Electroencephalographic Evidence of Arousal in Dogs from Halothane after Doxapram, Physostigmine, or Naloxone

Raymond C. Roy, Ph.D., M.D.,* and Edward H. Stullken, M.D.*

The clinical impressions of enhanced arousal from halothane anesthesia and improvement of postanesthesia recovery scores after doxapram, physostigmine, or naloxone have not been verified in laboratory studies based on the effect of these drugs on MAC. With induction of anesthesia, a shift in the amplitude of the EEG from low to high occurs at anesthetic concentrations well below MAC and appears to coincide with the loss of consciousness. The authors examined the effect of arousal agents on the end-tidal halothane concentration required to produce this shifting EEG. In 24 unmedicated dogs, the end-tidal halothane concentration was elevated to 20 per cent above the shift point concentration (from 0.61 ± 0.03 to 0.73 ± 0.03 per cent) and maintained at this level for 30 min. Doxapram, 1 mg/kg, iv, and physostigmine, 0.03 mg/kg, iv, converted the EEG from a high amplitude to a low amplitude tracing in 22 ± 3 s in eight of eight, and 225 ± 37 s in seven of eight dogs, respectively. The end-tidal halothane concentration required to restore the shifting EEG was elevated above control for 50 ± 7 min and 109 ± 7 min, respectively. Naloxone, 0.06 mg/kg, iv, produced an awake EEG in two of eight dogs in 233 ± 18 s which persisted for 22 ± 4 min, and a transiently shifting EEG in three of eight dogs between 200 and 240 s. Naloxone 0.006 mg/kg, iv, produced an awake EEG in 80 ± 8 s in four of four dogs who had previously received doxapram 3 h earlier. In this model doxapram and physostigmine paralleled the clinically observed onset and duration of arousal. The inconstant arousal from halothane anesthesia induced by naloxone was interpreted in terms of an opiate receptor independent action. (Key words: Analgesics: doxapram. Anesthetics, volatile: halothane. Antagonists, miscellaneous: physostigmine. Antagonists, narcotic: naloxone. Brain: electroencephalography. Potency, anesthetic: MAC.)

Prompt arousal from inhalational anesthesia at the end of surgery is a desirable anesthetic objective obtained by careful titration and early discontinuation of the potent inhalational agent. Variability in patient response to anesthesia and difficulty in assessing surgical progress occasionally result in prolonged postoperative somnolence. The results of several clinical studies suggest that the administration of doxapram,† physostigmine,‡ or naloxone§ facilitates patient arousal from inhalational anesthesia and improves postanesthesia recovery scores. However, in humans, halothane 0.1 MAC attenuated and 1.1 MAC abolished the ventilatory responses to 0.4 mg/kg doxapram, iv.¶ Also in humans, 1.2 mg naloxone, iv administered during surgical levels of halothane anesthesia produced no circulatory or electroencephalographic evidence of arousal. In dogs, physostigmine was shown to decrease MAC. Naloxone was reported to have no effect on MAC but direct infusion of naloxone into a dog’s fourth ventricle has produced arousal.

The lack of experimental confirmation of the clinical impression of arousal induced by these drugs may be related to the selection of MAC as the end-point to be influenced. Tinker et al. have reported in primates that as the end-tidal halothane concentration was increased beyond 0.4 MAC, the EEG pattern shifted abruptly from posterior to anterior dominance in amplitude. This shift appeared to coincide with a loss of ability to respond to commands in humans. In dogs there is no spatial shift in dominance with increasing anesthetic concentrations; rather, there is a generalized shift from a low-amplitude to a high-amplitude pattern. Stullken et al. demonstrated a sigmoid-shaped CMRO₂-end-tidal halothane concentration curve in dogs and noted that a shifting EEG was associated with the steepest rate of decline of CMRO₂ and that MAC was well beyond this point, on the “flat” portion of the curve. Thus, measuring the influence of drugs on the end-tidal concentration producing this shift in the EEG may be a more appropriate method for judging their efficacy as arousal agents than determining their effect on MAC. The purpose of the present study was to test this hypothesis in dogs using doxapram, physostigmine, and naloxone.

Materials and Methods

Twenty-four fasted, unmedicated mongrel dogs (16–21 kg) were anesthetized with halothane in oxygen. Succinylcholine (3 mg/kg, iv) and atropine (0.4 mg, iv) facilitated endotracheal intubation. A continuous succinylcholine infusion was used to maintain paralysis as determined every 30 min by a Burroughs Wellcome BlockAid® monitor with needle electrodes applied to the sciatic nerve. Mechanical ventilation was maintained with a Harvard® respiration pump. Cannulae were placed in the femoral veins for fluid and drug administration and in the femoral artery for blood sampling.

