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A New Look at the Respiratory Stimulant Doxapram

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ABSTRACT

A number of life-threatening clinical disorders may be amenable to treatment with a drug that can stimulate respiratory drive. These include acute respiratory failure secondary to chronic obstructive pulmonary disease, post-anesthetic respiratory depression, and apnea of prematurity. Doxapram has been available for over forty years for the treatment of these conditions and it has a low side effect profile compared to other available agents. Generally though, the use of doxapram has been limited to these clinical niches involving patients in the intensive care, post-anesthesia care and neonatal intensive care units. Recent basic science studies have made considerable progress in understanding the molecular mechanism of doxapram's respiratory stimulant action. Although it is unlikely that doxapram will undergo a clinical renaissance based on this new understanding, it represents a significant advance in our knowledge of the control of breathing.

INTRODUCTION

Doxapram is a drug that was synthesized initially in the 1960s and then investigated clinically and used therapeutically over the next 20 years. Its use has remained in a narrow niche but recent experimental evidence from various research laboratories, including our own, has rekindled interest into the mechanism of action of doxapram and other related drugs. This review will summarize the history, development and clinical use of doxapram and discuss current insights into its molecular mode of action.

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DISCOVERY

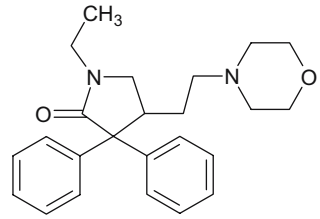

Fig. 1. Chemical structure of doxapram.

The structure of doxapram is shown in Fig. 1; it is known chemically as 1-ethyl-4-(2-morpholinoethyl)-3,3-diphenyl-2-pyrrolidinone. Doxapram was first synthesized in 1962 and found to have a strong, dose-dependent respiratory stimulant action in mammals (53). A pressor response following doxapram administration was also noted. Both of these effects were perceived to occur via stimulation of the central nervous system (CNS). In fact, animals "anesthetized" with phenobarbital were awakened by high dose intravenous doxapram (5 mg/kg) while untreated animals developed convulsions. As such doxapram has been categorized as an analeptic agent (a stimulant of the central nervous system) with greater margin of safety than other CNS stimulants available at that time such as picrotoxin or pentylenetetrazol (PTZ). Its oral LD_{50} in rats is 211 mg/kg (40).

EARLY CLINICAL STUDIES

One of the first investigations of its clinical use in humans was that of Stephen and Talton at Duke University (51). They found that, while doxapram had minor respiratory effect on patients given spinal anesthesia alone, it substantially increased respiratory rate and tidal volume in patients anesthetized with potent inhalational anesthetics (halothane, cyclopropane, ether, or methoxyflurane). Arterial blood gas analysis showed that doxapram induced respiratory alkalosis with lower pCO_2 and higher pH compared to control patients. A mild hemodynamic pressor effect was noted (10–20 mm Hg increase in blood pressure) as well as increased cerebral arousal and more rapid awakening from the inhaled anesthetic. These authors recommended its use in post-anesthetic care units for patients who displayed central nervous system or respiratory depression.

Winnie and Collins went on to coin the term "pharmacologic ventilator" to describe the action of doxapram and other analeptic agents being investigated at that time (55). They directly compared doxapram to other stimulants such as PTZ, nikethamide, bemegride, ethamivan, benzquinamide and methylphenidate (Ritalin) in healthy women undergoing light barbiturate anesthesia. Doxapram produced a significantly greater increase in minute ventilation compared to the other agents but had only a middling effect on arousal or recovery time from anesthesia in this study. This and other studies heightened interest within the anesthesia community about the utility of doxapram as an "antagonist" to general anesthetics and led to studies by pulmonologists and neonatologists in other patient groups.

