Effects of a Respiratory Stimulant on Intracranial Pressure and Cerebral Blood Flow

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Abstract

The main cause of sudden death in patients with intracranial hypertension is respiratory failure. This study was a search for a clue to respiratory treatment which could be used at the scene of an accident. For this purpose, intravenous administration of respiratory stimulants was thought to be the most simple measure.

Doxapram hydrochloride (Doxapram) was used to stimulate respiration impaired by balloon-induced intracranial hypertension in cats. Intravenous administration of Doxapram resulted in sufficient respiratory stimulation at the dose of 1.0 mg/kg, but could not decrease PaCO₂ lower than 25 torr. In 4 out of 10 cats, administration of Doxapram improved the respiratory condition and increased cerebral perfusion pressure and regional cerebral blood flow. Further investigation was required to find the best timing of Doxapram administration to maximize life preservation.

Key words: Doxapram, respiratory stimulant, intracranial pressure, cerebral blood flow

Introduction

Sudden death in patients with intracranial hypertension is mainly due to respiratory failure. It is crucial to begin adequate respiratory support as soon as possible to avoid irreversible brain damage following the progressive increase of intracranial pressure associated with accumulation of intravascular and interstitial PCO₂. We considered the immediate use of a respiratory stimulant on such patients via a venous route to maintain their good respiratory condition until they could receive more intensive management. Doxapram hydrochloride (Doxapram) was introduced as a new respiratory stimulant with a wide convulsant to therapeutic ratio (70:1) by Funderburk and Alphine,4) Ward and Franko15) (1962). The aim of this investigation was to observe the effects of Doxapram on respiration, intracranial pressure (ICP), regional cerebral blood flow (rCBF), and regional cerebral tissue oxygen tension (PtO₂) in the cat with intracranial hypertension.

Material and Methods

Thirty cats of either sex weighing between 2.3 and 4.2 kg were used. The animals were anesthetized with intraperitoneal injection of pentobarbital sodium (30 mg/kg) followed by intravenous supplemental doses. All the cats were tracheotomized and allowed to breathe spontaneously (Fig. 1). The respiratory rate and pattern were monitored with a thermister element. Both femoral arteries were cannulated for measurement of systemic arterial blood pressure (BP), arterial carbon dioxide pressure (PaCO₂), and oxygen pressure (PaO₂). Arterial carbon dioxide (Kurare) and oxygen pressure (Roche 636) were continuously measured by two ion sensors. At the beginning of the experiment, arterial blood gases and acid-base balance were confirmed to be within the normal range. A femoral
vein was cannulated for drug administration. Body temperature was maintained within the normal range throughout the experiment.

The animals were fixed to a stereotactic apparatus and a small parietotemporal craniectomy was performed on the left side. ICP was monitored with an epidural ICP sensor (Toyoda AA-1161). rCBF was measured by the thermoelectrical method (Unique Medical UM-2000) and the hydrogen gas clearance method (Unique Medical PHG-201; calculated by initial slope method): the former was a qualitative, continuous measurement and the latter a quantitative but intermittent measurement. PtO$_2$ was continuously measured with an electrochemical sensor (Roche 636). Three holes were drilled: two for electroencephalography (EEG) and one for the Fogarty balloon catheter, inserted into the epidural space to increase ICP. All phenomena were recorded by a polygraph (San-Ei 142-8).

The animals were divided into three groups.

**Group 1:** ICP was increased, but Doxapram was not administered. The ICP of these 10 cats was increased with an epidural balloon inflated with water, and the natural course after induced intracranial hypertension was observed.

**Group 2:** ICP was normal, and Doxapram was administered. These 10 cats underwent the same surgical procedures, but an epidural balloon was not inflated. Doxapram, in graded doses of 0.1 to 5.0 mg/kg, was administered intravenously and the effects on various parameters of these normal ICP cats were observed.

**Group 3:** ICP was increased, and Doxapram was administered. The ICP of these 10 cats was increased by the same method as in Group 1, and when irregular respiratory patterns with hypercapnia were observed, Doxapram in dose of 1.0 mg/kg was administered intravenously. The effects on respiration, ICP, rCBF, arterial blood gases, and PtO$_2$ were observed.

### Results

I. **Group 1** (Figs. 2, 3 and 4)

Intracranial pressure was gradually elevated by repeated injection of 0.1 ml of water into the balloon.

