INFLUENCE OF DOXAPRAM HYDROCHLORIDE ON RECOVERY FROM THIOPENTAL ANAESTHESIA

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MANY DRUGS known as respiratory stimulants have been used to accelerate recovery from poisoning by barbiturates and other sedative drugs These stimulants have also been used to initiate and sustain breathing in the newborn, and to accelerate the rate of recovery from general anaesthesia Perhaps the most common practice in years past has been to add carbon dioxide inhalation at the end of an anaesthetic to accomplish this goal Even though many feel that these practices may be inherently dangerous, they are still used [1,2]

Recently, several new drugs have been developed which can augment breathing and may accelerate recovery from anaesthesia with far less likelihood of producing dangerous irritation of the gastrointestinal tract (vomiting), respiratory tract (coughing, sneezing), or neuromuscular system (muscle twitching, convulsions) [3–6] Some of these drugs are now being used effectively in the management of chronic incapacitating lung diseases, and they may be useful for reversing respiratory depression produced by analgesics [7–10] Although their action is of short duration when given as a single injection, they increase the sensitivity of the respiratory centres to the arterial blood pCO_2 during postanaesthetic respiratory depression and may be useful in this condition, especially if given as a continuous infusion rather than as a single injection [3,6,11]

A drug of this kind, which was recently introduced, is 1-ethyl-4(2-morpholinoethyl)-3,3-diphenyl-2 pyrrolidinone hydrochloride hydrate (Doxapram®) [12] It is prepared as a 2 per cent stable aqueous solution having a pH of 3 5 to 5 0, which is compatible with 5 or 10 per cent dextrose in water and with 0 9 per cent saline, but is not compatible with any solutions which are alkaline Radioactive carbon-tagged studies of Doxapram in dogs showed that 29 per cent of the C^{14} is excreted in the faeces in the first 48 hours and no Doxapram in the unchanged form is found in the urine

This study was undertaken to determine whether Doxapram effectively shortens the recovery time from thiopental anaesthesia in dogs and to evaluate its efficacy for accelerating recovery from thiopental-nitrous oxide anaesthesia when used following a relatively standard clinical operation in women The influence of Doxapram on the respiratory and cardiovascular systems in the immediate post-anaesthetic periods was also evaluated clinically

Methylphenidate and *d*-amphetamine were tested in the animals for comparison with Doxapram, but they were not used in the clinical study because the former frequently causes gastrointestinal disturbances, and the latter causes cardiac arrhythmias

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Methods

Animal Study

Cross-over experiments were performed four times, at weekly intervals with Doxapram, *d*-amphetamine, and methylphenidate, using 10 mongrel dogs of comparable age and size (13 to 25 kg, mean 21 kg) Prior to each test the dogs were weighed after a 12-hour fast In every experiment, each dog received 25 mg/kg thiopental in a 2 5 per cent solution, injected intravenously in a forepaw vein at the approximate rate of 150 mg per minute This was followed immediately, in alternate experiments, by injection of one of the test drugs The dose selected for the test drug was based on the therapeutic range of usefulness Immediately after injection, the dog was placed on the floor of the laboratory and allowed to recover without being disturbed or stimulated The recovery time of each animal was recorded as the time which elapsed from the beginning of the injection until the dog lifted its head, and then until it attempted and was able to stand on all four paws without collapsing As soon as a dog recovered, it was removed from the room so that it would not disturb the remaining dogs

Clinical Study

Female patients, scheduled for elective uterine dilation and curettage, who were in good general health and in the age range of 17 to 50 years, were selected as subjects for the tests If the anaesthetic course was not smooth, or if the patient did not have a tidal volume of at least 300 ml as determined by a Wright respirometer, at the termination of the anaesthetic, but *before* the administration of Doxapram, the patient was not included in the study

