% confidence intervals 14.0–19.6) litre min\(^{-1}\) kPa\(^{-1}\) to 12.0 (9.1–15.0) litre min\(^{-1}\) kPa\(^{-1}\) after extradural morphine (\(P = 0.002\)) and increased from 15.6 (13.7–17.5) litre min\(^{-1}\) kPa\(^{-1}\) to 18.0 (15.4–20.7) litre min\(^{-1}\) kPa\(^{-1}\) after extradural lignocaine (\(P = 0.011\)). The power of the study to detect a difference in \(\dot{V}E/\dot{P}CO_2\) was 87% in group M and 74% in group L. Extradural morphine and lignocaine did not significantly alter mean \(\dot{V}E/\dot{P}CO_2\) (14.6 (12.1–17.1) to 15.3 (13.1–17.6) litre min\(^{-1}\) kPa\(^{-1}\)).

Individual change in \(\dot{V}E/\dot{P}CO_2\) are shown in figure 2. Mean \(\dot{V}E\) decreased significantly from 22.5 (19.3–25.7) litre min\(^{-1}\) to 18.2 (15.5–20.9) litre min\(^{-1}\) after extradural morphine (\(P < 0.001\)) and increased from 21.4 (18.8–24.1) litre min\(^{-1}\) to 23.7 (20.4–27.0) litre min\(^{-1}\) after extradural lignocaine (\(P = 0.047\)). The power of the study to detect a difference in \(\dot{V}E\) was 82% in group M. The power was low (44%) in group L, although a statistically significant difference was shown.

Extradural morphine and lignocaine did not significantly alter mean \(\dot{V}E\) (22.8 (18.1–27.5) to 22.8 (17.3–28.3) litre min\(^{-1}\)).

Mean plasma concentrations of lignocaine 30 min after extradural injection in group L (\(n = 6\)) and group ML (\(n = 5\)) were 1.8 (sd 0.13) \(\mu\)g ml\(^{-1}\) and 2.0 (0.2) \(\mu\)g ml\(^{-1}\), respectively. There was no statistically significant difference between the two groups.

**Discussion**

Extradural analgesia with morphine 2 mg significantly reduced the ventilatory response to carbon dioxide while ventilatory depression was not suggested by the other ventilatory values of \(f_j\), \(V_T\), \(\dot{V}E\) and \(P_{a\text{CO}_2}\). This suggests that potential ventilatory depression exists during extradural opioid administration and that the likelihood of hypoxic episodes might be increased. However, extradural co-administration of morphine and lignocaine did not produce
any, significant changes in ventilatory response. The mechanism may differ from that of the synergistic analgesic effects, that is modulation of binding to opioid receptors [12]. The study suggests that co-administered lignocaine does not increase the risk of respiratory depression.

Ventilatory response was investigated soon after (30 min) administration of extradural morphine in the present study. The results are consistent with those of a previous report in which a significant reduction in slope of the ventilatory response to carbon dioxide and $V_E$ 54 was demonstrated after extradural morphine [13]. Plasma and CSF concentrations of morphine increased within 30 min after extradural administration [14]. These results show that depression of ventilatory response can occur early after extradural morphine, probably because of systemic absorption and rostral CSF spread of morphine [15].

Morisot and colleagues [3] reported that extradural fentanyl combined with lignocaine produced a significant reduction in the ventilatory response to carbon dioxide. The difference between their results and the present study may be caused by different measurement times and different drugs. They measured the ventilatory response 1 and 2 h after extradural anaesthesia, at which times the effect of lignocaine appears to be diminished. Extradural lignocaine produced no change in ventilatory response in that study, while lignocaine caused an increase in the present study. Differences in rostral spread of fentanyl and morphine may contribute also to the different interactions with local anaesthetics.

Bourke and Warley [16] reported that morphine caused a parallel right shift of the steady state carbon dioxide response curve and a right shift of the rebreathing carbon dioxide response curve with a small decrease in slope. The rebreathing method is affected by changes in cerebral blood flow, transport time, time constant of the central chemoreflex and cerebral and whole body carbon dioxide production, while the steady state method is less sensitive to these variables. Opioids and local anaesthetics may affect several of these variables.

Extradural or i.v. lignocaine increases the ventilatory response to carbon dioxide [9,10]. The correlation between plasma lignocaine concentrations and changes in the ventilatory response to carbon dioxide was significant with i.v. lignocaine and extradural lignocaine, suggesting that this is a systemic effect [17]. Lignocaine may act on both central and peripheral chemoreceptors. Labaille and colleagues [9] demonstrated a significant increase in ventilatory response to carbon dioxide after extradural lignocaine, when the plasma lignocaine concentration was 1.79 (sd 0.42) $\mu g/ml$, which is similar to that in the present study. The effect of lignocaine on ventilatory response may counteract the depressant effect of morphine, resulting in no net change in the ventilatory response after extradural morphine and lignocaine.

Kochi and colleagues [18] reported a decreased ventilatory response to carbon dioxide after high thoracic extradural anaesthesia with lignocaine (upper level T2 to C5) because of mechanical impairment of rib cage movement. In the present study, ventilatory values at rest and the ventilatory response did not decrease after extradural anaesthesia. The upper level of block was insufficient to impair the intercostal muscles and the increased ventilatory response resulting from central effects of lignocaine was not attenuated.

Most drugs given during anaesthesia may enhance depression of respiratory drive after extradural morphine, including inhalation [19] and i.v. anaesthetics [20]. Previous studies [21, 22] of the effects of extradural morphine on ventilatory response have been conducted after surgery when other factors may be present. Therefore, we studied the effect on ventilatory response without premedication and before surgery.

Continuous infusion of opioids and local anaesthetics is now a popular method for pain management [1–3]. We could not follow the time course of the ventilatory response because of the limited amount of time available before surgery. Depr edation of the ventilatory response after extradural morphine lasts for several hours [13]. Our results suggest that attenuation of the ventilatory depression caused by extradural opioids may be preserved if opioids and local anaesthetics are administered continuously, as adequate plasma concentrations of local anaesthetics are preserved during continuous extradural infusion [23].

References


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