

Monoamine Oxidase Inhibitors: Should They Be Discontinued Preoperatively?

Abdel Raouf El-Ganzouri, MD, Anthony D. Ivankovich, MD, Berton Braverman, PhD, and Robert McCarthy, D Pharm

EL-GANZOURI AR, IVANKOVICH AD, BRAVERMAN B, McCARTHY R. Monoamine oxidase inhibitors: should they be discontinued preoperatively? *Anesth Analg* 1985;64:592-6.

Adverse cardiovascular responses to anesthesia during either electroconvulsive therapy (ECT) or elective surgical procedures were evaluated in 27 patients maintained on chronic (3 months-3 yr) monoamine oxidase inhibitor (MAOI) therapy. Changes in blood pressure and heart rate in study patients (n = 22 ECTs in 13 patients) undergoing ECT were not significantly different from those observed in pa-

tients having ECT without prior treatment with MAOIs (n = 45 ECTs in 45 patients). In both groups, blood pressure and heart rate increased significantly after ECT, but returned to baseline levels within 15 min. No complications attributable to MAOIs were observed in study patients (n = 14) undergoing elective surgical procedures. We conclude that discontinuing chronic MAOI therapy prior to anesthesia and surgery is not necessary.

Key Words: ATARACTICS—MAO inhibitors. ANESTHESIA—electroshock.

Monoamine oxidase (MAO) is a general term for a group of intramitochondrial enzymes distributed widely throughout the body. One type of MAO is intraneuronal MAO that is responsible for the deactivation of certain biologically active amines including norepinephrine, 5-hydroxytryptamine, and dopamine (1). Monoamine oxidase inhibitors (MAOIs) increase intraneuronal neurotransmitter pools by inhibiting MAO. Depolarization of these cells results in an increased amount of neurotransmitter being released into the synaptic cleft, thereby increasing postsynaptic depolarization and adrenergic stimulation. MAOIs are currently being used in the treatment of severe depression. The maximal inhibition of MAO by the MAOIs is achieved within a few days, even though their behavioral antidepressant effect may not be observed for 2-3 weeks.

The current recommendation is that MAOIs be discontinued 2 weeks prior to anesthesia because of the potential for serious adverse drug interactions (2-4). Reports of adverse responses in patients taking MAOIs include hypertension, hypotension, hyperpyrexia, hyperreflexia, convulsions, and hepatotoxicity (5,6).

Received from the Department of Anesthesiology, Rush Presbyterian-St. Luke's Medical Center, Chicago, Illinois. Accepted for publication January 25, 1985.

Address correspondence to Dr. Ivankovich, Rush Presbyterian-St. Luke's Medical Center, 1753 West Congress Parkway, Chicago, IL 60612.

However, no controlled prospective evaluations of the risks involved in anesthesia practice in patients chronically treated with MAOIs have been reported. The purpose of this study was to observe cardiovascular responses and adverse reactions to a variety of anesthetic, ECT, and surgical procedures in these patients.

Methods

Twenty-seven patients, 15 females and 12 males, between the ages of 23 and 84 volunteered to participate in the study and gave informed consent. This study was reviewed and approved by the Human Investigation Committee of Rush Presbyterian-St. Luke's Medical Center. All patients were on chronic MAOI therapy and were scheduled for either electroconvulsive therapy (ECT) (group I) or elective surgical procedures (group II).

The first group ($n = 13$) received 0.4 mg of atropine intravenously prior to induction of anesthesia. ECTs were often performed more than once in the same patient and thus a total of 22 ECTs were performed in these 13 patients; each procedure was considered an independent event. Anesthesia was induced with thiopental, 1-3 mg/kg, and muscle relaxation was achieved with succinylcholine, 0.5-1.0 mg/kg intravenously. Heart rate, blood pressure, and body (axillary) temperature were recorded prior to, 1 min after,

