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### The Interaction of Fentanyl on the Cp<sub>50</sub> of Propofol for Loss of Consciousness and Skin Incision

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IN this study, Smith *et al.* (page 820) have quantitated the interaction of fentanyl and propofol on the clinical endpoints of loss of consciousness to verbal stimuli and prevention of purposeful movement from skin incision. Surgical patients had propofol and fentanyl administered with a computer-controlled infusion pump, which rapidly attained, then maintained constant drug blood concentrations. For induction of anesthesia, patients received propofol alone at target blood concentrations ranging from 1.5 to 10  $\mu\text{g/ml}$ , or additional fentanyl target plasma concentrations of 0.2–4.5  $\text{ng/ml}$ . After a defined period of constant drug concentrations that allowed blood:central nervous system equilibrium, verbal responsiveness was assessed; similar methodology also was used for assessment of skin incision. Fentanyl and propofol had a profound interaction, such that the propofol concentration blocking a verbal response in 50% of the patients (Cp<sub>50</sub>) decreased from 3.5  $\mu\text{g/ml}$  when propofol was used alone to 40% of that value at a fentanyl plasma concentration

of 3  $\text{ng/ml}$ . For skin incision, the propofol Cp<sub>50</sub> decreased from 15.2  $\mu\text{g/ml}$  with propofol alone to 37% of this value at a fentanyl plasma concentration of 1  $\text{ng/ml}$  and 11% at a fentanyl plasma concentration of 3  $\text{ng/ml}$ . This study demonstrates the significant decrease of propofol blood concentrations necessary when concurrent fentanyl is present. This study and that of Vuyk *et al.* (ANESTHESIOLOGY 78:1036–1045, 1993) represent the first quantitation of the interaction of propofol with opioids using clinically relevant methodology. When used concurrently, much lower plasma concentrations of either propofol or opioid are necessary for adequate clinical anesthesia, requiring a decrease of the respective dose administered. Appreciation of this anesthetic drug interaction can prevent excessive intraoperative dosing and subsequent delayed postanesthetic recovery.

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### Influence of a Subanesthetic Concentration of Halothane on the Ventilatory Response to Step Changes into and out of Sustained Isocapnic Hypoxia in Healthy Volunteers

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### Does Subanesthetic Isoflurane Affect the Ventilatory Response to Acute Isocapnic Hypoxia in Healthy Volunteers?

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IN his original series of articles, Knill demonstrated that subanesthetic concentrations of halothane, enflurane, and isoflurane significantly decrease the ventilatory response to hypoxemia. (For example, see ANESTHESIOLOGY 49:244–251, 1978.) Subsequently, Davies *et*

*al.* established that subanesthetic concentrations of halothane decrease the electrical response of the canine carotid body to hypoxic stimulation, providing a physiologic basis for Knill's findings (ANESTHESIOLOGY 57: 153–159, 1982). More recently, however, Temp *et al.*

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were unable to reproduce Knill's results (ANESTHESIOLOGY 77:1116–1124, 1992). During subanesthetic (0.1 MAC) isoflurane inhalation, they found only trivial, nonsignificant changes in hypoxic ventilatory response, leading to considerable controversy.

In this issue of ANESTHESIOLOGY, Dahan *et al.* (page 850) and van den Elsen *et al.* (page 860) have provided us with yet additional data regarding the somewhat controversial subject of the effects of subanesthetic concentrations of volatile anesthetics on ventilatory response to hypoxia. First, they found that, during halothane (0.22% inspired), the increase in  $\dot{V}_E$  associated with an acute hypoxic stimulus was only 35% as great as in the awake state; furthermore, after 20 min of hypoxia ( $P_{ET}O_2 \approx 44$  mmHg),  $\dot{V}_E$  decreased to less than baseline during halothane administration. Possible explanations for the discrepancy between these results and those of Temp *et al.* include: use of halothane as opposed to isoflurane (although Knill's data were similar for the two agents); use of a slightly larger dose of anesthetic (the *inspired* concentration of halothane in Dahan *et al.*'s study was 0.22%, or 0.26 MAC, as compared to an *end-tidal* concentration of 0.1 MAC in Temp *et al.*'s study); and differences in subjects' level of consciousness during the ventilatory determinations (Dahan *et al.*'s protocol *required* that subjects' eyes not open spontaneously when measurements were made during halothane administration; Temp *et al.*'s subjects watched Ken Burns' "Civil War" documentary video during isoflurane administration).