Premedication consisted of atropine or scopolamine 0 4–0 5 mg, i m, administered 30–45 minutes prior to anaesthesia Induction was achieved with thiopental 2 5 per cent solution administered intravenously through a three-way stopcock connected to an intravenous infusion of 500 c c 5 per cent dextrose in water A test dose of 75–100 mg of thiopental was given After 1 minute, the patient was asked to look at the ceiling and count aloud during the slow injection of thiopental (25 mg/sec) When the patient stopped counting and/or closed her eyes and wouldn't open them when requested to do so, a face mask was applied and nitrous oxide-oxygen mixture (6 litres/2 litres) was administered using a semi-closed method and assisted breathing A second dose of thiopental, equal to the total induction dose, was then injected at the same rate When abdominal relaxation was required to facilitate bimanual pelvic examination, a small dose of succinylcholine was administered intravenously Respiratory rate, blood pressure, and pulse rate were recorded throughout the procedure

At the termination of the surgical procedure, the patient's tidal volume was measured by a Wright respirometer, along with the other vital signs Then, an intravenous infusion of Doxapram 0 1 per cent solution in 5 per cent dextrose in water was begun by connecting it to the existent intravenous infusion via the three-way stopcock It was previously decided that 400 mg would be the maximum dose of Doxapram administered at the rate of 13 3 mg per minute

Thereafter, vital signs were recorded at 1 minute intervals until the patient was fully recovered from the anaesthetic, as evidenced by her answering questions and

executing verbal commands [2,13] The Doxapram infusion was discontinued when the desired end point was reached and the patient was then taken to the recovery room where another reading of tidal volume, respiratory rate, blood pressure, and pulse was taken, usually within 5 minutes after Doxapram infusion was stopped. All patients were observed carefully during their stay in the recovery room for 1–2 hours postoperatively to determine the occurrence of side-effects.

Results

The responses to Doxapram, *d*-amphetamine, and methylphenidate in dogs are summarized in Table I No untoward effects occurred following injection of the analeptics, and each invariably caused an appreciable reduction in the recovery time from thiopental anaesthesia The effects of Doxapram and *d*-amphetamine were essentially the same, while methylphenidate was evidently the weaker analeptic according to the dosage selected

TABLE I

Effect of Respiratory Stimulants on Thiopental Recovery in Dogs

	Dose (mg /kg)	Recovery time (min) Head up Mean*	S E	Difference (%)	Significance *p*	Recovery time (min) Legs up Mean*	S E	Difference (%)	Significance *p*
Thiopental alone	25	33	6	33	<0 01	53	7	35	<0 001
+ doxapram	10	22	5		>0 001	34	6		
Thiopental alone	25	30	5	24	<0 001	44	6	32	<0 001
+ amphetamine	0 1	23	4			30	7		
Thiopental alone	25	34	5	15	<0 01	49	7	22	<0 01
+ methylphenidate	1 0	29	7			38	7		

*Each mean time represents 20 administrations of thiopental alone or with test drug

A summary of the clinical data is shown in Table II The first effects of Doxapram were a rapid increase in tidal volume and respiratory rate These changes usually became apparent in less than one minute and, in all cases, before three minutes following the initiation of the Doxapram infusion Then a plateau was reached and, after about three to four minutes, there was a gradual decrease in both respiratory rate and tidal volume, with subsequent levelling off The initial increase in tidal volume was usually more prominent and striking than the effect on the respiratory rate Pulmonary ventilation remained stable during the period of observation after the infusion was discontinued In no instance did the tidal volume or respiratory rate decrease below the values noted immediately prior to the administration of Doxapram

Circulatory changes observed during the administration of Doxapram were not appreciable No instances of frank hypertension occurred, a slight increase in blood pressure occurred in four patients (> 20 mm Hg) and an increase in heart rate occurred in only five patients (10 to 20 beats/minute)

Neuromuscular irritation appeared in four patients and consisted of muscular rigidity in two of the patients and mild twitching of the small muscles of the face