---

* Assistant Professors of Anesthesia.

Received from the Department of Anesthesia, North Carolina Baptist Hospital, and Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, North Carolina 27103. Accepted for publication March 25, 1981. Supported in part by a grant from the North Carolina United Way. Presented in part at the annual meeting of the American Society of Anesthesiologists, San Francisco, California, October 1979.

Address reprint requests to Dr. Raymond C. Roy: Department of Anesthesia, Wake Forest University, Bowman Gray School of Medicine, 300 South Hawthorne Road, Winston-Salem, North Carolina 27103.

0003-3022/81/1000/0392 $00.80 © The American Society of Anesthesiologists, Inc.
AROUSAL AFTER DOXAPRAM, PHYSOSTIGMINE, OR NALOXONE

and continuous arterial pressure monitoring. $P_{CO_2}$, $P_{O_2}$, and $pH$ were measured using an Instrumentation Laboratory Micro 13® $pH$/Blood-Gas Analyzer with the electrodes at 37°C. The $P_{CO_2}$ was maintained at 40 ± 3 torr; $P_{O_2}$ at greater than 200 torr; and $pH$ 7.34–7.38. Twelve subdermal Grass E2B electrodes were placed to yield a four-lead bipolar electroencephalogram recording activity across the midline anteriorly, antero-laterally, posterolaterally, and posteriorly with reference to an indifferent ear electrode. The dog's eyes were closed and covered and the ears were occluded with cotton. Arterial and airway pressures were transduced by strain gauge (Statham® P23ID) and recorded continuously along with the EEG, ECG, and heart rate with a Grass 78D Polygraph. End-tidal halothane was continuously sampled from a catheter passed through the endotracheal tube to the carina and was measured with a calibrated Beckman® LB-2 Medical Gas Analyzer. Nasopharyngeal temperature was maintained at 37 ± 1°C.

The shift point concentration of halothane was determined in each dog after reducing the end-tidal halothane to 0.3 per cent, a level which gave an awake EEG pattern characterized by low amplitude tracings in all four leads. The end-tidal halothane concentration was then increased at a rate of 0.05 per cent every 5 min until the EEG presented an intermittent asleep-awake pattern characterized by a 1:1 mixture of high- and low-amplitude waves in all four leads. The shift point was always determined going from the awake to the anesthetized state to avoid possible hysteresis.

Then the end-tidal halothane concentration was increased to 20 per cent above the shift point concentration. This level resulted in an anesthetic EEG pattern in all dogs and was maintained for 30 min prior to drug injection. The anesthetic EEG was characterized by increase in amplitude in all four leads.

The dogs were then divided into three groups of eight. Group I dogs received 1 mg/kg doxapram, iv; Group II, 0.03 mg/kg physostigmine, iv; and Group III, 0.06 mg/kg naloxone, iv. The effect of drug administration on EEG pattern was noted and the shift point concentration of halothane was then determined and recorded at 10-min intervals in each dog in Groups I and II for two hours. In Group III, the end-tidal halothane concentration was maintained at 20 per cent above the control shift point concentration for a 2-h period. All eight dogs from Group I were given an additional hour of halothane anesthesia at 20 per cent above the original shift point concentration, i.e., three hours after doxapram, and either 0.006 mg/kg naloxone, iv or 0.03 mg/kg physostigmine, iv, was administered. Data were analyzed for significance using Student's $t$ test and for extrapolation using regression line analysis by the method of least squares. Difference were considered statistically significant if $P < 0.05$. Values were expressed as means ± SEM.

Results

The end-tidal halothane concentration at which the EEG shifted from an awake to an anesthetic pattern was 0.61 ± 0.03 per cent ($n = 24$) and did not differ significantly between groups. Mean arterial pressures, $P_{CO_2}$, $P_{O_2}$, and temperature before drug administration in the three groups also were not significantly different. The intravenous injection of normal saline in the eight dogs in Group I prior to doxapram administration produced no EEG or cardiovascular effects within 10 min. The shift point was characterized by an amplitude increase in all four leads. Consistent with what has been reported,9,10 no spatial shift in amplitude dominance from posterior to anterior was seen in these dogs.

