Doxapram Hydrochloride as a Respiratory Stimulant in Anesthetized Man

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THE USE of analeptics in the management of respiratory depression has been limited because of: (1) the failure of respiratory stimulation to occur in some cases; (2) accompanying increase in metabolism which could offset the increased ventilation and decrease the oxygen available for utilization; and (3) short-lived stimulation, frequently followed by a longer depression.

The recent introduction of new respiratory stimulants [1, 2] has renewed interest in these drugs. One of these, doxapram hydrochloride (AHR-619), 1-ethyl-(2-morpholinoethyl)-3, 3-diphenyl-2-pyrrolidinone hydrochloride hydrate, has been recently synthesized [3] and tested in animals [2, 3] and in awake man.[4]

The purpose of the present study was to determine the usefulness of the drug in the treatment of respiratory depression due to general anesthesia or overdosage of barbiturates in man. The observations to be reported include the acute effects of doxapram hydrochloride on ventilation, arterial blood oxygen and carbon dioxide tensions, *p*H, arterial blood pressure, heart rate, electrocardiogram and electroencephalogram in seven subjects under thiopental anesthesia.

Doxapram hydrochloride was given to seven adults who were hospitalized for elective surgical procedures. With the exception of one patient with moderate arterial hypertension, none had respiratory or cardiovascular abnormalities.

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Preanesthetic medication consisted of atropine 0.4 mg. intramuscularly approximately one-half hour before the induction of anesthesia with 2.5 per cent thiopental sodium. Orotracheal intubation was performed following the intravenous administration of 40 to 60 mg. of succinylcholine and spraying of the vocal cords with 2 per cent lidocaine. An airtight system was accomplished with a cuffed endotracheal tube, coated with 2 per cent lidocaine jelly. Anesthesia was maintained with a mixture of nitrous oxide and oxygen, delivered at a rate of 6 and 2 liters per minute, respectively, and sufficient thiopental sodium to maintain an EEG pattern characterized by waves of 10–50 microvolts at a frequency of 8–15 cycles per second, superimposed on waves of lower voltage at a frequency of 1 to 2 cycles per second. This pattern has been described by Brechner *et al.*[5] in deep anesthesia, just before "burst suppression."

Following the surgical procedure, the subjects were taken to an adjoining recovery room and were allowed to breathe room air for 20 minutes to permit redistribution of thiopental sodium in blood and tissue and elimination of nitrous oxide. All observations were made during air breathing, at least 20 minutes after the last dose of thiopental sodium. In one subject the drug was given on two occasions, one hour apart. In two subjects the observations were recorded before the surgical procedure, and anesthesia was limited to thiopental sodium. The average total dose of thiopental sodium given was 1.872 g. (31 mg./kg. body weight) administered over an average of two hours and 23 minutes. In all subjects, however, the EEG pattern at the time of control measurements was as described previously.

Control arterial blood samples were drawn through an indwelling Cournand or Riley needle in the brachial artery, for P_{O_2}, P_{CO_2},

*p*H and barbiturate. Each arterial blood P_{O_2} and P_{CO_2} determination was done both by means of the Riley bubble equilibration technique[6] and by O_2 and CO_2 electrodes[7]; in all cases there was agreement in the results obtained by the two techniques. *p*H was measured in a model R Cambridge potentiometric *p*H meter. Thiopental sodium plasma levels were measured by the method of Goldbaum.[8] Arterial blood pressure, EEG and ECG were recorded continuously on a Sanborn polyviso recorder (model 964). Tidal volume and respiratory rate were recorded on a Stead-Wells spirometer. Minute ventilation was calculated from continuous recordings of tidal volume and respiratory rate. Esophageal temperature was monitored continuously with a Yellow Springs electric telethermometer. Gas volumes and blood gas tensions were corrected for the esophageal temperature at the moment of sampling.