![Image of polygraph recording from a cat in Group 1.](image)

Intracranial pressure began to increase followed by decrease of rCBF and PtO$_2$ with some slowing of EEG (volume of epidural balloon: 0.3 ml). Spontaneous hyperventilation was observed (0.6 ml). Respiration became irregular (0.7 ml). ICP was progressively increased with depressed respiration; EEG flattened (0.8 ml). Respiration was arrested and the animal died (0.9 ml). The marks of a, b, c, and d for EEG correspond to those for BP.

**Fig. 2** Polygraph recording from a cat in Group 1. Intracranial pressure began to increase followed by decrease of rCBF and PtO$_2$ with some slowing of EEG (volume of epidural balloon: 0.3 ml). Spontaneous hyperventilation was observed (0.6 ml). Respiration became irregular (0.7 ml). ICP was progressively increased with depressed respiration; EEG flattened (0.8 ml). Respiration was arrested and the animal died (0.9 ml). The marks of a, b, c, and d for EEG correspond to those for BP.

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Following a spatial compensatory period in the course of repeated ICP increases, rCBF and PtO₂ decreased with some slowing of EEG. BP also increased and a spontaneous hyperventilatory period was observed in most animals. Further increase of ICP resulted in an irregular respiratory pattern and accumulation of PaCO₂. Further increase of BP was observed. At this terminal stage, ICP was entirely dependent on BP, and the cerebral perfusion pressure (CPP) decreased, which lead to cerebral hypoxia with flattening of the EEG.

The relationships between rCBF and CPP (Fig. 3), and PtO₂ and CPP (Fig. 4), when CPP was decreased by elevated ICP are shown. Both rCBF and PtO₂ abruptly decreased when the CPP decreased below 100 torr in most cases.

II. Group 2 (Figs. 5 and 6)

Doxapram was administered in graded doses of 0.1 to 5.0 mg/kg by intravenous injection (each bolus injection of 20 second duration) to cats with normal ICP. As small a dose as 0.1 mg/kg of Doxapram stimulated respiration, resulting in decreased PaCO₂ and PtO₂. BP was also elevated. rCBF and ICP showed biphasic (increase-decrease) patterns.

The dose relationship of Doxapram and PaCO₂ is shown in Fig. 6. PaCO₂ decreased until the 1.0 mg/kg dose of Doxapram, but subsequent doses did not decrease PaCO₂ remarkably (exponential relationship). The optimum dose of Doxapram for sufficient respiratory stimulation was considered to be 1.0 mg/kg.

III. Group 3 (Figs. 7 and 8)

An epidural balloon was inflated as described for Group 1. When the respiratory pattern was disturbed with an increase of PaCO₂, Doxapram in dose of 1.0 mg/kg was administered intravenously.

Administration of Doxapram improved the respiratory condition and increased CPP and rCBF in 4 out of the 10 cases studied here (Fig. 8), but in the other 6 cases it failed to stimulate respiration and these cats followed almost the same process as described for Group 1.

Discussion

It is a common experience for a clinician to find patients with depressed respiration, almost to apnea, though their circulatory system is still in good condition, on their arrival to the hospital. Actually, in daily medical practice not a small number of patients with cerebral insult die before arrival to the well-equipped hospital.
because of acute respiratory failure. The purpose of this study was not to find an alternative method comparable to "controlled ventilation", but to search for a clue to respiratory treatment which would be used at the scene of an accident, for example at the roadside or in the home.

Endotracheal intubation or tracheotomy followed by controlled ventilation is undoubtedly an ideal treatment for the comatose patient with any severe brain insult. However, such procedures are risky when an anesthetist is not available or there is inadequate instrumentation.

We therefore searched for a respiratory stimulant used via a venous route to maintain good respiratory condition in such patients until they can receive more intensive management.

In the group of animals with increased ICP, respiratory dysfunction was confirmed to be the main cause of sudden death. Secondary to respiratory failure, accumulation of PaCO₂ caused progressive increase of ICP. If the increased ICP was not controlled at this stage, cerebral perfusion would be impaired and cerebral ischemia would progress, resulting in a "vicious circle". Once vasomotor paralysis was complete, the treatment was no longer of any benefit.

