

cheal intubations; inadvertent rupture of a laryngeal web or scar could lead to recurrence, and possibly formation, of a symptomatic occlusive scar.

The authors thank librarians Mrs. H. Pilikian and Mrs. V. Frankel for their assistance, and Mrs. A. Morrow for her help.

#### REFERENCES

1. Holinger PH, Brown WT: Congenital webs, cysts, laryngoceles and other anomalies of the larynx. *Ann Otol Rhinol Laryngol* 76:744-752, 1967
2. Batsakis JG: Laryngeal webs and clefts, Tumors of Head and Neck, Second Edition. Baltimore, The Williams and Wilkins Co., 1979, p 529
3. Hannallah R, Rosales JK: Laryngeal web in an infant with tracheoesophageal fistula. *ANESTHESIOLOGY* 42:96-97, 1975
4. Stewart S, Pinkerton HH: Unusual stenosis of trachea in an adult. *Br J Anaesth* 27:492-494, 1955
5. Colgan FJ, Keats AS: Subglottic stenosis: a cause of difficult intubation. *ANESTHESIOLOGY* 18:265-269, 1957
6. Schaffer AJ, Avery ME: Diseases of the Newborn, Fourth Edition. Philadelphia, WB Saunders, 1977, pp 99-100
7. Dedo HH: Endoscopic teflon keel for anterior glottic web. *Ann Otol Rhinol Laryngol* 88:467-473, 1979
8. Stauffer JL, Olson DE, Petty TL: Complications and consequences of endotracheal intubation and tracheotomy: A prospective study of 150 critically ill adult patients. *Am J Med* 70:65-76, 1981
9. Baron SH, Kohlmoos HW: Laryngeal sequelae of endotracheal intubation. *Anesth Analg (Cleve)* 54:767-772, 1975
10. Miller DR, Sethi G: Tracheal stenosis following prolonged cuffed intubation: cause and prevention. *Ann Surg* 171:283-293, 1970
11. Khan F, Reddy NC: Enlarging intratracheal tube cuff diameter: A quantitative roentgenographic study of its value in the early prediction of serious tracheal damage. *Ann Thorac Surg* 24:49-53, 1977
12. Bryce DP: Laryngeal stenosis. *Clinical Otolaryngology*, Edited by Maran AGD, Stell PM. Oxford, Blackwell Scientific Publications, 1979, pp 400-404
13. Johnsen S, Steensen H, Gerwat J: Surgical treatment of acquired subglottic stenosis. *J Laryngol Otol* 95:95-100, 1981
14. Funk D, Raymond F: Rheumatoid Arthritis of crico arytenoid joints: An airway hazard. *Anesth Analg (Cleve)* 54:742-745, 1975
15. Dane T, King EG: A prospective study of complications after tracheotomy for assisted ventilation. *Chest* 67:398-404, 1975
16. Al-Bazzaz F, Grillo H, Kazemi H: Responses to exercise in upper airway obstruction. *Am Rev Respir Dis* 111:631-640, 1975
17. Geffin B, Grillo HC, Cooper JD, Pontoppidan H: Stenosis following tracheostomy for respiratory care. *JAMA* 216:1984-1988, 1971

Anesthesiology  
57:125-127, 1982

## Physostigmine Reversal of Midazolam-induced Sedation

CRAIG B. CALDWELL, M.D.,\* AND JEFFREY B. GROSS, M.D.\*

Midazolam is a new, water-soluble benzodiazepine currently being evaluated for induction of anesthesia. Properties of midazolam include rapid induction of anesthesia, absence of pain or phlebitis following intravenous injection, hemodynamic stability, and anterograde amnesia. Like other benzodiazepines, midazolam causes respiratory depression<sup>1</sup> which may be prolonged,<sup>2</sup> but few other side effects have been reported.

As part of an institutionally approved study on consenting ASA physical status III and IV patients, we observed three cases of prolonged postoperative somnolence following induction of anesthesia with midazolam. In all instances, sedation was rapidly reversed by physostigmine after other measures to awaken the patients had failed.

\* Assistant Professor of Anesthesiology, University of Pennsylvania, and Staff Anesthesiologist, Philadelphia Veterans Administration Medical Center.

Received from the Department of Anesthesiology, Philadelphia Veterans Administration Medical Center, University and Woodland Avenues, Philadelphia, Pennsylvania 19104. Accepted for publication February 4, 1982. Supported by a grant from Hoffmann-LaRoche, Inc.

Address reprint requests to Dr. Gross.

Key words: Hypnotics, benzodiazepines: midazolam. Antagonists, miscellaneous: physostigmine.