METABOLISM

Doxapram is metabolized very rapidly when given intravenously. Pharmacokinetic studies in dogs and humans demonstrated that blood levels decline rapidly after a single intravenous dose (Fig. 2) (6,10,45), consistent with the short duration of action reported in

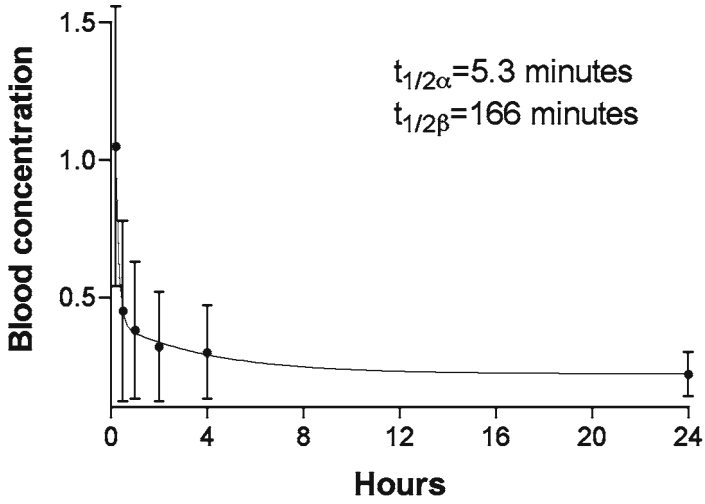

Fig. 2. Pharmacokinetics of doxapram. Blood concentration of doxapram-related compounds determined in 12 dogs. A bolus dose of 20 mg/kg was given at time $t = 0$ and then blood samples were collected. Samples were analyzed for total doxapram content (unchanged plus metabolites) and are reported as mean+std deviation. Continuous line represents non-linear regression using a two-exponential model. Adapted from ref. 6. The α and β half-lives from human pharmacokinetic studies after a single intravenous bolus (1.5 mg/kg) have been reported as 5.5 and 62 min (10).

humans (8–10 min) (51). Approximately 40–50% of a bolus dose can be recovered as metabolites in the urine after 24–48 h. The effective blood concentration is approximately 2 μg/mL (9), which can be reached in patients by administering a loading dose of 1 mg/kg followed by an infusion of 1 mg/kg/h (42).

CELLULAR AND MOLECULAR ACTIONS

As described above, the ability of doxapram to stimulate the respiratory drive was recognized soon after its discovery. However controversy still exists as to its principal site of action — centrally, on brainstem respiratory centers or peripherally on carotid and aortic chemoreceptors. For example, Calverly et al. in a study of humans treated with doxapram found evidence not only for central sensitization to hypercarbia by doxapram but also for peripheral sensitization to hypoxemia (9). Data from both animal and human studies have been conflicting. Presented below are studies that support both effects. Figure 3, adapted from a recent review of respiratory control (16), outlines the principal elements involved in chemosensory control of breathing. Peripheral chemoreceptors in the neck and aorta, activated by hypoxemia ($PaO_2 < 55$) and acidosis, and brainstem centers activated by pH changes in CSF induced by hypercarbia ($pH < 7.3$, acute rise in $pCO_2 \approx 10$ Torr) stimulate ventral nuclei, such as pre-Boltzinger complex to drive increased depth and rate of respiration.

