EFFECT OF DOXAPRAM ON CONTROL OF BREATHING IN CATS

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DOXAPRAM is a respiratory stimulant which has been shown to increase the activity of the peripheral chemoreceptors and may be a useful drug for assessment of their influence on respiration.⁴ Although this action of doxapram has been well documented,^{8,14,19} the effects that it has on ventilation have not been fully described. The increase in ventilation that it produces could be the result of an increase in the rate of pressure generation by the respiratory muscles (neuromuscular inspiratory drive), or could be the result of a change in the timing of the phases of respiration, or could possibly be caused by changes in the mechanical properties of the respiratory system.

This investigation was designed to study the action of doxapram infusion in detail using two classical methods for the study of ventilation: the spirogram and the ventilatory response to increased alveolar carbon dioxide concentrations. In addition, two more recent methods of analysis were used. In the first the mean inspiratory flow rate was expressed as the ratio of tidal volume to inspiratory time (V_T/T_i) and the ratio of inspiratory time to total respiratory cycle duration (T_i/T_{TOT}) was calculated. These indices are based on the following modification of the usual expression for $\dot{V}_E$:

$$\dot{V}_E = V_T \times 1/T_{TOT} \times 60$$

which can be written

$$\dot{V}_E = V_T/T_i \times T_i/T_{TOT} \times 60$$

where T_i/T_{TOT} is a dimensionless index of the respiratory timing, or inspiratory "duty cycle"; and V_T/T_i is a translation into mechanical terms of the activity of the respiratory motor neurones.¹² In the second method the pressure generated by an inspiration against an occluded airway was also recorded (tracheal occlusion pressure). Since there is no gas flow or change in lung volume during the occluded inspiratory effort, this

pressure is not influenced by possible changes in the mechanical properties of the lung and consequently many of the mechanical factors involved in the transformation of muscle activity into ventilation are eliminated.¹¹

METHODS

Four adult cats, weighing between 3 and 4 kg, were anaesthetized with pentobarbitone 35 mg·kg⁻¹ intraperitoneally. A tracheal cannula was inserted through a tracheostomy and an intravenous infusion of 0.9 per cent sodium chloride was started. The cats were placed into a volume body plethysmograph (Emerson). Rectal temperature was measured with a thermistor probe and was kept constant with a heating pad under the animals. The cats breathed 50 per cent oxygen from a non-rebreathing T-piece system. Airway pressure was measured from a side arm in the tracheal cannula using a Sanborn 267B transducer. Gas was aspirated at 200 ml/min from another sidearm and analyzed using a Beckman LB2 carbon dioxide analyzer to allow estimation of end tidal carbon dioxide (P_{ETCO_2}). The volume, pressure and carbon dioxide signals were recorded using a Honeywell Accudata 125 recorder.

The animal was left for 15 minutes to achieve a steady state and then five sets of measurements were made. Each was a record of one control breath followed by an inspiratory effort with the airway occluded at the end of the control expiration (Figure 1). Occlusions were made for one respiratory cycle at intervals of about 10 to 15 breaths. The carbon dioxide response was then measured by adding first about three per cent and then five per cent carbon dioxide to the inspired

FIGURE 1 A representative record showing a control breath (upper trace) followed by airway occlusion and the development of a subatmospheric airway pressure (lower tracing).

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TABLE I

Cat	Intercept kPa (mm Hg)		(slope ml · min ⁻¹ · mm Hg ⁻¹)	
	Control	Doxapram	Control	Doxapram
1	2.54 (19.1)	1.49 (11.2)	99.6	108.9
2	2.46 (18.5)	2.10 (15.8)	211.6	308.1
3	2.70 (20.3)	2.45 (18.4)	214.2	258.4
4	2.09 (15.7)	1.90 (14.3)	121.4	183.9

Values of intercepts at $\dot{V}_E = 0$ and slopes of the ventilatory response curves to carbon dioxide in four cats before and during doxapram infusion.

gas and repeating the measurements after a ten minute equilibration period. The cat was then returned to 50 per cent oxygen and was allowed to recover. An infusion of doxapram was next started at a rate of $0.25 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. This was chosen as 5 times the suggested clinical rate¹⁵. The measurements were repeated after 15 minutes of infusion, during which time the $\text{P}_{\text{E}}\text{CO}_2$ was allowed to decrease.

