EFFECT OF MEDROXYPROGESTERONE ACETATE ON THE
CONTROL OF BREATHING

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INTRODUCTION

Patients with severe chronic obstructive pulmonary disease (COPD) are often not capable to keep bloodgas values at a normal level, they are hypoxaemic and/or hypercapnic. During sleep these patients are even more hypoxaemic and/or hypercapnic due to hypoventilation, especially during the REM state (Vos, 1992). To improve bloodgas values respiratory stimulants such as medroxyprogesterone acetate (MPA) can be used.

The mechanisms by which MPA achieve the ventilatory effects are not well understood. Several mechanisms are described.

A. Stimulation via progesterone receptors present in the optic area, N. Suprachiasmaticus and the eminentia mediana of the hypothalamus, which even can be potentiated by estrogen. This is described by Bayliss et al., 1987, who found a diminished effect of progesterone after midcollicular decerebration of cats, while the effect remained preserved after decortication.

B. Stimulation via the peripheral and central chemoreflex loops. Zwillich et al., 1978 found an increase in gain of the ventilatory CO₂ response curve indicating stimulation of ventilation by chemical route.

C. An effect of progesterone on muscular receptors. Hensley et al., 1980 found a reduction of upper airway obstruction in patients, possibly by promoting motor activity of the upper-airway muscles.

AIM OF THE STUDY

The aim of the present study was to investigate the effect of MPA on the ventilatory CO₂ response curve in cats. To study the ventilatory effects of MPA we applied the dynamic end-tidal forcing (DEF) technique. This technique is designed to separate the effects of drugs into actions on the peripheral and central chemoreflex loops (DeGoede et al., 1985).

METHODS

Eight chloralose-urethane anaesthetized, ovariectomized cats, pre-treated with 17β estradiol, breathed spontaneously in a closed respiratory circuit, in which end-tidal PO₂ and PCO₂ could be controlled independently from each other. Animals were
connected to an extra-corporeal circuit in which arterial pH, pCO$_2$ and pO$_2$ were measured continuously. Anaesthesia was maintained constant during the experiment (Teppema et al., 1997).

Experimental protocol. The ventilatory response to step changes in end-tidal PCO$_2$ were measured using the DEF technique. The $P_{ET}$CO$_2$ was elevated by 1–1.5 kPa within one or two breaths, maintained constant for about seven minutes and then lowered stepwise to the previous value and kept constant for about seven minutes before repeating the run. First, at least three control runs were performed when the animal had stabilized. Then, one hour after intravenous infusion of 4 μg.kg$^{-1}$ MPA, another three DEF runs were performed.

Data analysis. In steady state conditions the ventilation can be described by:

$$\dot{V}_1 = \dot{V}_p + \dot{V}_c = -(S_p + S_c)(P_{ET}CO_2 - B)$$

in which $V_p$ and $V_c$ are the contributions of, respectively, the peripheral and central chemoreflex loop to the ventilation ($V_1$), $S_p$ and $S_c$ are the sensitivities of, respectively, the peripheral and central chemoreflex loops to changes in end-tidal PCO$_2$, and $B$ represents the apnoeic threshold (=extrapolated end-tidal PCO$_2$ at zero ventilation). By analyzing the dynamic response to step changes in end-tidal PCO$_2$ with a two compartment model (DeGoede et al., 1985), we determined the values of $S_p$, $S_c$ and $B$ both in the control situation and after 4 μg.kg$^{-1}$ MPA. Differences between model parameters obtained after control and MPA runs were analyzed with two-way ANOVA.

RESULTS

MPA decreased the sensitivities of both the peripheral ($S_p$) and the central chemoreflex loops ($S_c$) as well as the apnoeic threshold ($B$)(Table 1).

<table>
<thead>
<tr>
<th></th>
<th>central slope ($S_c$) (1.min$^{-1}$.kPa$^{-1}$)</th>
<th>peripheral slope ($S_p$) (1.min$^{-1}$.kPa$^{-1}$)</th>
<th>total slope ($S_{tot}$) (1.min$^{-1}$.kPa$^{-1}$)</th>
<th>quotient $S_p/S_c$</th>
<th>x-intercept B (kPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>control</td>
<td>1.01±0.38</td>
<td>0.22±0.09</td>
<td>1.23±0.39</td>
<td>0.26±0.19</td>
<td>4.02±0.27</td>
</tr>
<tr>
<td>MPA</td>
<td>0.88±0.32*</td>
<td>0.13±0.06*</td>
<td>1.02±0.33*</td>
<td>0.17±0.08*</td>
<td>3.64±0.42*</td>
</tr>
</tbody>
</table>

Table 1: The effects of 4 μg.kg$^{-1}$ MPA on the model parameters$^1)$

$^1)$ mean of the means per animal ± S.D. *p<0.05.
The results imply that MPA, when infused at a constant $P_{ET}CO_2$ of 4.5 kPa, will result in an increase of minute ventilation of approximately 30%. This is illustrated in figure 1.

**Figure 1.**
The effect of $4 \mu g.kg^{-1}$ MPA on the ventilatory CO$_2$ response curve.
DISCUSSION

1. At resting PCO₂ values (in the cat ± 4.5 kPa) ventilation will increase by 30 % after injection of 4 µg.kg⁻¹ MPA.

2. MPA stimulates ventilation considerably, and therefore will be helpful in patients who are hypercapnic and hypoxaemic during sleep.

3. The decrease in S_p and S_c may be due to an effect of MPA at either the level of the brainstem or hypothalamus. However, the decrease in the ratio S_p/S_c may be due to a selective effect of MPA on the peripheral chemoreflex loop, possibly at the level of the peripheral chemoreceptors. This makes the mechanism proposed by Zwillich et al., 1978 less likely.

4. The decrease of the apnoeic threshold B may be due to an effect on both the peripheral and central chemoreflex loops, to an additional ventilatory drive from hypothalamic neurons suggested by Bayliss or to an effect on the upper airway muscles (Hensley, et al., 1980).

5. Due to the DEF technique used in this study it was possible to investigate the effects of MPA on the peripheral and central chemoreflex loops. However, more studies are needed to get more information about the effects of MPA on hormonal and muscular level.

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REFERENCES


