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In reply:—We appreciate the additional comments and the pharmacokinetic analysis of the dosage requirements of sufentanil provided by Drs. Hilberman and Hyer. Underestimation of the potency of sufentanil was a common clinical problem when it was first introduced. Sufentanil used in smaller doses as a component of balanced anesthesia, as Hilberman and Hyer suggest, would not be expected to cause frequently the complication we reported. We agree that comparative pharmacokinetic analysis and clinical experience with sufentanil should result in modification of the package insert.

MARC GOLDBERG, M.D.
Assistant Professor of Anesthesia

JAMES MCKENNA, M.D.
Fellow in Anesthesiology

Department of Anesthesiology
Hahnemann University
Broad and Vine
Philadelphia, Pennsylvania 19102

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In reply:—Hilberman and Hyer have provided a well-thought-out assessment of the pharmacokinetic differences between SUFENTA® and fentanyl in their review of Goldberg's report of postoperative rigidity following a "substantial sufentanil overdosage" in a patient undergoing *elective lumbar laminectomy.*

The parameters for dosing as described by Hilberman closely reflect those found during the clinical trials conducted in support of marketing approval for sufentanil in the United States. The mean dose for supplementation of a thiopental N_2O–O_2 muscle relaxant anesthetic was found to be 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ or less of sufentanil. It should also be noted that approximately 75% of the dose required for the duration of the surgical procedure was administered during the induction phase. Overall maintenance dosages for an anesthetic duration of 0–2 h were 0.26 μg/kg; 2–4 h, 0.66 μg/kg; 4–6 h, 0.76 μg/kg; 6–8 h, 1.71 μg/kg. These dosages again are remarkably similar to the 11–22 μg/h maintenance dosage predicted by Hilberman. It should be noted that the mean induction dose of thiopental following a preloading dose of sufentanil was less than 2 mg/kg when dosed to effect.

Protocols for the study of sufentanil dosing were designed to use sufentanil to control breakthrough. By protocol, a volatile inhalation agent was used after two successive doses of sufentanil failed to control increases in blood pressure or heart rate. In the Flacke study[1] there were no patients who required an inhalation agent in the sufentanil group as compared with 29% in the fentanyl control group.

Original Janssen dosage guidelines were kept relatively broad to maximize the flexibility for anesthesiologists in their use of sufentanil. We have since revised the package insert in June 1985 to provide dosage requirements relative to the expected duration of the procedure. Using the guidelines outlined previously, the expected total dose of sufentanil in Goldberg's patient would be 1 $\mu g \times 75 \times 2.5$ h, or 187.5 μg.

Dr. Hilberman has pointed out the 41% requirement for naloxone in the Flacke study. It is important to note that the last administration of narcotic in the sufentanil group was closest to the end of surgery as compared with the fentanyl, morphine, and meperidine groups. The fact that the opioids were administered in a blinded fashion in fixed dosages speaks to the need to titrate maintenance dosages to the individual patient and to use nonopioid supplements when appropriate to maintain anesthesia near the end of the surgical procedure.

Further, regarding Goldberg's findings of rigidity in the postoperative period, Flacke *et al.* found that 47% of the sufentanil-treated patients lost consciousness at less than 1.5 μg/kg without thiopental. It has been postulated that there is a close correlation between the dose (plasma level) of an opioid that produces unconsciousness and that which causes rigidity, with rigidity occurring immediately prior to onset of unconsciousness. An outside consultant who reviewed the Goldberg case report postulated that with the dose of sufentanil administered (300 μg for the 2.5-h duration of the case) it would be possible to have a sustained plasma level near that which produces unconsciousness, and administration of any sedative medications would further enhance this effect. Because plasma levels tend to fall off more steeply with sufentanil than with fentanyl, careful titration of dose to patient needs should minimize this potential pharmacologic effect.

In conclusion, while Hilberman's formula and the initial clinical research produce dosing guidelines that are remarkably similar, they reflect average sufentanil dosage