Analysis of results

Tidal volume (V_T), inspiratory time (T_I) and duration of total respiratory cycle (T_{TOT}) were measured directly from the breath preceding occlusion. Frequency (f) was calculated as $60/T_{\text{TOT}}$ and minute ventilation ($\dot{V}_E$) as $V_T \times f$. The pressure in the airway 0.5 second after the onset of an occluded breath was taken as an index of neuromuscular respiratory drive ($\text{P}^0.5$). The volume achieved after the same time ($V_{0.5}$) was measured for the control breaths (Figure 1).

Linear regression analysis was done by a least squares method using the individual measurements and group data are presented as means ± 1 standard deviation. Differences were tested for significance by Student's *t*-test for group or paired data, as appropriate.

RESULTS

The mean effects of doxapram in the four animals are summarized in Figure 2. Ventilation increased significantly in three of the four animals. The increase was small in relation to the infusion rate (5 times the therapeutic dose) but was associated with a significant and marked reduction in end-tidal carbon dioxide.

The effects of doxapram on the $\dot{V}_E$, V_T and f responses to carbon dioxide are shown for a representative cat in Figure 3 and ventilatory responses are summarized for the four animals in Table I. The response line is displaced to the left

FIGURE 2 Mean values $\pm$ standard deviation for $\dot{V}_E$, V_T , f , V_T/T_I , T_I/T_{TOT} , $\text{P}^0.5$ and $\text{F}_{\text{E}}\text{CO}_2$ in the four animals while breathing 50 oxygen with nitrogen before and during doxapram infusion. The values are expressed as per cent of the mean control value in each case. Results of paired *t*-test analysis are also shown. Significant changes are taken as $P \leq 0.05$.

FIGURE 3 Effects of doxapram on the relationships of $\dot{V}_E$, V_T and f with $\text{F}_{\text{E}}\text{CO}_2$ in a representative animal.

and increased in slope. Correlation values were greater than 0.96 in all cats.

Doxapram has a similar influence on the ratio of tidal volume to inspiratory time (V_T/T_I) and of neuromuscular respiratory drive after 0.5 second occlusion to end-tidal carbon dioxide ($\text{P}^0.5$)

FIGURE 4 Effects of doxapram on the relationships of V_T/T_i and $P'0.5$ with $F_E CO_2$ in same cat as Figure 3.

FIGURE 5 Relationship between $P'0.5$ and $V0.5$ in same cat as Figure 3 during control and doxapram infusion.

$F_E CO_2$). Results for a representative cat are shown in Figure 4. The response line is moved to the left and increased in slope. This suggests that the mechanical properties of the respiratory system have not changed after doxapram infusion and is confirmed by the constant relationship of pressure to volume after 0.5 second tracheal occlusion ($P'0.5/V0.5$) shown in Figure 5. Thus doxapram does not influence the "effective" inspiratory impedance ($P'0.5/V0.5$).

Doxapram caused a small decrease in the ratio of inspiratory time to duration of total respiratory cycle (T_i/T_{TOT}) which was significant in only two animals (Figure 2).

DISCUSSION

Drugs may affect ventilation in several ways and their action may best be analyzed by separating the effect on medullary inspiratory neurone activity from the combined bulbopontine and vagal reflex influences on timing.² For example, some stimulants and depressants act by influencing the rate of increase of activity of respiratory motor neurones. This increase of activity can be measured in terms of rate of increase of integrated phrenic nerve or diaphragmatic electrical activity, tracheal occlusion pressure or mean inspiratory flow rate.¹³ As both V_T/T_i and

FIGURE 6 A diagrammatic representation of the spirogram before and during doxapram infusion using mean values for the four animals studied.

$P'0.5$ increased (Figure 2), doxapram seems to stimulate respiration in this way.

Some agents have been shown to stimulate respiration by altering respiratory timing. For example, diethyl ether increases T_i/T_{TOT} in newborn rabbits.²² Other agents such as methoxyflurane, have been shown to decrease the ventilatory response to carbon dioxide mainly by increasing the "effective" inspiratory impedance of the respiratory system;³ and atropine increases ventilation during enflurane anaesthesia probably by reducing airway resistance.²³ Doxapram, at least in cats, appears to have little or no effect on either T_i/T_{TOT} or "effective" inspiratory impedance ($P'0.5/V0.5$).

