

## What Constitutes Adequate Anesthesia in Animals? In Neonates?

*To the Editor:*—The article in ANESTHESIOLOGY by Yaster *et al.*<sup>1</sup> raises the important question of what comprises “adequate anesthesia” in animals, and, by extension, in newborn humans and others unable to communicate effectively. In their study, all of the newborn lambs that received very high-dose fentanyl (3000  $\mu\text{g}/\text{kg}$  iv) without muscle relaxants were catatonic and had profound respiratory depression. In addition, the authors describe only minimal hemodynamic changes to the noxious stimulus. Yet clamping of the tail with a hemostat (and “then moving it and the tail continuously”) resulted in what the authors called “purposeful” movement.

It is possible that newborn lambs are different in their response to opioids from most prey animals (and humans). However, in the face of the other classical manifestations of high-dose opioids, the lambs must have had profound analgesia. Thus was the occurrence of “purposeful” movement really an indication of inadequate anesthesia? The response to noxious stimuli applied to the tail can be a spinally mediated reflex. In the apparent absence of hemodynamic response to stimuli, additional information would be necessary to determine whether the “purposeful” movement was due to peripheral reflexes as opposed to inadequate depression of consciousness.

The situation is complex: a high dose of opioids given to many classes of prey animals results in a constellation of behavioral signs indistinguishable from the “death-feign reflex.”<sup>2</sup> The animals become rigid, akinetic, analgesic, and hypothermic. Yet in response to auditory or tactile stimuli, they exhibit “explosive motor behavior,” consisting of a startle response followed by festinating forward locomotion.<sup>3</sup> The same constellation of signs can be elicited by extreme stress and appears to be mediated by endogenous opioid systems. This reflex is, therefore, believed to be protective in the event of sudden predator attack. Were the newborn lambs in Yaster’s study simply expressing “explosive motor behavior” in response to tail stimulation? Is this a conscious (*i.e.*, purposeful) act or simply a primitive reflex? This cannot be ascertained from the information provided by Yaster *et al.*

Lack of movement in response to surgical stimulation has been the traditional gold standard of depth of anesthesia but may have less meaning with the receptor-specific iv anesthetic agents, especially the opioids. Minimum alveolar concentration (MAC) was originally defined for inhalational agents as the “minimum concentration in the alveolus required to keep a dog from responding by gross purposeful movement to a painful stimulus”<sup>4</sup> and was subsequently modified for application to humans as the alveolar anesthetic concentration at which one-half of the patients move in response to a surgical stimulus.<sup>5</sup> Intravenous anesthetics produce effects that are both clinically and neuropharmacologically different from the volatile agents. Until better measures of level of consciousness or brain function are developed, perhaps the criteria for anesthesia should be tailored to the agent in question as well as to the species under study.

Others have suggested that the proper assessment of anesthetic potency requires several different endpoints of anesthetic effect corresponding to the different components of general anesthesia.<sup>6,7</sup> The components of general anesthesia include a decreased level of consciousness, amnesia, lack of movement, analgesia, and blunted cardiovascular reflexes. Kissin *et al.*<sup>6,7</sup> have demonstrated (in rats) that the ED<sub>50</sub> values, slopes of the dose-response curves, and the relative potency ratios for different endpoints of anesthesia are, in fact, different for different anesthetics. For example, in one study,<sup>7</sup> they found that much lower doses of fentanyl were required to block the movement response to a noxious tail stimulus (ED<sub>50</sub> = 9  $\mu\text{g}/\text{kg}$ ) than to block the heart rate response (>1% increase above baseline) to the same noxious stim-

ulus (ED<sub>50</sub> = 312  $\mu\text{g}/\text{kg}$ ). In contrast, with morphine, similar doses (ED<sub>50</sub> = 5.8 mg/kg) blocked both the heart rate and movement responses to stimulation. Interestingly, the loss of righting reflex (considered by some to be a good measure of the consciousness-depressing effects of anesthetics in animals) occurred at relatively modest fentanyl doses (ED<sub>50</sub> = 23  $\mu\text{g}/\text{kg}$ ) but only at very high morphine doses (ED<sub>50</sub> = 45.2 mg/kg).

Although opioids when given alone may not always block movement responses to surgical stimulation, does this contraindicate their use as anesthetic agents? Except in selected surgical situations (*e.g.*, “open eye,” microsurgery, etc.), movement *per se* seems to be a relatively unimportant component of anesthesia. Rather, unconsciousness, amnesia, and the obtundation of cardiovascular reflexes seem more essential. What then constitutes a successful anesthetic in a patient population (*e.g.*, neonates or infants) where the occurrence of perioperative awareness cannot be easily assessed yet the possibility of long-term psychological consequences cannot be excluded?

There is a significant body of literature which suggests that opioids, even at very low doses, are potent amnesic agents in rodents and other small animals.<sup>8</sup> For example, mice injected with morphine or heroin immediately after daily conditioning sessions in a discriminative avoidance task show retrograde amnesia.<sup>9</sup> Similar results have been observed using an inhibitory avoidance task in rats.<sup>10</sup> Are lambs more like rats than they are like humans? Are infants (either animal or human) more susceptible to the amnesic properties of opioids?