The effect of 1 mg/kg doxapram in all eight dogs with end-tidal halothane concentrations maintained at 20 per cent above the control shift point concentration was to convert the EEG to an awake pattern in 22 ± 3 s (fig. 1). The results of repeated shift determinations at 10-min intervals after doxapram administration are shown in figure 2. To convert the EEG back to a shifting pattern required significant elevations of the end-tidal halothane concentration. A linear extrapolation of shift point concentrations of halothane to the time of drug administration suggests that 1 mg/kg doxapram had increased the shift point concentration from 0.61 to 0.94 per cent end-tidal halothane. The halothane concentration required to produce a shifting EEG was the same as control 50 ± 7 min after doxapram administration.

The effect of physostigmine was to produce an awake EEG in seven of eight dogs in 225 ± 37 s. The duration of physostigmine effect was 109 ± 7 min (fig. 2). In one dog there was no evidence of arousal. Extrapolation of shift point concentrations suggests that physostigmine 0.03 mg/kg increased to 1.15 per cent the end-tidal concentration required for anesthesia. In four of four dogs from Group I who had previously received doxapram, physostigmine produced arousal identically to that seen above.

Following 0.06 mg/kg naloxone, EEG evidence of arousal was seen in only two of eight dogs in Group III. The onset time in these two was 233 ± 18 s and the duration of effect 22 ± 7 min. In three of eight dogs a transiently shifting EEG pattern was noted between 200–240 s. In the remaining three dogs no EEG changes in amplitude were observed. Administration of 0.006 mg/kg naloxone (one tenth the dose in Group III), produced arousal in 80 ± 8 s in four of four dogs from
Group I who had previously received doxapram. The time for return to a sleeping pattern at a constant end-tidal halothane concentration 20 per cent above the control shift point concentration was 18 ± 7 min.

The cardiovascular effects are summarized in table 1. Doxapram and physostigmine gave the expected responses, but naloxone produced no significant hemodynamic changes. In the doxapram and physostigmine groups, cardiovascular changes were transient while the EEG changes were of longer duration.

Discussion

Doxapram, physostigmine, and naloxone are frequently given at the end of an anesthetic to arouse patients. However, other arousal maneuvers performed concurrently complicate evaluation of drug effectiveness. These variables were eliminated by avoiding premedication and intravenous inducing agents, by using only one agent, by maintaining a constant end-tidal halothane concentration, by controlling ventilation to normocarbia, by maintaining normothermia, by minimizing external stimulation, by using a muscle relaxant without known effect on MAC, and by maintaining paralysis to avoid muscle artifact in the EEG.

The EEG shift in amplitude from high to low appears to be a good arousal marker. It is obvious, nonsubjective, and reproducible. It appears to parallel changes in CMRO₂ regardless of the anesthetic agent or CBF. It appears to coincide with the loss of ability to obey commands in humans. Finally, it supports the clinical impression of arousal with doxapram and physostigmine.

One criticism of this model is that only the occurrence of a shift in the EEG with drug administration yields conclusive information. If a shift is not observed, then an uncertainty exists. It may not occur because the drug is not an arousal agent, because the drug dose is not high enough to produce arousal, or because 20 per cent above the shift point is too far out on the CMRO₂-concentration curve. Species differences will additionally complicate extrapolation to the human situation. Fortunately with doxapram and physostigmine, doses comparable to those used clinically in humans produced a shift. However, with naloxone, ten times the clinical dose for humans did not give unequivocal results in dogs except in the circumstance when doxapram had been given previously.

The effectiveness of doxapram as an arousal agent in early studies seemed to parallel its effectiveness as a respiratory stimulant. Knill and Gelb demonstrated that halothane sedation (0.1 MAC) attenuates and anesthesia (1.1 MAC) abolishes the ventilatory response to dox-
Arousal after doxapram, physostigmine, or naloxone

EEG shift points

- Doxapram
  ET [halothane] = -0.007 (time) + 0.95
  n = 6  m = 0.007  r = 0.99  b = 0.95

- Physostigmine
  ET [halothane] = -0.005 (time) + 1.11
  n = 8  m = -0.005  r = 0.96  b = 1.11

Fig. 2. The effect of doxapram and physostigmine on the end-tidal halothane concentrations required to produce a shifting EEG as a function of time.

Doxapram. Mitchell and Herbert have suggested that not only the ventilatory response but also the arousal response to doxapram could be mediated through peripheral receptors. In support of this is the observation in figure 1 that the EEG evidence of arousal coincided with the onset of the cardiovascular and ventilatory effects in the partially paralyzed dog. The onset time of 22 s agrees with that reported by Scott et al. in humans breathing 100% oxygen. However, Deming reported a 75 to 108 s delay between the respiratory response and arousal at doses of 1.5–2 mg/kg in humans, but her study population included patients anesthetized with cyclopropane, ether, and methoxyflurane at end-tidal concentrations closer to 1 MAC than to the shift point concentration. A central mechanism is also suggested because the duration of the EEG effect was significantly longer than the duration of the cardiovascular effects (50 vs. 8 min). Thus, while the exact mechanism of doxapram arousal is not known, it clearly is not due to the elimination of the inhalational agent by increased ventilation as has been suggested.