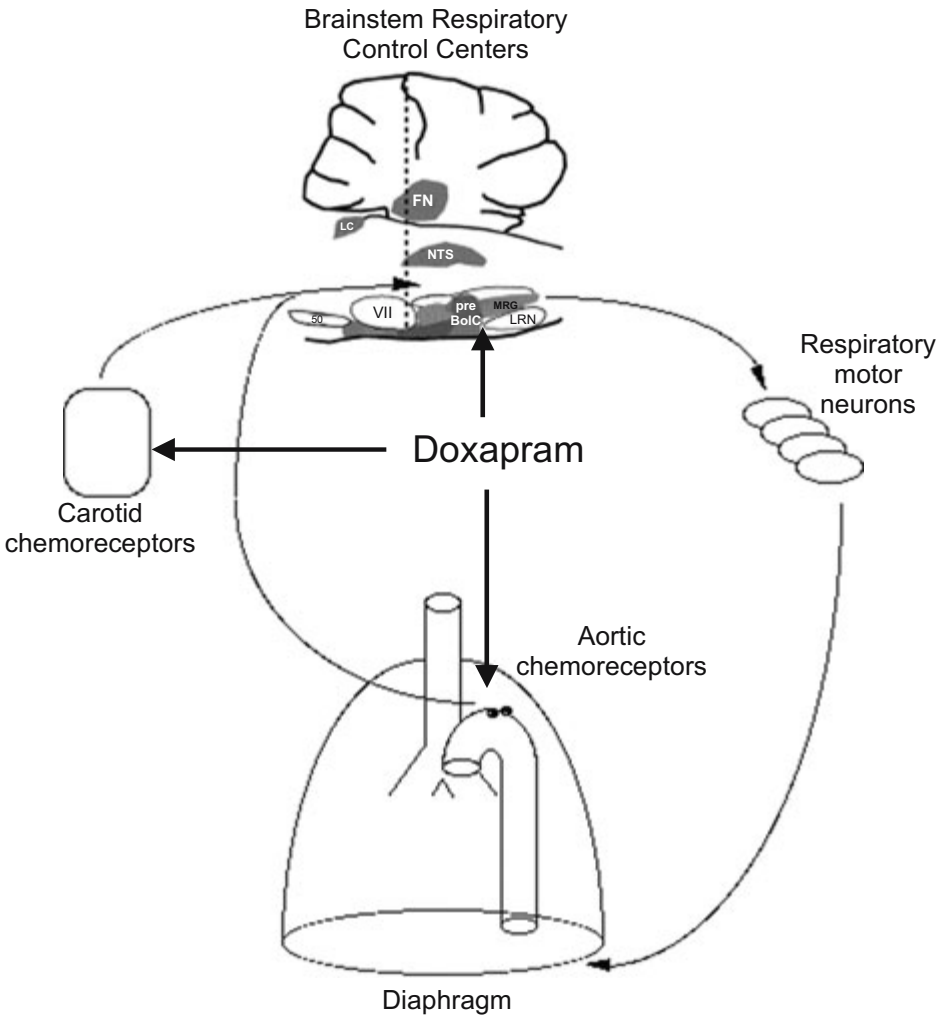

Fig. 3. Major elements in the control of breathing and site of action of doxapram. Peripheral chemoreceptors located in the carotid body and aortic arch provide input to brainstem respiratory control nuclei. The output from these nuclei drive respiratory motor neurons that control the activity of the diaphragm, chest wall, and other accessory muscle of respiration. Doxapram exerts stimulatory effects both peripherally and centrally.

SITES OF ACTION

Evidence for the Central Site of Action

The initial report of doxapram's effect as a respiratory stimulant in dogs found that this effect was not abolished by sectioning the sinus or vagus nerves but was abolished by high spinal cord transection (C2) (53). This finding implied that brainstem respiratory centers, but not peripheral chemoreceptors were stimulated by doxapram. Polak and Plum recorded increased activity of brainstem inspiratory and expiratory neurons in response to

doxapram (41). Direct electrophysiologic study of the effects of doxapram on feline and canine brainstem confirmed a strong increase in inspiratory and expiratory neuronal activity following 0.2 to 1 mg/kg boluses (18). These doses had no detectable effect on other brain regions. At higher doses, up to 40–60 mg/kg, doxapram caused cortical excitation and convulsions. These findings correlated well with the estimated safety margin of 20–40:1 for doxapram.

