Title: BIPHASIC DEPRESSION OF THE MINUTE VENTILATION RESPONSE TO CO_2 FOLLOWING EPIDURAL MORPHINE

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Introduction. Epidural morphine results in prolonged and selective pain relief. Although the incidence of complications is low, case reports of severe respiratory depression 4-12 hours postinjection have led to questions about the safety of epidural morphine. We examined the hypotheses that depression of control of ventilation following epidural morphine is biphasic and results from two mechanisms. Diffusion of morphine into the epidural veins with circulatory redistribution to the brain results in an early depression 1-2 hours postinjection. A late phase of depression is the result of cephalad diffusion of morphine in the CSF.

Methods. Institutional approval of the protocol was granted and informed consent obtained from each patient. We examined the effects of lumbar epidural morphine (0.1 mg/kg) on the control of ventilation by measurement of minute ventilation and its component responses to CO_2 (rebreathing method), pain relief, elevation of mood, segmental level of analgesia (absence of pain in response to a painful stimulus) and plasma morphine concentration in 7 patients (age 39±SD12 years) with chronic low back pain the day before (control) and at 1,2,4,8, 12 and 24 hours postinjection. Unconjugated and conjugated plasma morphine concentrations were measured by a specific radioimmunoassay technique (1).

Results. Maximal depression of the CO_2 responses occurred at 1-2 hours postinjection and as a percent of control (±SE) were minute ventilation, ($\dot{V}_I$), slope -35±7% ($P<0.01$), and $\dot{V}_I$ at $P_{ET}CO_2$55 -42±3% ($P<0.001$); tidal volume at $P_{ET}CO_2$55 -29±3% ($P<0.01$), and average inspiratory flow ($\bar{V}$) at $P_{ET}CO_2$55, -37±4% ($P<0.001$). At 8 hours postinjection the $\dot{V}_I$ and $\bar{V}_I$ at $P_{ET}CO_2$55 were -52±19% ($P<0.05$) and -36±13% ($P<0.05$), respectively. At 4,12 and 24 hours postinjection the CO_2 responses were not significantly different from control. Elevation of mood at 1-2 hours postinjection was statistically significant. In different patients the level of analgesia rose to trigeminal, cervical or upper thoracic segments and were maximal at 8 hours postinjection. Plasma concentrations of unconjugated morphine were highest at 15 minutes postinjection (37.9±SE4.5 ng/ml) and declined polyexponentially with a $t_{1/2\beta}$ phase of 2.38 SE±0.23 hours. Conjugated morphine concentrations exceeded markedly those of unconjugated morphine at all times. At 1,2,4, 8,12 and 24 hours postinjection the vital capacity, blood pressure and heart rate were not significantly different from preinjection.

Discussion. Depression of the minute ventilation response to CO_2 following epidural morphine is biphasic. The early phase which follows the peak in plasma morphine occurs simultaneously with an elevation in mood and results in depression of the slope of the minute ventilation response. The later phase which is associated with a rise in the segmental level of analgesia is characterized by parallel displacement of the minute ventilation and average inspiratory flow responses to CO_2. The concentration of morphine following administration into the lumbar epidural space peaks in the lumbar CSF at 2-4 hours postinjection (2) and as a result of poor lipid solubility concentrations sufficient to depress control of ventilation diffuse cephalad (3) to the brain stem. The rise in segmental level of analgesia is therefore an essential clinical sign of impending late depression of control of ventilation.

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References

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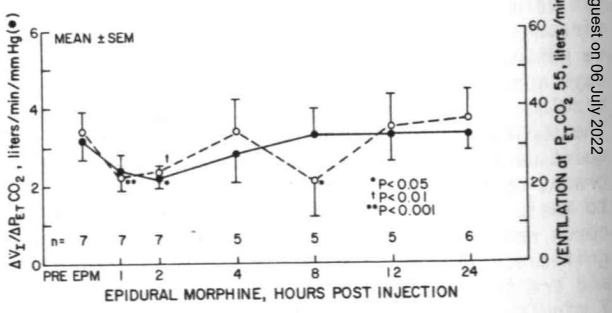

Figure 1. Biphasic depression of the minute ventilation response to CO_2: slope (●), position, $\dot{V}_I$ at $P_{ET}CO_2$55 (○). P values are for statistical significance of difference from control. At 4,8 and/or 12 hours postinjection 3 patients had nausea or vomiting and their CO_2 responses were not measured.