In reply.—It was our intention to alert readers that we had developed an assay that could detect sufentanil and its metabolites in the 50–200 picogram range. All our prior studies to detect sufentanil by packed-column gas chromatography had been hampered by poor sensitivity and the appearance of interfering substances in the chromatographic profiles. Thus, we considered this a major, reportable discovery. To our knowledge there is no published technique for ready detection of sufentanil at the levels commonly used for anesthesia.

We stated in the discussion that the use of this assay for pharmacokinetic studies will be difficult because the terminal elimination phase of sufentanil is at or less than the limits of detection. As we suggested, we are currently analyzing larger plasma samples to increase our sensitivity and are not experiencing any problems with interfering substances. It should be noted that we have used this assay for drug abuse and overdose cases as well as patient studies (cardiac and chemotherapeutic) where higher doses of sufentanil are administered. In these analyses, we have found the assay quite adequate in the range of 100–200 picogram sufentanil/ml plasma.

The extraction efficiency and coefficient of variation in the early stages of our assay were not ideal. The extraction efficiency for sufentanil from serum is 77–82%. Extreme care must be taken to minimize evaporation or physical losses during the reconstitution of the extracted sufentanil into microliter volumes of toluene. The coefficient of variation for 5,000, 1,000, 500, 100, 50, and 25 picograms/ml of sufentanil in serum was 13% (3), 7% (6), 15% (8), 21% (6), 55% (7), and 42% (4), respectively, with the N-value indicated in parentheses. We are currently trying to increase our precision and accuracy along with increasing our sensitivity.

We cannot offer a satisfactory explanation for the rapid drop in plasma sufentanil concentrations between 13 and 17 h in the chronic renal failure patient. The complications we reported were not unique to this patient, because a second chronic renal failure patient experienced respiratory depression. However, with this patient, the plasma sufentanil concentrations were within those found for control patients. We have since terminated our studies using sufentanil in renal failure patients until a suitable explanation for the complications can be found.

Because there are no published studies concerning the metabolism of sufentanil, primarily due to the previous absence of suitable assays for sufentanil and its metabolites, we felt at liberty to speculate on its metabolism. Because the major metabolic pathways for alfentanil and sufentanil are similar, it did not seem inappropriate to apply the possibility of polymorphic metabolism.

Our articles and the letter by Avram et al. emphasize the need for cautious use of this potent anesthetic. The use of an agent that has one published pharmacokinetic study, one published analytical assay, and no published metabolic studies should be of considerable concern.

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(Accepted for publication February 24, 1986.)

Anesthesiology
65:112–113, 1986

Reliability of Sufentanil Plasma Level Assays in Patients

To the Editor:—We would like to comment on the recent articles by Weldon et al. and Wiggum et al. concerning sufentanil plasma levels in patients. In the first article, the authors describe a capillary gas chromatographic (GC)
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method enabling the measurement in plasma of sufentanil and two metabolites, norsufentanil (MPPP) and desmethyl sufentanil, with detection limits varying from 20 to 50 pg/ml. Analytic evidence, however, is not provided for either detection limit. In one patient who received a 1.5 µg/kg dose, plasma levels of sufentanil were quantifiable up to 150 min after dosing, whereas both metabolites were only detectable before 30 min, giving at least ten times lower plasma levels. Since the analgesic potency of desmethyl sufentanil is one-tenth that of the parent drug and because of the extremely low plasma levels, one can hardly speak, as the authors do, about an "active metabolite" because its real contribution to the overall pharmacologic effect is negligible.

The sensitivity of the applied GC method is comparable with that of a radioimmunoassay (RIA) developed by Michiels et al. Because of the specificity of the sufentanil antibodies, the RIA is not able to measure plasma levels of the metabolites. Especially for samples with low concentrations (&leq;1 ng/ml), we prefer to include an extraction step prior to RIA. This improves the sensitivity and overcomes problems of differences in nonspecific binding of different types of plasma, as mentioned by Weldon et al. Instructions for the extraction procedure have been included in the manual of the available sufentanil RIA kit.

Recently, we also developed a capillary gas chromatographic mass spectrometric (GC/MS) method with similar detection limits to quantify sufentanil and both metabolites in plasma and urine.* Correlations between this assay and RIA (after extraction) were excellent over a wide concentration range. We could not find norsufentanil and desmethyl sufentanil in plasma of patients after a 3 µg/kg dose. In urine, desmethyl sufentanil was a minor metabolite, amounting to not more than 0.3% of the dose.

In the article of Wiggum et al., a case is reported of prolonged postoperative respiratory depression associated with (apparently) abnormally elevated plasma sufentanil levels in a patient with end-stage renal failure. Plasma levels of sufentanil were measured by the GC method described by Weldon et al. The inconsistent pharmacokinetic profile of sufentanil in this patient is most likely explained by interference of concomitantly administered drugs, e.g., quinidine. We have had a similar experience with the GC analysis of fentanyl plasma levels in patients medicated with quinidine. In addition, we want to stress again that even in this patient, there is no evidence for the presence of a sufentanil metabolite in plasma. Hence, this could not be the reason for the prolonged respiratory depression seen in this patient, as further supported by the failure of naloxone to reverse these effects.

In conclusion, the sufentanil GC method of Weldon et al. is questionable, especially for the assay of plasma from surgical patients routinely receiving a number of different drugs. In such cases, the higher specificity of a GC/MS method is desirable to minimize artifacts. We feel that because of its high specificity, the RIA (after extraction) could be the routine method of choice to study the pharmacokinetics of sufentanil in patients. In either case, authors should be required to validate properly their analytic methods prior to submission of their assay results.

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Drug Infusion with a Paceport™ Swan-Ganz Catheter during Cardiopulmonary Bypass

To the Editor—When drug therapy is necessary during full cardiopulmonary bypass (CPB), drugs may be injected directly into the venous reservoir of the bypass pump. However, it is often more convenient to administer con-

Anesthesiology
65:113–114, 1986

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