In a recent editorial in ANESTHESIOLOGY, Robotham suggested that subjects' level of consciousness may play a key role in determining the outcome of ventilatory control measurements during sedation (ANESTHESIOLOGY 80:723–726, 1994). In the second of their papers in this issue, van den Elsen *et al.* have elegantly answered Robotham's call for a systematic determination of this effect. They evaluated the effect of isoflurane (0.1 MAC end-tidal) on the ventilatory response to a hypoxic step stimulus under two conditions: (1) room darkened and silent, no tactile or verbal stimulation, eyes closed, and (2) music videos with sound playing on a video monitor, eyes open, verbal stimulation to "open your eyes" if spontaneous eye closure occurred. In the absence of audiovisual stimulation, 0.1 MAC isoflurane caused a 48% decrease in the ventilatory response to hypoxia (as assessed by the increment in  $\dot{V}_E$  associated with a decrease in  $P_{ET}O_2$  from 110 to 43 mmHg). In contrast,

during the videos, isoflurane caused only a nonsignificant (10%) decrease in hypoxic ventilatory response. These results are comparable to the 57% decrease observed by Knill *et al.* (quiet room) and the 15% decrease reported by Temp *et al.* (documentary video), respectively.

What, then, is the clinical importance of these laboratory findings? Patients recovering from general anesthesia are likely to have central nervous system concentrations of anesthetics in the 0.1–0.2 MAC range. In a busy, noisy postanesthesia care unit, Temp *et al.*'s observations may be more relevant, particularly in patients who have received no other sedative or analgesic medications. With the constant prodding, poking, and stimulation to breathe when  $SpO_2$  decreases to less than 98%, significant respiratory depression from subanesthetic concentrations of potent agents in the recovery room is unlikely. However, a more ominous situation exists after patients leave the confines of the postanesthesia care unit and return to their quiet, darkened hospital rooms. Once the initial transfer is complete, patients may not be observed or stimulated for hours at a time (particularly if a "really sick" patient is elsewhere on the ward). It is under these circumstances that patients' lives may depend on intact ventilatory control mechanisms; as shown in the present article as well as by Knill *et al.*, it is these same conditions that predispose to significant depression of hypoxic ventilatory response by residual anesthetics. This suggests that measurements of the ventilatory effects of sedatives (including subanesthetic concentrations of inhaled agents) and analgesics should be performed with as little extraneous stimulation as possible. If research subjects spontaneously close their eyes in the busy laboratory environment, patients are certain to fall asleep in their comfortable hospital beds.

van den Elsen *et al.* are to be congratulated for resolving the apparently conflicting findings of the previous investigations. By emphasizing the importance of defining the degree of external stimulation during evaluation of ventilatory control, they have reduced the likelihood of inconsistencies in future studies. Finally, their observations should remind us all that patients may remain at risk even after we discharge them from the postanesthesia care unit.

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## Spinal Delivery of Sufentanil, Alfentanil, and Morphine in Dogs: Physiologic and Toxicologic Investigations

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“BEFORE the generally accepted use of the anilino-piperidines can be undertaken for chronic intrathecal or epidural administration, an extensive histomorphologic study in an animal model is required.” So begins a safety and pharmacodynamic study (page 899) of intrathecal and epidural sufentanil, alfentanil, and morphine in dogs. This study is remarkable for two reasons. First, it reminds us of the need for safety studies before general use of spinally administered drugs. Clearly, the rationale that drugs that are safe for intravenous use must therefore be safe for epidural/spinal use is incorrect, and the thousands of patients who have been exposed to epidural/spinal sufentanil and alfentanil before proper safety testing attests to both good fortune and a laissez faire attitude that should not be condoned. Nonetheless, the current study uses a detailed, powerful, and expensive animal model to demonstrate that there is no preclinical evidence for concern in the epidural/spinal administration of these drugs. Second is the thorough and exhaustive nature of the current study, which provides a wealth of information that could have (and still can) guide clinical use of these

compounds while providing testable hypotheses for future research. Little is known about the factors governing distribution of opioids after epidural/spinal administration and correlations between their concentrations in various biophases and clinically relevant effects. The late Harlan Hill, followed by Christopher Bernards, embarked upon a series of studies in collaboration with Tony Yaksh to determine these factors and describe these pharmacodynamics. The current study, although not formally a part of these studies, shows the remarkably fast absorption of intrathecally administered opioids into the systemic circulation and the lack of alteration in these kinetics with prolonged drug exposure and prolonged catheterization, despite fibrotic investment of the catheter. These observations may clarify clinically recognized acute respiratory effects after intrathecal sufentanil administration in parturients and point the way toward formal kinetic studies in patients with cancer. Perhaps the most apt description of this superlative study is “better late than never.”

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