With the patient in a "steady state," indicated by an unchanging EEG level as described above and stable clinical signs, doxapram hydrochloride was injected intravenously in single doses of either 0.5 or 1.0 mg./kg. of body weight. The injection of drug was made directly into a forearm vein in two subjects, and into the intravenous tubing in the others. Vital signs were recorded continuously and arterial blood samples were taken at two, five, and ten minute intervals. A separate arterial sample was taken at approximately ten minutes after the injection of doxapram hydrochloride for the determination of thiopental sodium levels.

Results

The results are summarized in table 1 according to the dose administered, 0.5 or 1.0 mg./kg. of body weight of doxapram hydrochloride. Four experiments were conducted at each dose level. These results were analyzed statistically by standard analysis of variance techniques on the data adjusted for control.

Tidal Volume. In six subjects tidal volumes increased from 100 to 200 per cent one-half minute after injection and fell to control values within five minutes. Greater increases were recorded initially in the subjects who received 1.0 mg./kg. b.w.

Respiratory Rate. The mean respiratory frequency increased within two minutes from 21 to 23 at 0.5 mg. kg. and from 23 to 29 at 1.0 mg./kg. and returned to control values within five minutes.

Minute Ventilation. Patients receiving 1.0 mg./kg. had a greater response in minute ventilation largely owing to increase in respiratory rate. Only the patients who received 1.0 mg./kg. had a statistically significant ($P \leq 0.05$) increase in respiratory minute volume at both one-half minute and one minute and a half after drug injection. Minute ventilation returned to control values approximately five minutes later. Although there was a greater increase in minute ventilation after the 1.0 mg./kg. dose than after the 0.5 mg./kg. dose, there was no statistically significant difference between the two groups at one-half and one and a half minutes; and there was no significant dose-time interaction. The most pronounced ventilatory response occurred in one subject who received a dose of 1.0 mg./kg. of body weight. The minute ventilation in this subject increased from a control value of 7,568 to 25,575 in half a minute, followed by 21,768 in one minute and a half, 10,948 at two minutes, and approached control values at five minutes. At 0.5 mg./kg. dose the increased ventilation was almost entirely due to an increase in tidal volume, at 1.0 mg./kg. dose to a combination of increased tidal volume and respiratory rate.

P_{O_2}. Patients who received 0.5 mg./kg. had a statistically significant increase ($P \leq 0.05$) in P_{O_2} two minutes post-injection. Patients who received 1.0 mg./kg. had an even greater increase ($P \leq 0.02$) at two minutes. Values returned to control levels between five and ten minutes. Although there was a greater increase in P_{O_2} after the 1.0 mg./kg. than after the 0.5 mg./kg. dose, the difference between the two was not statistically significant.

P_{CO_2}. Two minutes after injection there was a significant decrease ($P \leq 0.01$) in P_{CO_2} in patients who received 0.5 mg./kg. The decrease was likewise significant ($P \leq 0.02$) in patients on 1.0 mg./kg. In all patients P_{CO_2} levels returned to control values within five

to ten minutes. There was no statistically significant difference between the two groups.

Hydrogen Ion Concentration. Arterial *p*H increased similarly in both groups and returned to control values within five minutes.

Blood Pressure and Pulse Rate. There was no statistically significant change in blood pressure at one minute, the time when the increase in blood pressure was greatest. In one subject, however, the blood pressure increased from 200/120 during the control period to 290/190 one minute after doxapram hydrochloride administration.

Pulse rate did not change significantly in patients who received 0.5 mg./kg. but increased significantly ($P \leq 0.02$) in patients who received 1.0 mg./kg. This change reveals a highly significant difference ($P \leq 0.005$) between both groups.

ECG and EEG pattern did not change throughout the procedure. Abundant oral mucous-serous secretions were noticed after the administration of doxapram hydrochloride.

Three patients receiving 1.0 mg./kg. had marked falls in arterial thiopental levels in samples taken 14 to 25 minutes apart, but in all cases ten minutes after the injection of doxapram. The decrease was on the order of 30 to 50 per cent. One patient who received 0.5 mg./kg. on two occasions showed a decrease of about 2 mg./liter in thiopental levels. On both occasions the samples were taken 14 minutes apart.