Evidence for a Peripheral Site of Action

On the other hand, Kato and Buckley, using a cross circulation preparation found that doxapram stimulated respiration through actions not only on central respiratory centers, but also through a stimulatory effect on carotid and aortic chemoreceptors (25). These findings confirmed previous work by Hirsh and Wang who found a biphasic effect of doxapram in cats: low dose doxapram (0.05–0.25 mg/kg) selectively but indirectly activated medullary respiratory neurons through carotid and aortic chemoreceptor stimulation whereas at higher doses doxapram directly and non-selectively stimulated both respiratory and non-respiratory medullary neurons (22). The combination of selective peripheral input plus non-selective central activation drove a large increase in brainstem respiratory activity. Later, Mitchell and Herbert demonstrated a predominant peripheral chemoreceptor effect of doxapram in cats (34). They found that doxapram increased carotid body afferent activity leading to increased phrenic nerve activity equivalent to that produced by severe arterial hypoxemia (PaO_2 = 35–40 mm Hg).

In summary, the effects of doxapram in different areas of the respiratory control system appear to be concentration-dependent. Both central (brainstem) and peripheral (chemoreceptors) sites can be stimulated by doxapram though it is controversial as to which area displays greater sensitivity. This distinction may now be better understood with the emerging understanding of the molecular neurobiology of the respiratory control apparatus.

MOLECULAR NEUROBIOLOGY

Role for K_{2P} Channels in Doxapram Action

Recent studies have identified some of the molecular determinants of peripheral chemosensing and respiratory control. Analysis of the membrane currents that can be isolated from carotid glomus (type I) cells, which are the primary chemosensing cell in carotid body, have found a special role for potassium currents in these cells (39). Buckler established that oxygen sensing in the carotid body occurs through the inhibition of a baseline K^+ current that was not inhibited by conventional K^+ channel blockers (7). These characteristics conform closely to those members of the K_{2P} channel family responsible for background K^+ currents (54). Background potassium channels have been found important in setting the resting membrane potential of cells and to control the overall excitability of neurons in the CNS. There are fifteen family members identified in the human genome that have been divided functionally and by sequence into six subfamilies (Table 1) (reviewed in ref. 20).

TASK-1 and TASK-3 (for TWIK-related Acid Sensitive K channel) are members of the family whose activities are regulated by pH changes within the normal physiologic range. In addition, TASK-1 and TASK-3 activities are modulated by oxygen levels. TASK-1 and

TASK-3 are known to be expressed in carotid bodies and the brainstem (56). Acidic pH values and hypoxia inhibit TASK-1 and TASK-3 channel function, while volatile anesthetics such as halothane and isoflurane enhance their currents (33,38). These data implicate K_{2P} channels in the mechanisms of both ventilatory regulation and volatile anesthetic action. An oxygen-sensitive K^+ current can be recorded from carotid body type 1 cells that have many but not all of the hallmarks of TASK-1 (54). Brainstem respiratory neurons also express TASK channels (4) where they may participate in regulating neuronal excitability changes caused by pH changes.

Doxapram stimulates carotid body through the same molecular mechanisms as hypoxemia. Takahashi et al. compared the effects of doxapram and hypoxia on isolated-perfused carotid bodies in rabbits (52). Doxapram stimulated the carotid body in a dose-dependent

