

Anesthesiology
65:441, 1986

Is Midazolam Desirable for Sedation in Parturients?

To the Editor:—We would like to report an observation concerning the use of midazolam (Versed®) for conscious sedation. It is common practice in our obstetric unit to administer small doses of diazepam and/or fentanyl (after the umbilical cord is clamped) to parturients experiencing minor discomfort during cesarean delivery under regional anesthesia. No adverse effects have been seen from this practice except for the frequent complaint of pain on injection produced by intravenous diazepam. We have recently begun to use midazolam, a water-soluble benzodiazepine, because of decreased pain after iv injection.¹ Other advantages claimed for midazolam are better amnesia and sedation when contrasted to diazepam.

We have recently treated several parturients with midazolam in doses of 2–7 mg iv that resulted in clinically satisfactory sedation during their cesarean delivery. These women, however, when interviewed 24–48 h postoperatively, complained of having no recall of the birth of their babies.

We suggest that the superior amnestic qualities of midazolam may be counterproductive in the obstetric unit by depriving new mothers of the memory of their birthing experience.

WILLIAM CAMANN, M.D.
MICHAEL B. COHEN, M.D.
GERARD W. OSTHEIMER, M.D.
*Department of Anesthesia
Brigham and Women's Hospital
75 Francis Street
Boston, Massachusetts 02115*

REFERENCE

1. Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ: Midazolam: Pharmacology and uses. *ANESTHESIOLOGY* 62:310–324, 1985

(Accepted for publication June 12, 1986.)

Anesthesiology
65:441–442, 1986

Succinylcholine in Peripartum Patients

To the Editor:—The article entitled “Succinylcholine pharmacodynamics in peripartum patients”¹ reports lower serum cholinesterase activity in both term and postpartum patients than in nonpregnant patients not using oral contraceptives. In addition, recovery of twitch response (injection to 25% recovery time) was prolonged in postpartum patients, but all four groups showed similar 25–75% recovery times. The authors hypothesized that succinylcholine duration is prolonged in postpartum patients because of its slower elimination, but not in pregnant patients at term because the volume of distribution of succinylcholine is increased and this offsets the reduced rate of elimination in term patients.

Further mathematical treatment of the authors' data may be informative. If it can be assumed that succinylcholine is eliminated by apparent first-order kinetics and its metabolite(s) are inactive, then the duration (t) and the rate of decline (R) of effect (paralysis) in the linear (25–75%) range can be related using the following equations, as derived previously for succinylcholine.^{2,3}

$$t = (2.3/k_{10})(\log A^0 - \log A_{\min}) \quad (\text{Eq. 1})$$

$$R = m(k_{10}/2.3) \quad (\text{Eq. 2})$$

$$t \times R = m(\log A^0 - \log A_{\min}) \quad (\text{Eq. 3})$$

where k_{10} is the apparent first-order rate constant for drug elimination from its site of action, A_{\min} is the minimum effective dose, and m is the slope of the log dose (A^0) response relationship for the relaxant. Thus, according to these three equations, four pharmacokinetic factors determine the duration and rate of decline of effect, with three of these terms (m , A^0 , and A_{\min}) appearing on the right side of equation 3, while k_{10} is implicit on the left-hand side but cancels out as such. Thus, in a group of patients given the same drug dose but showing different durations of effect, the product of duration (t) and rate of decline (R) of effect will yield a constant value if the differences in the observed time course of effect are solely the result of differences in k_{10} , the elimination rate constant. If, however, the values of $t \times R$ differ between the patients, then it must be concluded that these patients differ with respect to m and/or A_{\min} and/or k_{10} .

The results obtained in the four patient groups of

TABLE 1. Pharmacokinetic Analysis of Recovery from the Neuromuscular Blocking Effect of Succinylcholine

Patient Group	25-75% Recovery Time (s)	25-75% Rate of Decline (R) (% min ⁻¹)	t × R	Injection-25% Recovery Time (s)
Term-pregnant	83	1.66	137.78	470
Postpartum	95	1.90	180.50	685
Control subjects	102	2.04	208.08	501
Oral contraceptives	104	2.08	216.32	499

t = duration.