Discussion

Under the conditions of this study, brief respiratory stimulation was a consistent effect of intravenous doxapram hydrochloride without subsequent respiratory depression. Although animal studies[9] suggested that the pharmacologic action of this drug is exerted through stimulation of the respiratory center, our results do not elucidate the mechanisms of respiratory stimulation. From the brevity of action found, it seems that a continuous intravenous infusion would be the most appropriate method of administration to achieve the desired improvement in minute ventilation. The effect on overall oxygen consumption was not measured. After injection of the drug, however, the respiratory stimulation must have increased the work of breathing and oxygen consumption; however, with the patient breathing room air the arterial P_{O_2} was increased, which would indicate that there was a net increase in oxygen supply.

The slight rise in arterial blood pressure in some patients and in pulse rate in patients who received 1.0 mg./kg. shows that this drug also has circulatory effects. A pressor response to doxapram hydrochloride has been described in dogs anesthetized with phenobarbital in doses of 1 mg./kg.[2] Hypertension was also reported in patients with pulmonary emphysema who were given the drug in doses generally larger than those employed in this study.[4]

All seven subjects exhibited clinical signs of arousal such as movement and chewing on the tracheal tube, but no change in the EEG pattern occurred in any patient. In view of the signs of arousal, it is surprising that the EEG did not change following the injection of doxapram hydrochloride. Although we have no explanation for the lack of change in EEG, it is probably due to the relatively small dose of the drug given (average, 0.75 mg./kg.) in relation to the dose of thiopental sodium (31 mg./kg.). Hypoxia and hypercarbia are known to modify the EEG patterns. Since our patients were in a mild hypoxic state (an average of 94 per cent arterial oxygen saturation) and in slight respiratory acidosis (an average P_{CO_2} of 46 mm. of mercury), when the patients were deeply anesthetized at the time the drug was injected, a change should have been seen with improved ventilation. Dissociation between behavior and the EEG pattern has been previously reported by Wikler.[10]

We do not know the reason for the decrease in the thiopental levels in two of five patients studied, other than redistribution. Since there was no control comparison, it is not known whether the decrease was an effect of the drug *per se*. It should be pointed out that the time interval between the control sample for thiopental levels and the second sample (taken 10 minutes post-doxapram injection) varied from 14 minutes to 25 minutes. The first samples were taken at an average of 32 minutes after the last dose of thiopental, the second at an average of 49 minutes. This may account for the changes in arterial level.

TABLE 1. Respiratory and Circulatory Changes Following 0.5 and 1.0 Mg./Kg. Doses of Doxapram

	Dose (mg./kg.)	Control	Minutes Post Doxapram Hydrochloride ½	1½	2	5	10
Tidal volume (ml.)	0.5	247.5 (±31.3)	435.8 (±157.8)	424.0 (±69.4)	375.3 (±81.5)	469.0 (±229.8)	
	1.0	265.5 (±27.7)	643.8 (±130.5)	543.8 (±123.6)	389.2 (±32.9)	275.0 (±30.7)	
Respiratory Rate (per minute)	0.5	21.0 (±1.1)	21.3 (±2.3)	22.3 (±1.8)	23.5 (±1.9)	20.0 (±2.8)	
	1.0	23.5 (±1.3)	23.3 (±1.6)	29.5 (±2.0)	29.0 (±2.1)	24.3 (±1.6)	
Minute ventilation (ml.)	0.5	5,116.5 (±421.6)	8,248.8 (±1,873.0)	9,083.8 (±711.8)	8,373.5 (±970.9)	7,736.8 (±2,452.9)	
	1.0	6,223.3 (±660.8)	15,097.0 (±3,544.8)	15,351.8 (±2,263.6)	11,112.3 (±516.4)	6,533.5 (±311.8)	
P_{O_2} (mm. Hg)	0.5	75.8 (±1.5)			83.8 (±2.1)	76.5 (±1.8)	
	1.0	79.2 (±1.2)			90.8 (±7.0)	84.0* (±3.5)	84.0* (±3.5)
P_{CO_2} (mm. Hg)	0.5	46.0 (±2.8)			37.0 (±0.8)	42.5 (±1.0)	
	1.0	45.8 (±3.0)			39.5 (±2.8)	47.0* (±3.2)	47.7* (±2.6)
*p*H (units)	0.5	7.385 (±.009)			7.418 (±.006)	7.386* (±.017)	
	1.0	7.388 (±.012)			7.415 (±.013)	7.390* (±.017)	
Blood pressure (mm. Hg)	0.5	103.0/64.8 (±10.1/±9.4)				101.8/66.3 (±10.3/±8.0)	
	1.0	121.0/79.8 (±26.4/±13.8)		131.3/80.3* (±46.4/±14.4)		136.0/91.5 (±34.8/±16.2)	
Pulse rate (per minute)	0.5	98.0 (±9.9)		96.8 (±10.1)	99.5 (±9.6)	95.8 (±8.7)	
	1.0	92.0 (±7.4)		115.0 (±6.6)	101.3 (±7.4)	97.5 (±5.1)	