TABLE II

INFLUENCE OF DOXAPRAM ON RECOVERY TIME FROM THIOPENTAL–NITROUS OXIDE ANAESTHESIA

				Pentothal		Doxapram		Recovery time (min)				
	Age	Weight (kg)	Anaesthesia time (min)	Total dose	mg/kg	Total dose	mg/kg	Response to verbal command	Sluggish verbal response	Alert verbal response	Hand face test	Total sleeping time
Control* (55 patients)	40	64	20	480	7 5	—	—	14	17	18	19	38
Control† (79 patients)	37	63	19	441	7 0	—	—	12	15	16	18	37
Mean (50 patients)	37	69	31	560	9 3	195	3 3	5	6	7	8	39
Highest	50	88	45	850	16 2	400	8 9	10	15	18	20	70
Lowest	17	40	15	400	6 6	80	1 3	1	2	3	3	18

*Previously reported (Ref 12)
†Previously reported (Ref 2)

and hands in all four These symptoms disappeared within a few minutes after the Doxapram infusion was discontinued

Recovery from Anaesthesia

Signs of recovery from the anaesthetic followed shortly after the respiratory changes Once the Doxapram infusion was discontinued, there was no return to the hypnotic state preceding the infusion The patients remained fully awake or slightly drowsy, but all were easily engaged in conversation None of the patients developed sneezing or salivation during the Doxapram infusion One patient coughed and one patient vomited during awakening

DISCUSSION

Continuous intravenous infusion of a dilute solution (0 1%) of Doxapram was chosen over the intermittent method of intravenous injection on the basis of previously reported data, as well as our own experience with Doxapram, because it permits minute-to-minute control of effects both desirable and undesirable, whereas a single injection of any analeptic produces an evanescent effect [2,3 11]

The decrease in recovery time was not statistically significant when compared to the expected recovery time following a double "sleep dose" of thiopental, since most adults "sleep" approximately 40 minutes after the injection of twice the amount of thiopental which causes unconsciousness [2,13,14] In the present study, the *total "sleeping time"* in the control and test groups was virtually the same, however, the *stages* of awakening appeared at a much faster pace in the latter—an effect observed by others who have studied the action of Doxapram in humans recovering from thiopental as well as from inhalational anaesthesia [3–6]

It is obvious, therefore, that one cannot categorically state that "awakening time" is changed by any therapeutic measure unless the average "sleeping time" for a given *dose* of an anaesthetic agent is determined first in a similar group or

in the same group of patients Using a dose of 5 mg /kg of thiopental, the fully awake responses after 30 minutes occurred oftener if 1 mg /kg Doxapram was given than in the control group, although the difference was not striking in the study reported by Siker, Mustafa, and Wolfson [5] In our study, the control groups had a much slower rate of awakening even though the average dose of thiopental was less and the duration of anaesthesia maintenance was appreciably shorter On this basis, it is possible that the Doxapram infusion did in fact accelerate the rate of recovery

In dogs, an accelerated arousal effect by Doxapram hydrochloride is an established fact, as has been shown for virtually all analeptics that have been tested during thiopental anaesthesia [15–17] To be certain that an accelerated recovery from anaesthesia occurs in humans, one must use a test in which each patient is anaesthetized at least twice with the same dose, once with and once without an analeptic, as was done in a cross-over test in animals

The respiratory stimulating action of Doxapram is beyond any doubt, as evidenced by the results of this study, as well as those reported by others [4–6] The increase in minute volume of breathing was due consistently to a rise in both tidal volume and respiratory rate [4 5] The duration of the respiratory-stimulating action with Doxapram hydrochloride appeared to be long-lasting because once the patients awakened they did not lapse back into sleep with recurrence of respiratory depression This effect may be attributed to the much larger dose that can be administered without provoking undesirable reactions when a slow dilute infusion is given Such an effect can be duplicated with several of the newer analeptics [3]

Augmented pulmonary ventilation is the most useful effect that one may desire from use of an analeptic at the end of an anaesthetic on account of the usual problems arising when postanaesthetic respiratory depression persists [2 7,8,18] The effect on breathing is more likely to accelerate awakening after an inhalation anaesthetic than one given by the intravenous route, because the inhaled agent may be eliminated more rapidly An acceleration of awakening by an analeptic may also inherently augment pulmonary ventilation [19]