Based on mean data from Leighton *et al.*¹

Leighton *et al.*¹ are summarized in table 1 in order of increasing duration and rate of decline of effect. Control and oral contraceptive users have similar $t \times R$ values that differ from those in term-pregnant and postpartum patients, which in turn differ from each other. Thus the observations of Leighton *et al.*¹ are due to differences in m and/or A_{\min} and/or k_{10} . Because equivalent (rather than equipotent) doses were administered, a difference in m could be the result either of a shift in the dose-response curve resulting from a pharmacokinetic perturbation (for example a change in the volume of distribution or clearance of succinylcholine), or of a change in succinylcholine pharmacodynamics, *per se* (*i.e.*, a change in cholinergic receptor sensitivity to a given concentration of succinylcholine). These changes may occur simultaneously, with the observed effect being the net result of either two opposing or additive effects. A change in m due to a pharmacokinetic perturbation will cause a resultant change in A_{\min} but not C_{\min} (threshold or minimum effective concentration), the latter reflecting a true change in pharmacodynamics. The longer injection -25% recovery time in postpartum patients reflects either a decreased volume of distribution (resulting in higher initial

concentrations and thus a longer time period for decline to the threshold for start of recovery) or to a change in C_{\min} such that recovery now starts at a different concentration. Clearance and elimination processes (as opposed to distribution) probably play a somewhat minor role in the injection -25% recovery times. On the other hand, the differences (albeit not statistically significant), in the rate of decline of effect (R) in the linear 25-75% effect range are more a reflection of changes in the elimination of succinylcholine, presumably due to differences in serum cholinesterase activity if this is assumed to be the major pathway of succinylcholine clearance from the body. The point to be made from the data of Leighton *et al.*¹ is that oral contraceptives and the physiologic perturbations of pregnancy and the postpartum period may modify not only the pharmacokinetics but also (and perhaps predominantly) the pharmacodynamics (concentration-effect relationship) of succinylcholine. Unfortunately, separation of these two effects must await the development of a sensitive and selective assay for succinylcholine in biologic fluids.

IQBAL M. RAMZAN, PH.D.

Assistant Professor

Department of Pharmaceutical Sciences

School of Pharmacy

University of Pittsburgh

Pittsburgh, Pennsylvania 15261

REFERENCES

1. Leighton BL, Check TG, Gross JB, Apfelbaum JL, Shantz BB, Gutsche BB, Rosenberg H: Succinylcholine pharmacodynamics in peripartum patients. *ANESTHESIOLOGY* 64:202-205, 1986
2. Levy G: Pharmacokinetics of succinylcholine in newborns. *ANESTHESIOLOGY* 32:551-552, 1970
3. Levy G: Differences in effect of suxamethonium in London, Los Angeles, and New York. *Br J Anaesth* 42:979-980, 1970

(Accepted for publication June 19, 1986.)

Anesthesiology
65:442-443, 1986

Animal Welfare and Biomedical Research

To the Editor:—Shapiro's otherwise excellent editorial, "Animal rights and biomedical research: No place for complacency,"¹ calls for additional comment.

The fact that research using animals has benefited mankind does not justify abuses that have occurred. In addition, Shapiro's point that nature itself is inhumane is not justification for cruelty.

The major humane groups are not antivivisectionist, but they do want to reduce pain and suffering in exper-

imental animals as much as possible. Scientists should want to do this also. A scale of pain and suffering has been devised by the Scientists Center for Animal Welfare.* This scale, together with peer review for importance, can be used to determine the ethical cost of most experiments

* Scientists Center for Animal Welfare, 4805 St. Elmo Avenue, Bethesda, MD 20814.