TABLE 1. Human K_{2P} channels and their modulation by various agents

Family	HUGO[1] name	Alternate name	Activators	Inhibitors
Mechano-sensitive	KCNK2	TREK-1	Arachidonic acid, volatile anesthetics[2], mechanical stress, gaseous anesthetics[3]	Bupivacaine, hypoxia, intracellular alkaline pH
	KCNK10	TREK-2	Arachidonic acid, volatile anesthetics, mechanical stress	Ba^{2+} (weakly)
	KCNK4	TRAAK	Arachidonic acid, mechanical stress, unsaturated fatty acids	Ba^{2+} (weakly)
Weak inward rectifier	KCNK1	TWIK-1	Volatile anesthetics (weakly)	Ba^{2+}, quinine, quinidine, bupivacaine
	KCNK6	TWIK-2	Arachidonic acid, volatile anesthetics	Ba^{2+}, quinine, quinidine
	The same	KCNK7	Non-functional	
Acid-sensitive	KCNK3	TASK-1	Volatile anesthetics	Doxapram, H^+ ion, bupivacaine, lidocaine, ropivacaine, tetracaine
	KCNK9	TASK-3	Volatile anesthetics	Doxapram, H^+ ion, bupivacaine, lidocaine
	KCNK15	TASK-5	Non-functional	
Alkaline-activated	KCNK5	TASK-2	Alkaline pH, volatile anesthetics	Bupivacaine, ropivacaine, lidocaine, H^+ ion
	KCNK16	TALK-1	Alkaline pH, volatile anesthetics	Ba^{2+}, quinine, quinidine
	KNCK17	TALK-2	Alkaline pH	Ba^{2+}, quinine, quinidine bupivacaine, lidocaine
Halothane-inhibited	KCNK13	THIK-1	Arachidonic acid	Halothane
	KCNK12	THIK-2	Non-functional	
Spinally-expressed	KCNK18	TRESK	Volatile anesthetics	Bupivacaine, lidocaine, mepivacaine, Zn^{2+}, Hg^{2+}

[1] Human Genome Organization nomenclature designation.

[2] Volatile anesthetics — halothane, chloroform, and isoflurane generally. Other drugs shown to activate some channels include diethyl ether, desflurane and sevoflurane.

[3] Gaseous anesthetics — nitrous oxide, xenon, cyclopropane.

manner and had an additive but not synergistic effect on the carotid body response to hypercapnia. Various potassium (K^+) channel modulators were also studied. Only halothane, an activator of K_{2P} channels reduced the response to hypoxia. Agents acting on K_{ATP} and Ca^{+2}-activated K channels had no effect. This report supports a role for K_{2P} channels in carotid body chemosensing and that doxapram acts through these channels.

Cotten et al. recently established that doxapram has potent direct inhibitory effects on cloned TASK-1 and TASK-3 channels (12). Doxapram inhibited TASK-1 (half-maximal effective concentration [EC_{50}], 410 nM), TASK-3 (EC_{50}, 37 μM), and TASK-1/TASK-3 heterodimeric channel function (EC_{50}, 9 μM). Other K_{2P} channels required significantly higher drug concentrations for inhibition. The inhibitory concentrations were well within the therapeutic range for doxapram and indicated that TASK-1 and TASK-3 are plausible molecular targets for the ventilatory effects of doxapram.

Therefore, it seems likely that at least some of the respiratory stimulant effects of doxapram are mediated through TASK K_{2P} channels. Clearly, other neurotransmitter pathways including serotonergic and noradrenergic elements integrate into central respiratory control, but K_{2P} channels appear to be basic cellular elements mediating the response to respiratory stimuli. These channels are expressed in the cells and tissues that control respiration. Their response to chemosensory input, inhibition by acidosis and hypoxia results in changes in carotid body output. In addition, the respiratory depression produced by volatile anesthetics may also be mediated by these channels by blunting the signaling that occurs in response to acidosis and hypoxia. Volatile anesthetic activation of TASK-1 and TASK-3 would produce hyperpolarization and inhibition of the neural tissues in which they are expressed.

The study by Knill and Gelb from the 1970s is particularly interesting in understanding this interaction (27). They studied the ventilatory response to hypoxia, hypercapnia and doxapram in humans receiving halothane. They found that halothane strongly blunted the increased respiratory response to doxapram and to hypoxia but had scant effect on the respiratory response to hypercarbia. Interpreted in light of the current knowledge of molecular pharmacology of K_{2P} channels, these observations imply that volatile anesthetic inhibition of respiratory control occludes the peripheral (carotid body) targets of doxapram and hypoxia (TASK-1 and TASK-3); however central respiratory drive responsive to hypercarbia, mediated perhaps by other mechanisms, remains intact.