#### REPORTS OF THREE CASES

*Patient 1.* A 60-year-old 52-kg man was scheduled for esophageal dilatation. He had previously undergone bilateral radical neck dissections for laryngeal carcinoma, with no apparent anesthetic complications. He had chronic obstructive airway disease and hypothyroidism which was treated with 0.05 mg thyroxine daily. He had also lost twenty pounds in the last year. Fifty minutes before induction of anesthesia, he received 5.2 mg morphine and 0.21 mg glycopyrrolate, im, for premedication. While breathing oxygen, 13.1 mg midazolam (0.25 mg/kg) iv resulted in loss of response to commands and of voluntary movements, but the eyelid reflex remained active; an additional 2.6 mg (0.05 mg/kg) of midazolam abolished this reflex. Ten min later, the patient moved in response to surgical stimulation, and was given 100 mg thiopental, iv. Twenty-five min after the initial injection of midazolam, surgery ended. In the post-anesthesia room, he remained asleep and unresponsive while breathing 40 per cent oxygen from a T-piece. Ninety min later, he began to open his eyes on command; however, he remained disoriented and lethargic for another ninety min (3 h after induction of anesthesia), at which time 0.2 mg naloxone given iv had little effect on his level of consciousness or degree of orientation. Five min later, 2 mg physostigmine and 0.2 mg glycopyrrolate were given iv, which resulted in a profound increase in the level of consciousness and orientation to place and time. He was then discharged to his room.

*Patient 2.* A 66-kg, 58-year-old man with mandibular atrophy was scheduled for vestibuloplasty. His medical problems included severe chronic obstructive airway disease requiring treatment with terbutaline and theophylline, mild congestive heart failure requiring digoxin therapy, and previously resected carcinomas of the colon and bladder. Forty-five min before induction of anesthesia, he received 6.6 mg mor-

phine and 0.26 mg glycopyrrolate im. Midazolam, 16.5 mg (0.25 mg/kg), induced anesthesia, which was maintained with enflurane, nitrous oxide, and oxygen. Succinylcholine provided relaxation for endotracheal intubation, while 7.2 ml of 1 per cent lidocaine with 1:100,000 epinephrine were injected locally by the surgeons at the beginning of surgery. Enflurane was discontinued 2 h after induction of anesthesia, nitrous oxide being discontinued twenty min later, at the end of surgery. On arrival in the post-anesthesia room, 2.5 h after induction of anesthesia, the patient was very lethargic. Analysis of arterial blood gases with oxygen 4l/min administered by nasal cannula revealed a  $P_{aO_2}$  of 83 mmHg,  $P_{aCO_2}$  of 60 mmHg, and a  $pH_a$  of 7.29. One hour later, the patient remained lethargic and disoriented; 2 mg physostigmine with 0.2 mg glycopyrrolate was given iv. Within minutes, he awoke and was oriented to person and place.  $P_{aO_2}$  was then 60 mmHg,  $P_{aCO_2}$  52 mmHg, and  $pH_a$  7.32. He remained in the post-anesthesia room for an additional four hours, at which time he was moved to the intensive care unit for continued observation. He was somewhat lethargic although he remained oriented to person and place. Twelve hours after induction of anesthesia, he was fully awake;  $P_{aO_2}$  was 66 mmHg,  $P_{aCO_2}$  45 mmHg, and  $pH_a$  7.36 with an  $FI_{O_2}$  0.24 by venturi mask.

*Patient 3.* An 86-year-old, 57-kg man with acute cholecystitis was scheduled for cholecystectomy. Medical problems included congestive heart failure treated with digoxin and furosemide, atrial fibrillation with a ventricular response of 80 to 100 beats/min, and mitral valve prolapse. Fifty min before induction of anesthesia, he received 5.7 mg morphine and 0.23 mg glycopyrrolate im. Midazolam, 14.3 mg (0.25 mg/kg), induced anesthesia, which was maintained with nitrous oxide, meperidine (100 mg total), and pancuronium. At the end of surgery, 1.5 h after induction of anesthesia, nitrous oxide was discontinued and the pancuronium was reversed by 3 mg neostigmine and 1 mg atropine. Spontaneous ventilation resumed, and neuromuscular function was adequate as evidenced by sustained contraction to a tetanic stimulus of 50 Hz. Two hours after induction of anesthesia, the patient remained unresponsive with his trachea intubated in the post-anesthesia room. With an  $FI_{O_2}$  of 0.4 by T-piece,  $P_{aO_2}$  was 126 mmHg,  $P_{aCO_2}$  41 mmHg, and  $pH_a$  7.36. Naloxone, 0.2 mg, iv, caused little change in his mental status. About 10 min later, 2 mg physostigmine with 0.2 mg glycopyrrolate given iv resulted in rapid awakening and response to commands for the first time. Analysis of arterial blood gases revealed a  $P_{aO_2}$  of 95 mmHg,  $P_{aCO_2}$  of 35 mmHg, and  $pH_a$  of 7.40. The trachea was extubated shortly thereafter. About two hours after the initial dose of physostigmine, the patient became lethargic and disoriented; an additional dose of 2 mg physostigmine with 0.2 mg glycopyrrolate resulted in rapid improvement. The patient was then discharged to the intensive care unit.