Table 1. Patients on MAOI Inhibitors Undergoing Surgical Procedures

| Operation | MAOI drug | Duration of MAOI drug | Anesthetic technique | Postoperative pain relief | Comments |
|--|---------------------------|-----------------------|--|------------------------------|---|
| Exploratory laparotomy | Tranlycypromine 30 mg/day | 7 months | Thiopental, succinylcholine, N ₂ O-O ₂ , enflurane, and pancuronium | Morphine | No adverse reactions; uneventful recovery |
| Tibial osteotomy | Tranlycypromine 30 mg/day | 1 year | Thiopental, N ₂ O-O ₂ , halothane | Morphine | " |
| Lipoma of thigh | Tranlycypromine 20 mg/day | 4 months | Thiopental, succinylcholine, N ₂ O-O ₂ -halothane | Morphine | " |
| Cystoscopy × 2 | Tranlycypromine 30 mg/day | 3 years | Thiopental, N ₂ O-O ₂ , diazepam, fentanyl | Fentanyl | " |
| Excision of popliteal cyst | Tranlycypromine 30 mg/day | 2 years | Etomidate, succinylcholine, N ₂ O-O ₂ -enflurane | Fentanyl | " |
| Removal of tibial plate | Tranlycypromine 20 mg/day | 3 years | Spinal tetracaine 1% 12 mg | Morphine | " |
| Vaginal hysterectomy | Tranlycypromine 20 mg/day | 1 year | Thiopental, succinylcholine, N ₂ O-O ₂ , isoflurane | Morphine | " |
| Total gastrectomy | Phenelzine 45 mg/day | 8 months | Thoracic epidural anesthesia, 13 ml, bupivacaine 0.5%, and thiopental, succinylcholine, N ₂ O-O ₂ , isoflurane | Continuous epidural morphine | Intraoperative hypotension treated by phenylephrine |
| Total knee replacement | Tranlycypromine 45 mg/day | 3 months | Thiopental, succinylcholine, N ₂ O-O ₂ -halothane | Morphine | No adverse reactions; uneventful recovery |
| Laparoscopy, exploratory laparotomy | Tranlycypromine 75 mg/day | 1 year | Thiopental, succinylcholine, N ₂ O-O ₂ , halothane and pancuronium | Morphine | " |
| Lumbar laminectomy | Tranlycypromine 30 mg/day | 2 years | Etomidate, succinylcholine, N ₂ O-O ₂ , isoflurane, and fentanyl 0.25 mg | Morphine | " |
| Transurethral resection of prostate | Tranlycypromine 30 mg/day | 3 years | Spinal anesthesia 10 mg tetracaine 1% | Morphine | " |
| Dilatation and curettage of the uterus | Isocarboxazid 30 mg/day | 4 months | Etomidate, diazepam, fentanyl | — | " |
| Cataract extraction | Pargyline 10 mg/day | 3 years | Intravenous sedation and analgesia by diazepam and fentanyl | Fentanyl | " |

and 15 min after ECT. The data were compared to a control group of patients having ECTs with identical premedication and anesthesia, but not taking MAOIs ($n = 45$ ECTs in 45 patients).

The second group ($n = 14$) (Table 1) received oral

diazepam, 10–15 mg, 2 hr preoperatively. Anesthesia was induced with 1–3 mg/kg thiopental intravenously ($n = 8$) or etomidate 0.3–0.6 mg/kg ($n = 3$). If indicated, their tracheas were intubated, facilitated by succinylcholine administration, 1.0–1.5 mg/kg intra-

Table 2. Responses During ECT With (MAOI) and Without (C) Chronic MAOI Treatment*

| | Before ECT | | After ECT | | | |
|------------------|----------------|-------------------|------------|------------|------------|----------|
| | | | 1 min | | 15 min | |
| | C ^b | MAOI ^c | C | MAOI | C | MAOI |
| Blood pressure | | | | | | |
| Systolic | 133 ± 4 | 129 ± 4 | 162 ± 5 | 149 ± 4 | 139 ± 4 | 131 ± 6 |
| Diastolic | 77 ± 2 | 77 ± 3 | 97 ± 3 | 93 ± 4 | 83 ± 3 | 84 ± 4 |
| Mean | 96 ± 3 | 94 ± 3 | 118 ± 3 | 112 ± 4 | 101 ± 3 | 100 ± 4 |
| Heart rate | 83 ± 2 | 84 ± 2 | 99 ± 2 | 102 ± 5 | 88 ± 2 | 84 ± 3 |
| Body temperature | 97.6 ± 0.1 | 97.9 ± 0.2 | 97.1 ± 0.1 | 98.0 ± 0.3 | 97.3 ± 0.3 | 97.6 ± 3 |

*Mean ± SEM. ^bn, 45 treatments in 45 patients. ^cn, 22 treatments in 13 patients.

venously. Anesthesia was maintained with halothane/N₂O (*n* = 4), enflurane/N₂O (*n* = 2) or isoflurane/N₂O (*n* = 3). Additionally, four patients had intravenous fentanyl, 0.05–0.25 mg anesthesia, two had spinal anesthesia, and one patient had thoracic epidural 0.5% bupivacaine anesthesia. One patient received epidural morphine 0.2 mg/hr during surgery and throughout the postoperative period. Twelve of the fourteen patients in group II received fentanyl or morphine intravenously for postoperative analgesia. The following were monitored from the preanesthetic period through postanesthetic recovery: blood pressure (direct or indirect), electrocardiogram, skin and core temperatures, and the degree of neuromuscular blockade.