Figure 6 summarizes the effect of doxapram on the spirogram in the four cats breathing 50 per cent oxygen in nitrogen. This diagram shows the marked effect of doxapram on V_T/T_i as shown by the increased slope of the inspiratory phase. T_i and T_{TOT} both decreased so that their ratio was relatively little affected.

During breathing of 50 per cent oxygen in nitrogen $\dot{V}_E$ increased in the four cats on the average by about 20 per cent. Under these conditions, however, the animals developed hypocapnia which limited the effect of doxapram on ventilation. The net influence of doxapram on ventilation is better expressed in terms of percentage increase in $\dot{V}_E$ under isocapnic conditions. This could be computed from the carbon dioxide response data. At a P_{ECO_2} of 3.32 kPa (25 mm Hg) the mean increase in $\dot{V}_E$ for the four cats that should be produced by doxapram was 70 per cent. Seventy-five per cent of this increase was

caused by an increase in V_T and only 25 per cent by increased frequency.

The carbon dioxide response curves show that doxapram produces a shift of the curves to the left associated with a change in the slope. The change in slope of the respiratory responses to carbon dioxide caused by doxapram is consistent with an action of the drug on the peripheral chemoreceptors, as hypoxia has the same effect.¹⁶ This multiplicative interaction of doxapram with carbon dioxide is of clinical interest as it implies that reduction in P_{aCO_2} caused by this drug will be more pronounced when the drug is used in the presence of hypercapnia.

SUMMARY

The effects of doxapram infusion ($0.25 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) were studied in cats anaesthetized with pentobarbitone ($35 \text{ mg} \cdot \text{kg}^{-1}$ intraperitoneally). Cats were studied breathing 50 per cent oxygen and the responses to two concentrations of inspired carbon dioxide were measured. Doxapram infusion increased pulmonary ventilation by increasing both tidal volume and respiratory frequency, and also caused increases in the volume inspired in the first 0.5 second after the onset of an inspiration ($V_{0.5}$) and the pressure generated in the airway 0.5 second after the onset of an inspiration when the airway had been occluded ($P_{0.5}$). $V_{0.5}$, $P_{0.5}$ and the mean inspiratory flow rate (V_T/T_i) were essentially equivalent indices of inspiratory drive. Doxapram infusion did not alter the effective impedance of the respiratory system ($P_{0.5}/V_{0.5}$). Doxapram infusion increased the ventilatory response to carbon dioxide. The slope of the ventilatory response to carbon dioxide was increased and the response line was shifted to the left. We conclude that the increase in pulmonary ventilation caused by doxapram infusion is due almost entirely to increased inspiratory neuromuscular drive ($P_{0.5}$).

RÉSUMÉ

Les auteurs ont étudié l'action du doxapram en perfusion à la dose de $0.25 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ sur le chat anesthésié au pentobarbital administré par la voie intrapéritonéale ($35 \text{ mg} \cdot \text{kg}^{-1}$). On a fait respirer à des chats de l'oxygène à 50 pour cent pendant qu'on mesurait la réponse à deux concentrations de gaz carbonique. La perfusion de doxapram a eu pour effet d'augmenter la ventilation et cette augmentation s'est manifestée sur le

volume courant, la fréquence, la fraction inspirée pendant la première demi-seconde ($V_{0.5}$) et la pression produite dans les voies aériennes 0.5 seconde après le début de l'inspiration lors de l'occlusion de celles-ci ($P_{0.5}$). Le $V_{0.5}$, la $P_{0.5}$ et le débit inspiratoire moyen (V_T/T_i) ont été en tout point des indices équivalents de l'influx inspiratoire. La perfusion de doxapram ne modifie pas l'impédance efficace du système respiratoire ($P_{0.5}/V_{0.5}$). La perfusion de doxapram augmente la réponse ventilatoire au gaz carbonique. La pente de réponse ventilatoire au gaz carbonique s'est accentuée et la ligne de réponse est déplacée vers la gauche. Les auteurs concluent que l'augmentation de la ventilation pulmonaire causée par la perfusion de doxapram est presque entièrement due à un accroissement de l'activité des motoneurones inspiratoires ($P_{0.5}$).

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