Effect on Neuromuscular Transmission

Improvement in respiration after anesthesia could also occur through a peripheral action of augmenting respiratory muscle function, especially if muscle relaxants had been administered. Pollard et al. studied the action of doxapram on neuromuscular transmission in the rat phrenic nerve-diaphragm preparation (42). Doxapram augmented neuromuscular transmission in a dose-related manner above a threshold concentration of 50 μM. *In vitro* study of the effect of doxapram on the activity of the acetylcholinesterase in rat diaphragm found no inhibitory effect in the concentration range that augmented neuromuscular transmission, excluding cholinesterase inhibition as the underlying mechanism. However, in the presence of partial neuromuscular block, a dose-dependent depression of neuromuscular transmission with doxapram was found. In this respect doxapram was most effective in the presence of neuromuscular blocking agents that have predominant presynaptic effect (β-bungarotoxin and tubocurarine). This study suggests that doxapram has a presynaptic facilitatory action at the neuromuscular junction. In the presence of partial neuromuscular

block, an inhibitory action is revealed that may be post-junctional. However the concentrations of doxapram at which these effects occurred were approximately five times higher than those reached in plasma after a standard clinical dose.

It appears, therefore, that doxapram may affect to some extent the recovery from neuromuscular block and its effect will depend on whether muscle relaxants with predominant pre-synaptic or post-synaptic effects are used. Cooper et al. found that, in humans, spontaneous twitch height recovery was significantly delayed by doxapram for a muscle relaxant with a postsynaptic action (vecuronium), whereas there was no change in recovery for a muscle relaxant with a presynaptic action (atracurium) (11). Doxapram had also no effect on twitch height recovery when the reversal agent neostigmine was used (11,37). Thus, the effect of doxapram on neuromuscular transmission appears to be relatively minor and probably not clinically significant.

CLINICAL STUDIES

Use as a Stimulant in Respiratory Failure

Doxapram has found use in the past as a temporary measure in patients with acute respiratory insufficiency generally superimposed on chronic obstructive pulmonary disease. Edwards and Leszczynski compared doxapram with four other respiratory stimulants (amiphenazole, nikethamide, ethamivan, and prethcamide) and found doxapram to be the most effective agent in reversing hypercapnia and hypoxemia (15). The landmark study by Moser et al. in 1973 demonstrated that doxapram could aid in the management of acute respiratory decompensation (acute respiratory acidosis) in patients with chronic obstructive pulmonary disease (35). The increase in ventilation has been found to be due in equal parts to an increase in tidal volume and frequency of ventilation (8).

Some traditional texts have proposed the use of doxapram for weaning from mechanical ventilation and advocated doxapram as the best agent available since it shows minimal tachyphylaxis. An intravenous infusion of 1–8 mg/min has been suggested to be started just before discontinuing ventilatory support (36). The infusion may be continued for several days with gradual reduction of the infusion rate over time. However its use, at least in the U.K., has declined probably due to the greater efficacy of other techniques such as nasal intermittent positive pressure ventilation as a temporizing measure in respiratory failure (2).

Doxapram has also been proposed as a useful treatment for obstructive sleep apnea. Houser and Schlueter reported successful treatment of a morbidly obese patient with moderate respiratory distress by continuous infusion of doxapram for 14 days (23). Controlled clinical trials of this use have not followed but given the rapid increase in morbid obesity in many countries and its association with obstructive sleep apnea, renewed interest in doxapram for this indication may arise.

Perioperative Actions

Post-anesthesia

As described above, Winnie and Collins used doxapram as a "pharmacologic ventilator" in reviving patients following general anesthesia (55). Doxapram not only stimu-

lates respiration but also arouses patients and has been used for post-anesthetic use as well as for emergency department treatment of drug-induced CNS depression (43). Numerous animal and human studies in the 1970s confirmed that doxapram improves arousal and level of consciousness following anesthesia induced by barbiturates, volatile anesthetics, nitrous oxide and benzodiazepines. A doxapram infusion improved oxygenation and reduced the incidence of pulmonary complications in patients recovering from upper and lower abdominal surgery (14,19,30). Doxapram also increased arousal and shortened recovery time in patients having outpatient surgery (44).