The statistical significance of intra- and inter-group differences in changes in blood pressure, heart rate, and body temperature were compared between group I and the control group and were evaluated by analysis of variance. Differences were considered statistically significant at the *P* < 0.05 level of probability. In group II patients, overall significant variations in response to anesthetic management were recorded.

Results

Group 1

Systolic, diastolic, mean blood pressures, and heart rates increased significantly 1 min after ECT in both the control group and the MAOI group (Table 2). The changes in mean blood pressure and heart rate from pre-ECT to 1 min post-ECT were not significantly different from the control group. In both groups blood pressure and heart rate returned to baseline values within 15 min. No significant changes were observed in body temperature. Additionally, no unusual clinical observations were made in patients in the study or control groups.

Group 2

Thirteen of the 14 patients undergoing elective surgery (Table 1) had no adverse reactions at any time during the perioperative period. The eighth patient had a brief episode of hypotension that responded to treatment with lactated Ringer's and phenylephrine (three divided doses of 0.1 mg intravenously). No adverse hemodynamic or psychological responses were noted postoperatively.

Discussion

Although many concerns have been expressed in the anesthetic literature about anesthetic management of patients on MAOI therapy (3,7), only a few published reports justify these concerns (5,6,8). Most reports of adverse effects have been related to MAOI overdose (1). A significant number of published cases ascribe adverse reactions to the "cheese effect" (9). This effect is attributed to the inhibition of liver monoamine oxidase that allows increases in plasma concentrations of tyramine, an amino acid present in a variety of foodstuffs that possesses indirect-acting sympathomimetic properties. Other indirect-acting sympathomimetic drugs have been reported to produce adverse reactions as well (10–12).

The literature on drug interactions during anesthesia in patients on MAOIs is limited. Potentiation and prolongation of the effects of meperidine, morphine, pentazocine, pentobarbital, amylbarbital, and thiopental have been reported (4,13,14). The mechanism of such interactions has been ascribed to decreased 5-hydroxytryptamine metabolism and inhibition of narcotic metabolism in the liver. However, a study examining the effects of narcotics in 15 volunteers who had been receiving an MAOI for 3–8 weeks found that all subjects reacted normally to intramuscular injections of meperidine and morphine (15). As we have demonstrated in the present study,

other investigators have shown no adverse responses in patients receiving chronic MAOI therapy undergoing narcotic anesthesia (16,17).

Chronic antidepressant therapy can be associated with diminished postsynaptic, central, β -adrenergic receptor activity (18-20). Down-regulation in the limbic system and other cerebral structures, measured by cyclic-AMP generation, has been demonstrated to occur over 7-21 days in chronic animal studies using MAOIs and tricyclic antidepressants (TCAs) (21-23). Similar investigations of TCAs have demonstrated a more complex chronic response for cerebral α -adrenergic and peripheral α - and β -adrenergic receptors. Menkes et al. (25,26), for example, found enhanced central α_1 -adrenergic receptor responses in rats as a result of increased receptor affinity after chronic TCA treatment. Responses of β_1 -adrenergic receptors have not been found to be altered by TCAs, but cardiac adrenergic nerves released more norepinephrine after stimulation, presumably from decreased α_2 -presynaptic inhibition (22,24). Thus TCAs and possibly MAOIs appear to induce reciprocal changes in central α_1 - and β -adrenergic receptors (26), but have little effect on peripheral β_1 responsiveness. The chronic effects of TCAs and MAOIs on peripheral α_1 -adrenergic receptors has not been well defined.

Acute treatment (8-15 days) with TCAs in dogs results in an increased arrhythmogenicity in response to various adrenergic challenges (27,28) but chronic treatment (6 weeks) failed to alter arrhythmogenicity or adrenergic responsiveness (29). Acute (8-14 days) treatment with MAOI and TCA in dogs followed by challenges with volatile anesthetics and epinephrine is associated with increases in arrhythmogenicity that are similar with both types of drugs (28). Our own initial studies (30) have demonstrated increased responses of heart rate and blood pressure to ephedrine and norepinephrine in dogs anesthetized with enflurane/fentanyl/ N_2O after 2 weeks of treatment with MAOI, but the responses returned to normal by the third week of treatment.