## DISCUSSION

A single intravenous dose of midazolam has not previously been reported to cause prolonged sedation. The failure of our patients to awaken following a prolonged period in the recovery room and (in two cases) the administration of intravenous naloxone, suggests that the sedation was not due to residual anesthetic gases or the effect of narcotics. Although prolonged effect from inhalational agents ( $N_2O$ , enflurane) cannot be unequivocally eliminated as a cause of our patients' delayed emergence, we feel that this is unlikely. Patient number one received  $N_2O$  and enflurane for only 25 min; it is unlikely that sufficient quantities of either agent would be absorbed in this time to account for 2.5 h of profound

postoperative sedation. The only inhalational agent given to patient number three was  $N_2O$ . Because of this agent's low solubility in tissues, the residual effects should be negligible 30 min after its discontinuation. Additionally, patient number three showed a decline in mental status 2 h after physostigmine was given, at a time when  $N_2O$  concentrations in his tissues were certainly low. No depressant drugs except for the morphine premedication were given within twelve hours of the start of anesthesia, making residual sedation from other agents unlikely. Glycopyrrolate, being a quaternary amine, does not readily cross the blood-brain barrier and therefore has minimal activity in the central nervous system.

The rapid awakening which followed the administration of physostigmine suggests a specific antagonism of the central depressant effects of midazolam. Physostigmine, an uncharged tertiary amine, readily crosses the blood-brain barrier and causes the accumulation of acetylcholine by inhibiting acetylcholinesterase. This results in increased cholinergic stimulation and explains the ability of physostigmine to reverse the central nervous system depression caused by drugs with anticholinergic properties, which include the belladonna alkaloids, phenothiazines, tricyclic antidepressants, and butyrophenones<sup>3-7</sup>; however, there are no data in the literature at present to suggest that physostigmine reverses sedation caused by thiopental, enflurane, nitrous oxide, or narcotics. Side effects which may accompany the use of physostigmine also are related to increased cholinergic stimulation at peripheral muscarinic cholinergic receptors. Predictably these include bradycardia, bronchoconstriction, nausea, vomiting, and increased salivary and bronchial secretions.<sup>8</sup> In view of these potential complications, reversal of midazolam sedation with physostigmine should not be attempted until other causes of sedation have been considered and treated.

Although the mechanism of action of the benzodiazepines is unclear, midazolam has been shown to have anticholinergic activity in the mammalian central nervous system<sup>9</sup>; the ability of physostigmine to reverse midazolam-induced sedation would be expected on this basis. The ability of physostigmine to reverse benzodiazepine delirium and sedation may, however, be the result of a nonspecific analeptic effect of the drug.<sup>10-12</sup> Conversely, Garber *et al.* failed to demonstrate improvement in psychomotor function or speed of recovery following administration of a physostigmine-atropine mixture to patients who had received diazepam for sedation during outpatient surgical procedures.<sup>13</sup> Regardless of the mechanism of action of midazolam in the central nervous system, physostigmine appears to provide rapid antagonism of its sedative effects.

In summary, we observed three instances of prolonged sedation (at least two hours) following induction of

anesthesia with midazolam (0.25–0.30 mg/kg) in patients premedicated with morphine and glycopyrrolate. The fact that sedation lasted several hours after the discontinuation of inhaled anesthetics and was not reversed by naloxone in two cases suggests that the sedation was caused by midazolam. The subsequent rapid reversal of the sedation with physostigmine suggests that a central anticholinergic mechanism may be involved.