Prevention of Shivering

Finally, a little known role for doxapram in terminating post-operative shivering was found in 1993 (48). The effectiveness of doxapram to prevent shivering on emergence from general anesthesia was compared to that of demerol. Sixty patients who shivered after routine surgery under general anesthesia were allocated randomly to receive normal saline ($n = 20$), doxapram 1.5 mg/kg ($n = 20$), or demerol 0.33 mg/kg ($n = 20$). Both doxapram and demerol were effective in treating postoperative shivering 2–3 min after intravenous administration. In the group who received normal saline, 15 patients were still shivering 10 min after treatment, while in the doxapram group only three patients were shivering at that time. In the demerol group, all patients had stopped shivering within 7 min of receiving the drug. Therefore, both doxapram and demerol were effective in the treatment of postoperative shivering, with demerol being perhaps slightly better. However, a more recent study has shown that doxapram's effect on shivering threshold is minor, lowering the shivering threshold in normal volunteers by only 0.5°C (28).

Use in Apnea of the Newborn

Since the 1970s, the first-line treatment for apnea of immaturity has been methylxanthines (theophylline or caffeine), the efficacy of which in preventing apneas has been well documented (39,47). Doxapram has also been used more recently for controlling apneas unresponsive to methylxanthines alone. A Cochrane review of the literature found only a few randomized, placebo-controlled trials comparing doxapram and methylxanthines (21, 41). Based on these few studies in a small number of patients, there is no significant difference between doxapram and the methylxanthines. Some treated newborns continue to have frequent spells of apnea and needed more vigorous ventilatory techniques such as nasal continuous positive airway pressure or mechanical ventilation. Additionally, several undesirable side effects such as hyperactivity, irritability, alteration of sleep, tachycardia, metabolic, gastrointestinal, and urinary disorders have been noticed in infants treated with doxapram. A significant side effect of doxapram is an increase in blood pressure which could enhance the risk of cerebral hemorrhage.

Furthermore, benzyl alcohol, the preservative in doxapram has been implicated in a fatal syndrome in premature infants. Neonates suffered cardiovascular collapse and death associated with metabolic acidosis, thrombocytopenia, gasping respirations, central nervous system depression, hepatic and renal failure due to benzyl alcohol poisoning. The toxic threshold was determined to be 130 mg/kg/day (5). The largest source of the benzyl alcohol arose from the preservative in flush solution used to keep intravenous access open and elimination of this source has eliminated the problem. Nevertheless, some neonatal

units have excluded all drugs containing benzyl alcohol despite the potential benefit of these drugs. Calculation of the amount of benzyl alcohol administered, based on the concentration of benzyl alcohol and the volume given indicate that there may be acceptable risk of a small amount of preservative versus the benefit of doxapram (31). For doxapram, if administered at recommended infusion rates of 2–2.5 mg/kg/h the current formulation would deliver 21–27 mg/kg per 24 h, which would be considered safe.

A recent case-control study reported that decreased mental capacity in very low birth weight infants that had been treated with doxapram correlated with the amount of doxapram they had received (49). The mechanism of this decrease is unclear. Nevertheless, the available literature supports a limited role for doxapram to increase respiratory drive in premature infants.

SIDE EFFECTS

The most common side effects of doxapram are relatively minor. The following symptoms were reported to occur in less than 5% of patients receiving the drug: cough, dyspnea, tachypnea, headache, dizziness, apprehension, hypertension, flushing, sweating, nausea and vomiting, diarrhea, urinary retention, and muscle spasticity.