Doxapram was used as a respiratory stimulant in this study because of its potency and wide safety range. Doxapram was introduced as a new respiratory stimulant by Funderburk and Alphine, Ward and Franko. Kato and Buckley reported that Doxapram stimulated respiration by acting directly on the respiratory centers of the medulla oblongata and also on the carotid and aortic chemoreceptors. Hirsh and Wang reported that Doxapram acted primarily on the carotid receptors while the brain stem was also directly stimulated only when large doses were used. Doxapram was reported to be one of the most potent and selective respiratory stimulants, and to have the widest convulsant to therapeutic ratio (70:1) by Funderburk and Alphine. The pressor and chronotropic responses to Doxapram were of a relatively small magnitude; Winnie called Doxapram the closest thing to a pure respirogenic agent.

We confirmed the dose of 1.0 mg/kg of Doxapram to produce sufficient respiratory stimulation and to decrease PaCO₂. rCBF and ICP showed biphasic patterns. At first they increased depending on BP, and then decreased by vasoconstriction secondary to lowered PaCO₂. PaCO₂ was not excessively decreased by

Fig. 5 Polygraph recording from a cat in Group 2. rCBF and ICP showed biphasic (increase-decrease) patterns. Reduction of rCBF was prominent when a dose of 2.0 mg/kg of Doxapram was administered.

\[ y = 29.9e^{-0.052x} \]
\[ r = -0.62 \]

Fig. 6 Dose relationship between Doxapram and PaCO₂. The dose of 1.0 mg/kg of Doxapram showed the maximum decrease of PaCO₂.
administration of Doxapram because its effect on respiration was diminished when PaCO2 decreased below 35 torr. In this study, PaCO2 was not decreased lower than 25 torr, even with as large a dose as 5.0 mg/kg of Doxapram.

Sudden death in patients with intracranial hypertension is mainly due to respiratory failure. When irregular respiratory patterns are observed in such patients, adequate respiratory treatment is mandatory to save their lives by avoiding further "vicious circling" and the completion of vasomotor paralysis. Hyperventilation therapy is thought to decrease PaCO2 and ICP, and increase of rCBF and PtO2. But the duration of the effect on respiration was too short and a second administration was required to save the animal. The marks of a, b, and c for EEG correspond to those for BP.

Many workers have emphasized the usefulness of controlled hyperventilation. Rossanda et al.13) stated that respiratory treatment reduced mortality from head injuries by increasing the oxygen supply to the diseased cerebral regions. Gordon et al.5, 6) studied 252 unconscious patients with traumatic brain lesions, 51 of whom were treated with artificial hyperventilation and they reported that the recovery rate was significantly higher and the mortality rate significantly lower in that group. Crockard et al.2) said that reduction of PaCO2 by mechanical hyperventilation (PaCO2 25–30 torr; PaO2 100–150 torr) might be beneficial in cases of severe head injury.

Lassen11) suggested that hyperventilation could produce therapeutic benefit by decreasing the blood flow in normal brain tissue and shifting it to the diseased brain, the so-called "inverse-steal" effect. Brock et al.1) stated that hypocapnea acted locally by a decrease of ICP in the normal tissue area, which leads to an increase of tissue perfusion pressure in the diseased area.

Other authors have given warning against excessive hyperventilation. Rudenberg et al.14) stated that the combination of decreased PaCO2 below 25 torr and...
elevated ICP might reduce CBF below the critical level and so lead to cerebral hypoxia. Harp and Wollman said that there was no evidence for a noxious effect even with marked hyperventilation, but that PaCO₂ should not be lower than 25 torr. Enevolden et al. showed that cerebral ischemia did not occur in head injury if the intraventricular pressure was kept below 45 torr, and they suggested the importance of preventing hypertension and the benefit of moderate hyperventilation.

To sum up the opinions of these authors, controlled hyperventilation is considered to be the most beneficial to patients with severe brain insult unless PaCO₂ is below 25 torr. As Doxapram did not excessively decrease PaCO₂, it would be a worthwhile treatment for such patients on an emergency basis.

Intravenous administration of Doxapram saved only 4 of the 10 animals studied in Group 3. We suppose that in the noneffective cases, the increase of ICP was too rapid and CPP lowered to a critical level, causing irreversible damage to the respiratory centers of the medulla oblongata. Further investigation is required concerning the method and the timing for administration of Doxapram.

References


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