#### REFERENCES

1. Forster A, Gardaz JP, Suter PM, Gemperle M: Respiratory depression by midazolam and diazepam. *ANESTHESIOLOGY* 53:494–497, 1980
2. Gross JB, Smith TC: Ventilatory depression following intravenous midazolam and thiopental in subjects with chronic obstructive pulmonary disease. *ANESTHESIOLOGY* 55:S384, 1981
3. Rumach B: Anticholinergic poisoning: treatment with physostigmine. *Pediatrics* 52:449, 1973
4. Bernards W: Reversal of phenothiazine-induced coma with physostigmine. *Anesth Analg (Cleve)* 52:938–941, 1973

5. Duvosin R, Katz R: Reversal of central anticholinergic syndrome in man by physostigmine. *JAMA* 206:1963–1965, 1968
6. Chin L, Havill J, Rothwell R, Bishop BG: Use of physostigmine in tricyclic antidepressant poisoning. *Anaesth Intens Care* 4:138–140, 1976
7. Bidwai A, Cornelius L, Stanley TH: Reversal of innovar-induced post-anesthetic somnolence and disorientation with physostigmine. *ANESTHESIOLOGY* 44:249–252, 1976
8. Goodman L, Gilman A: *The Pharmacological Basis of Therapeutics*, Fifth Edition. New York, Macmillan Publishing Co., Inc., 1975, pp 453–455
9. Davies J, Polc P: Effect of a water-soluble benzodiazepine on the response of spinal neurones to acetylcholine and excitatory amino acid analogues. *Neuropharmacology* 17:217–220, 1978
10. Larson GF, Hurlbert B, Wingard D: Physostigmine reversal of diazepam-induced depression. *Anesth Analg (Cleve)* 56:348–351, 1977
11. DiLiberti J, O'Brien M, Turner T: The use of physostigmine as an antidote in accidental diazepam intoxication. *J Pediatrics* 86:106–107, 1975
12. Blitt CD, Petty W: Reversal of lorazepam delirium by physostigmine. *Anesth Analg (Cleve)* 54:607–608, 1975
13. Garber J, Ominsky AJ, Orkin F: Physostigmine-atropine solution fails to reverse diazepam sedation. *Anesth Analg (Cleve)* 59:58–60, 1980

Anesthesiology  
57:127–129, 1982

## Low-dose Enflurane Does Not Increase Blood Loss during Therapeutic Abortion

MOHAN S. SIDHU, M.D.,\* AND BRUCE F. CULLEN, M.D.†

Therapeutic abortion is a common outpatient procedure which is performed frequently with local anesthesia.<sup>1</sup> However, many patients and physicians prefer general anesthesia to minimize the discomfort and anxiety associated with the operation. Volatile anesthetics, as opposed to intravenous anesthetics, are ideal for outpatient procedures because they allow faster recovery<sup>2</sup>; however, their usage for therapeutic abortion is limited because of their propensity at concentrations of one MAC or above, to cause myometrial relaxation and an increase in blood loss.<sup>3</sup> We undertook the following study to determine if uterine blood loss during therapeutic abortion could be kept to a minimum by utilizing relatively low concentrations of enflurane. The blood loss was compared to that observed when patients were anesthetized

with a more routinely accepted nitrous oxide/narcotic technique.

#### METHOD

Thirty-four healthy, *unpremedicated*, women undergoing elective suction therapeutic abortion were studied. This study was reviewed and approved by the Human Subject Committee of the University of California, Irvine. Patients ranged in age from 16–29 years, and were at 8 to 13 weeks gestation. After informed consent was obtained, the patients were anesthetized with one of two anesthetic techniques.

Patients in Group 1 (n = 18) were given 50–100 µg of fentanyl intravenously. Anesthesia was then induced with thiopental (4–5 mg/kg) and maintained with 70 per cent nitrous oxide in oxygen. Additional thiopental was administered during the procedure in response to the patient moving, swallowing, breath holding, or exhibiting other signs of inadequate anesthesia. No additional fentanyl was required.

Patients in Group 2 (n = 16) had anesthesia induced with a small dose of thiopental (3–4 mg/kg) and maintained with 1 per cent inspired enflurane and 66 per cent nitrous oxide in oxygen. At no point was the concentration of inspired enflurane increased to more than 1 per cent. Additional thiopental was administered in response

\* Assistant Professor and Director of Outpatient Anesthesia, Department of Anesthesiology, University of California, Irvine.

† Professor and Chairman, Department of Anesthesiology, University of California, Irvine.

Received from the Outpatient Surgical Unit, University of California, Irvine Medical Center, Orange, California 92668. Accepted for publication February 4, 1982. Presented at the annual meeting of the American Society of Anesthesiologists, New Orleans, Louisiana, October 1981.

Address reprint requests to Dr. Sidhu.

Key words: Anesthetics, intravenous: fentanyl; thiopental. Anesthetics, volatile: enflurane. Blood: loss. Pregnancy: abortion.