Effects of Doxapram on the cardiovascular system, as judged by changes in blood pressure and heart rate, were negligible in the patients observed and confirms similar observations by others [4–6]

Complications such as sneezing, salivation, coughing, and nausea and vomiting were uncommon, occurring only in 2 of the 50 patients in the present study Four patients developed signs of central nervous system irritation, but, upon discontinuing the Doxapram infusion, there was an immediate abatement of this response Undesirable effects thus appeared to occur less frequently than with other analeptics [2]

The advantages and disadvantages of using pharmacological versus mechanical hyperventilation is a subject which remains controversial [11] However, pharmacological hyperventilation supplemented by oxygen inhalation offers advantages over mechanical methods provided that the analeptic drug does not interfere with any physiological functions aside from stimulating or augmenting pulmonary ventilation As with any other method of intensive care, constant attendance by

personnel familiar with the use of analeptic agents and full knowledge of how to manage possible neuromuscular complications remain essential

Since Doxapram appears to possess a high relative safety factor, it may be efficacious if used in the following situations postanaesthetic respiratory depression *not* due to excessive doses of muscle relaxants, postanaesthetic shallow breathing due to incisional pain ("splinting"), especially after thoracic and upper abdominal procedures, to accelerate arousal after short surgical procedures, and to augment breathing in instances of mild or moderate overdosage with central depressant drugs

It is probably wise to avoid the use of Doxapram hydrochloride in patients with a history of epilepsy, petit mal, and other convulsive disorders and in patients with severe hypertensive cardiovascular disease

Summary

Cross-over experiments performed in dogs showed that Doxapram hydrochloride in a single-dose injection was as effective as *d*-amphetamine in shortening the recovery time from a standardized dose of thiopental anaesthesia and was more effective than methylphenidate in the dosages that were compared No untoward effects were observed in any of these experiments

When Doxapram hydrochloride was used in an intravenous infusion method for 50 healthy female patients following an elective dilatation and curettage of the uterus, the drug was effective for stimulating respirations (both tidal volume and respiration rate) without producing any appreciable circulatory changes In four instances, there were signs of central nervous system irritation which subsided promptly upon discontinuation of the Doxapram infusion

An appreciable difference in the time for full recovery to occur was found between patients receiving the analeptic and others who did not Direct clinical observation leaves no doubt that an arousal effect is produced which persists along with the augmented breathing response However, an accelerated recovery from thiopental anaesthesia is not a prominent effect with respect to the expected recovery time because it did not appreciably reduce the total "sleeping time" following a double "sleep dose" of thiopental in humans

Résumé

A la suite d'expériences croisées chez des chiens, nous avons constaté que le chlorhydrate de doxapram, administré en une seule dose, était aussi efficace que l'amphétamine pour accélérer le réveil à la suite d'une anesthésie produite par une dose standard de thiopental et était plus efficace que le phénidate de méthyl à des doses comparables Au cours de ces expériences, nous n'avons pas observé d'effets secondaires

Chez 50 malades en bonne santé, opérées pour dilatation et curetage, nous avons employé le chlorhydrate de doxapram en perfusion endoveineuse, nous avons observé une stimulation de la respiration (l'air courant et le rythme) sans changement circulatoire important Chez quatre malades, des signes d'irritation du système nerveux central sont apparus, mais, en arrêtant la perfusion, ils sont disparus rapidement

Nous avons observé une différence appréciable dans le délai du réveil complet chez les malades qui avaient reçu l'analeptique et chez ceux qui ne l'avaient pas reçu L'observation clinique directe nous permet d'affirmer qu'il se produit un réveil qui persiste et ainsi qu'une augmentation des échanges respiratoires Toutefois, un réveil précoce d'une anesthésie au thiopental ne constitue pas un facteur important si l'on considère le délai normal prévu pour le réveil, le médicament n'a pas diminué, de façon appréciable, la durée du sommeil chez l'humain, à la suite d'une double dose de thiopental

ACKNOWLEDGMENT

This study was supported by a grant-in-aid from Dr W R Tabor of A H Robins Co , Inc , Richmond, Va

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