Neurologic Effects

Doxapram should probably not be used in patients with epilepsy or other convulsive disorders. There is some controversy whether doxapram is proconvulsant. Electroencephalograpic arousal in dogs sedated with halothane was reliably produced by doxapram (46). However doxapram did not intensify seizures in rats that were elicited by electrical stimulation (1). These authors also compared doxapram to the known convulsant pentylenetetrazol and anticonvulsants phenobarbital and diazepam (1). They found that doxapram produced no change in seizure threshold in this model whereas PTZ lowered and phenobarbital and diazepam raised the threshold, as expected. In humans, doxapram has been associated with CNS excitation, especially in the setting of liver failure where drug metabolism may be impaired. Baxter reported four cases of sustained agitation following the administration of doxapram in ICU patients with some degree of liver insufficiency (3). Doxapram is contraindicated in patients with evidence of head injury or cerebral vascular accident because its cardiovascular stimulatory effect could worsen the neurologic status. However, doxapram has been used to stimulate ventilation in a brain damaged infant without causing a change in intracranial pressure (17).

Cardiac Effects

The cardiac effects of doxapram in humans are mild, perhaps less so than in dogs, which may reflect species differences. A mild pressor effect, more marked in hypovolemic than in normovolemic states (26) is probably due to release of catecholamines. Critically ill patient in the intensive care unit (ICU) demonstrated a 25% increase in cardiac output with doxapram, an effect best explained by an increase in cardiac contractility (26). A latter study found no change in blood pressure or hemodynamics in patients given doxapram following thoracic surgery (29). Cardiac rhythm disturbances have occasionally

been seen in patients receiving doxapram. Huffington and Craythorne saw ventricular ectopy in 3 of 17 patients given doxapram, but in two of them, the arrhythmias had occurred before doxapram administration (24). Stephen and Talton identified non-life threatening dysrhythmias in five of twenty-nine patients given doxapram under general anesthesia using older anesthetic agents (cyclopropane, ether, methoxyflurane) (50). In contrast, no rhythm changes were identified in one hundred adults receiving doxapram in an outpatient surgery setting (44). Therefore, doxapram appears safe in most clinical settings, including ICU patients although doxapram may still be considered contraindicated in those with significant cardiovascular impairment or severe hypertension.

More serious rhythm disturbances have been seen in infants. De Villiers et al. described three neonates who developed second degree heart block, possibly related to prolonged QT interval during the administration of high dose doxapram (13). A follow-up study found that doxapram infusion to neonates caused mild lengthening of the Q-T interval (32). However, six of forty infants studied developed QTc (corrected QT interval) >440 msec, a length considered a significant risk for life-threatening arrhythmias. Accordingly, heart monitoring is recommended when doxapram is given to premature infants.

DRUG INTERACTIONS

Administration of doxapram to patients who are receiving sympathomimetics or monoamine oxidase inhibiors may result in an additive pressor effect. Doxapram does not appear to interact with anesthetic agents that sensitize the heart to catecholamines, such as halothane (50). In patients who have received muscle relaxants, doxapram may temporarily mask the residual effects of muscle relaxant drugs.

CONTRAINDICATIONS

Due to its benzyl alcohol content, doxapram injection is contraindicated in prematurely born neonates. Doxapram is also contraindicated in patients with mechanical disorders of ventilation such as mechanical obstruction, flail chest, pneumothorax, acute bronchial asthma, pulmonary fibrosis, or other restrictive lung diseases as the increase in respiratory drive does not address the primary pathophysiologic problem and may worsen respiratory fatigue.

CONCLUSIONS

The fundamental understanding of doxapram's mechanism of action has recently emerged. These studies have provided new insight into the control and regulation of breathing. However, doxapram continues to have a limited role in clinical medicine. At one time its ability to improve respiration and consciousness following general anesthesia

was significantly useful but as safer and shorter-acting anesthetic agents have arrived, the need for doxapram in the recovery room has declined. Similarly, the use of doxapram in the intensive care unit, whether in adults or neonates with respiratory insufficiency is also reduced, having been supplanted by other agents or techniques. Whether doxapram could find a new niche in the management of patients with obstructive sleep apnea remains to be seen.

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