All figures are mean values (standard errors in parenthesis). Calculations are based on 4 subjects, except those marked.*

We believe that this drug has potential practical applications in the treatment of patients with respiratory depression due to barbiturates. It has been previously reported[2] that the convulsant dose of doxapram hydrochloride in unanesthetized cats is approximately 25 times the respiratory stimulant dose, compared to a 2:1 ratio for picrotoxin and 4:1 for pentamethylenetetrazol (Metrazol). Polak and Plum[11] have recently reported on the relatively wide safety margins of doxapram hydrochloride. Further studies of this compound should be carried out to resolve the questions raised in the present study.

Summary and Conclusions

1. Brief respiratory stimulant and arousal effects of doxapram hydrochloride given at 0.5 or 1.0 mg./kg. were demonstrated in seven subjects under thiopental anesthesia.

2. The most marked effect was an increase in tidal and minute volume with a rise in arterial P_{O_2}, a fall in P_{CO_2}, and a rise in *p*H at both dose levels. There was a significant increase in heart rate at 1.0 mg./kg. only, and no changes in EEG, ECG or blood pressure with either dose.

3. In the doses studied doxapram hydrochloride appears to be a transient potent respiratory stimulant in anesthetized human subjects. Further work remains to be done concerning the efficacy and mode of action under various depressant circumstances.

Dr. Sidney Kaye performed the barbiturate determinations; Dr. Sami I. Said assisted with the respiratory studies; Mr. L. W. Preston performed the statistical analysis. A. H. Robins Company, Richmond, Virginia supplied the doxapram hydrochloride.

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EPIDURAL BLOCK For arteriospasm regardless of etiology and for arterial thrombosis, continuous epidural anesthesia was of help in 49 consecutive patients with arterial occlusive disease. The technique also is helpful postoperatively in reducing pain and preventing pulmonary complications. *(Gwathmey, O., and others: Continuous Epidural Sympathetic Block as a Diagnostic and Therapeutic Aid for Peripheral Arterial Disease, Ann. Surg. 157: 989 (June) 1963.)*

NERVE ROOT BLOCK Treatment of pain slowly responsive to physiotherapy was often successful when nerve root block was used. An advantage of this technique is the elimination of frequent, repeated trigger point injections. Prior to injection a general medical evaluation and appropriate roentgenograms were obtained. Distinction between scleratome and dermatome pains should be made although the treatment is block of the nerve root. Cephalgia often responded to block of the third cervical root while block of the sixth cervical root relieved many cases of brachialgia. Sometimes a trigger point must be injected along with nerve root block. Common low back pain often responds to block of the third lumbar nerve root. Lumbar sympathetic block was the most difficult and least successful block tried. The main justification of this block is swift relief of pain, ease of rehabilitation, shortening of the hospital stay, and the pain relief may last six months. *(Belam, O. H., and Dolmey, G. H.: Scope of Nerve Root Block in Physical Medicine, Proc. Roy. Soc. Med. 56: 444 (June) 1963.)*