It seems entirely possible that the newborn lambs receiving fentanyl alone in the study by Yaster *et al.* had no awareness of the noxious stimulus. One must thus consider, in the face of quite stable hemodynamics, good analgesia, amnesia, and respiratory support, whether excellent anesthetic conditions would have prevailed if muscle relaxants had also been administered. A former colleague was often fond of saying, “if the patient lies still and doesn’t remember, then the rest is a private matter between the anesthetist and the patient’s cardiovascular system.”

In summary, one of the conclusions of Yaster *et al.* may not be warranted on the basis of the data presented in their paper. Because of their minimal cardiovascular depression, a high dose of opioids (in combination with muscle relaxants) may, in fact, provide superior anesthesia in the newborn animal to that provided by barbiturates alone or the combination of opioids and barbiturates. While the opioids may not be particularly effective amnesic agents in adult humans, further studies on their amnesic properties in neonates and infants are necessary before definitive clinical recommendations can be made.

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*In Reply*—We could not disagree more with Drs. Weinger and Koob or with the implications of their letter. We absolutely disagree that clamping an animal's tail with a hemostat elicits only a "spinally mediated reflex" and is an inappropriate method of testing "anesthesia." Movement in response to tail clamping is the time-tested, gold standard method of assessing anesthesia and has been since the concept of "MAC" was introduced 20 yr ago.<sup>1,2</sup> In fact, this technique has been used by many different investigators using various animal species, including rats, dogs, and sheep because it produces a supramaximal stimulus.<sup>1-5</sup> When investigating the anesthetic effects of either iv or inhalational agents, a supramaximal stimulus is necessary in order to avoid misleading results and conclusions that may occur when a submaximal stimulus is used.<sup>1,2,4</sup> In our studies of the newborn lamb's peripheral and cerebral hemodynamic responses to high-dose fentanyl administration, we assessed anesthesia using a 10-inch hemostat, clamped to the first ratchet for 30 s.<sup>6,7</sup> It was clear in both studies that fentanyl could not reliably prevent purposeful movement to this stimulus.

Nevertheless, even if Drs. Weinger and Koob were correct about tail clamping, there is ample evidence to support our conclusion that fentanyl, when administered alone, does not produce anesthesia in newborn lambs. In our study, when fentanyl was administered alone, all of the lambs appeared awake; that is, their eyes were open and they turned their heads to sound.<sup>7</sup> The addition of a subanesthetic dose of pentobarbital abolished these responses. Second, fentanyl administration was always accompanied by apnea which we treated with rapid endotracheal intubation and mechanical ventilation.<sup>6,7</sup> All of the lambs physically resisted intubation by head withdrawal and closure of their vocal cords. They also developed tachycardia and hypertension during intubation. These behaviors and responses are commonly associated with inadequate anesthesia. Indeed, during the subsequent mechanical ventilation, the animals chewed on their endotracheal tubes. These physical behaviors and autonomic responses were similarly abolished with the addition of small, subanesthetic doses of pentobarbital.<sup>7</sup> Third, systolic arterial blood pressure also increased following the tail clamp when fentanyl was administered alone. Adding a barbiturate abolished this autonomic reactivity. This confirmed our previous finding that increases in arterial blood pressure in response to a painful stimulus are directly related to the strength of the withdrawal response and are abolished when consciousness is lost.<sup>7</sup> Finally, the effects of fentanyl

on cerebral blood flow (CBF) and oxygen consumption (CMRO<sub>2</sub>) also support our belief that the lambs were not anesthetized when fentanyl was administered alone. In our studies, when lambs responded to tail clamping and appeared awake, CBF and CMRO<sub>2</sub> did not decrease.<sup>6,7</sup> On the other hand, when the lambs appeared unconscious and did not respond to tail clamping, which occurred following the administration of both fentanyl and pentobarbital, CBF and CMRO<sub>2</sub> significantly fell.<sup>7</sup> In this way fentanyl may act like other anesthetic agents, such as the barbiturates, which decrease CBF and CMRO<sub>2</sub> only when consciousness is lost.<sup>8</sup>

Based on our clinical and laboratory experience, we and many others believe that fentanyl, when administered alone, should not be considered an "anesthetic" nor should it even be expected to produce unconsciousness or amnesia in animals or humans.<sup>9,10</sup> Indeed, it is precisely because patients may be awake during high-dose fentanyl anesthetics that most anesthesiologists add benzodiazepines, barbiturates, low-dose potent vapors, or nitrous oxide to their anesthetic regimens. In fact, this was the impetus behind our study.

Unfortunately, as our laboratory study and the clinical studies of Lunn *et al.* and Stanley *et al.*<sup>11,12</sup> demonstrate, the addition of other agents may significantly affect the hemodynamic stability and safety of fentanyl "anesthesia." Thus, when used as a single agent, in the newborn, in critically ill patients, or in the laboratory for scientific investigation, fentanyl may not be a total anesthetic agent. However, the solution is not, as Drs. Weinger and Koob suggest, to add a muscle relaxant and think the problem is solved. Paralyzing an awake subject for surgery to prevent movement is an unconscionable approach that is insupportable, either clinically or in the laboratory. Indeed, in this era of heightened concern for the welfare of animals, and by extension, for human newborns and others who are unable to communicate, we must increase our sensitivity to this issue and provide "anesthesia" when we say we are.

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