Hill et al. found that physostigmine significantly reduced postoperative somnolence from halothane anesthesia. Horrigan reported that 0.04 mg/kg physostigmine aroused five of six dogs from 1 MAC halothane. But with the maintenance of anesthesia this arousal effect persisted for only 2–30 min and was followed by a 6.8 per cent decrease in anesthetic requirement in the 30- to 90-min period after intravenous administration. Consistent with the latter are the observations by Sitaram et al. of an antinociceptive effect to electrical stimulation of the forearm in unanesthetized humans from 0.007 mg/kg physostigmine 20 min after intravenous injection, and by Weinstock et al. who found that 0.1 mg/kg physostigmine antagonized morphine-induced respiratory depression but not analgesia in dogs and rabbits. The present study documents an arousal effect in dogs which persists for 109 min.

These five studies are not strictly comparable. First, in the studies by Hill et al. and Sitaram et al., and in this study, belladonna anticholinergics were given (glycopyrrolate would have been a better choice); Horrigan and Weinstock et al. gave none. Secondly, Sitaram et al. used no anesthesia; Hill et al. made observations in the recovery room; Weinstock used ketamine anesthesia; and Horrigan and we maintained anesthesia, though at different end-tidal levels (MAC vs. 20 per cent above shift point concentration). Thirdly, Sitaram et al., Horrigan, and Weinstock et al. used painful stimuli, Hill et al. presumably did not, and we avoided stimulation.

The discrepancy between the effect of physostigmine on MAC and on arousal is further evidence that anesthesia is a complex state. Halothane decreases ace-
tylcholine turnover in all parts of the central nervous system. Physostigmine may act by crossing the blood-brain barrier, blocking acetylcholinesterase activity centrally, and permitting the build-up of acetylcholine at muscarinic receptors in the ascending reticular activating system. However, this mechanism does not explain the antinociceptive effect and does not take into account either Horrigan’s observation that neostigmine, which presumably does not cross the blood barrier, also lowers MAC, or the recent observation that pancuronium, which inhibits muscarinic receptors peripherally, also lowers MAC.

Arndt and Freye reported arousal with naloxone infused directly into the fourth ventricle within 5 min in dogs receiving halothane approximately 20 per cent above the shift point concentration of our study. The reported time to reverse narcotic effects when given intravenously is 1–2 min. They attributed their longer onset time to a prolonged diffusion time for naloxone to go from the fourth ventricle to receptors below the surface as compared to circulation time plus diffusion from blood vessels to the same receptors. However, intravenous administration in our study produced EEG evidence of arousal in five of eight dogs (two sustained, three transient) in 200–240 s. Also, Artru et al. noted a rise in EEG frequency and a fall in amplitude 5 min after intravenous 10 mg/kg naloxone given to dogs receiving halothane anesthesia 40 per cent above the shift point concentration (0.87 per cent). Thus, the explanation for the delayed onset does not appear to be a difference in route of administration.

The above data are consistent with an opiate receptor independent arousal action for naloxone. The peak brain level for naloxone administered intravenously is within 5 min. Artru et al. detected no significant change in CMRO₂ at halothane concentrations 40 per cent above the shift point concentration despite transient EEG changes which are supposed to parallel CMRO₂ changes. Had they been closer to the shift point concentration would they have observed a sustained arousal or an increase in CMRO₂? Would we have seen sustained arousal in more dogs at a higher dose of naloxone?

Unexplained is the narcotic antagonist-like reversal of halothane anesthesia by naloxone in dogs who had received doxapram about 3 hours earlier. Also unexplained is the absence of a significant cardiovascular response to naloxone in this study. Arndt and Freye with well documented arousal and Artru et al. with transient EEG changes at much higher naloxone doses (10 mg/kg) reported increases in blood pressure and heart rate in dogs.

In conclusion, the influence of doxapram and of physostigmine on the end-tidal halothane concentration required to produce a shifting EEG parallels the clinically observed onset and duration of arousal seen with these two drugs. When the same model is used to evaluate naloxone, the equivocal results obtained suggest that naloxone is not a clinically useful reversal agent for halothane anesthesia. Arousal effects which are inconsistently seen with naloxone may be related to an opiate receptor independent action of the drug.

References