Extrapolation from these animal studies suggests that patients on chronic MAOI therapy would not be adversely affected during anesthesia or by adrenergic challenges. A similar lack of adverse responses to adrenergic challenges has been observed in patients on chronic TCA therapy (31). Studies with MAOIs and TCAs suggest that this may be a result of adaptations occurring during chronic antidepressant therapy.

In summary, a group of 27 patients on chronic (greater than 3 weeks) MAOI therapy was found to have no adverse responses in the perioperative period while receiving anesthesia for ECT or elective surgical procedures. We did not evaluate patients who had

recently (less than one month) begun MAOI therapy. These later patients may be potentially at a higher risk before adaptation has occurred, and more work is needed to determine the potential for adverse responses in this group. Furthermore, we did not evaluate indirect-acting sympathomimetic amines or meperidine because of the number of previously reported adverse interactions with these agents. More studies in animals and volunteers are needed in this area, but, based upon our findings and those of other investigators, as well as an understanding of the neuropharmacology involved with chronic antidepressant therapy, we believe that discontinuation of chronic MAOI therapy prior to surgery is not necessary.

The authors wish to thank Ms. Patricia Ferris and Ms. Diane Dusault for their secretarial skills, and the patients for their cooperation.

References

- Baldessarini RJ. Chapter 19: Drugs and the treatment of psychiatric disorders. In: Gilman AG, Goodman LS, Gilman A, eds. The pharmacological basis of therapeutics. New York: Macmillan, 1980:427-30.
- Perks ER. Monoamine oxidase inhibitors. *Anaesthesia* 1964;19:376-86.
- Schwartz AJ, Wollman H. Anesthetic considerations for patients on chronic drug therapy: L-Dopa, monoamine oxidase inhibitors, tricyclic antidepressants, and propranolol. *Anesthesiology* 1976;4:98-111.
- Viegas OJ. Psychiatric illness. In: Stoeling RK, Deerdort SF, eds. *Anesthesia and Co-existing Disease*. New York: Churchill Livingstone, 1983:663-71.
- Shee JC. Dangerous potentiation of pethidine by iproniazid and its treatment. *Br Med J* 1960;2:507-9.
- Jenkins LC, Graves HB. Potential hazards of psychoactive drugs in association with anaesthesia. *Can Anaesth Soc J* 1965;12:121-8.
- Roizen MF. Preoperative evaluation of patients with diseases that require special preoperative evaluation and intraoperative management, II. In: Miller RD, eds. *Anesthesia*. New York: Churchill Livingstone, 1981:21-105.
- Cocks DP, Passmore-Rowe A. Dangers of monoamine oxidase inhibitors. *Br Med J* 1962;2:1545-6.
- Blackwell B. Hypertensive crisis due to monoamine-oxidase inhibitors. *Lancet* 1963;2:849-51.
- Hirsch MS, Walter RM, Nasterlik RJ. Subarachnoid hemorrhage following ephedrine and MAO inhibitors. *JAMA* 1965;194:1259.
- Horler AR, Wynne NA. Hypertensive crisis due to paralyline and metaraminol. *Br Med J* 1965;2:460-1.
- Mason A. Fatal reaction associated with tranlycypromine and methylamphetamine. *Lancet* 1963;1:173-7.
- Rogers KJ, Thornton JA. The interaction between monoamine oxidase inhibitors and narcotic analgesics in mice. *Br J Pharmacol* 1969;36:470-80.
- Domino EF, Sullivan TS, Luby ED. Barbiturate intoxication in a patient treated with a MAO inhibitor. *Am J Psychiatry* 1962;118:941-3.
- Evans-Prossor CDG. The use of pethidine and morphine in the

- presence of monoamine oxidase inhibitors. *Br J Anaesthesia* 1968;40:279-82.
16. Michaels I, Serrins M, Shier NQ, Barach PG. Anesthesia for cardiac surgery in patients receiving monoamine oxidase inhibitors. *Anesth Analg* 1984;63:1041-4.
 17. El-Ganzouri A, Ivankovich AD, Braverman B, Land PC. Should MAOI be discontinued preoperatively? *Anesthesiology* 1983;59:A384.
 18. Banerjee SP, King LS, Riggi SJ, Chandra SK. Development of beta-adrenergic receptor subsensitivity by antidepressants. *Nature* 1977;268:455-6.
 19. Pandey GN, Davis JM. Treatment with antidepressants and down regulation of beta-adrenergic receptors. *Drug Dev Res* 1983;3:393-406.
 20. Yeh HH, Woodward DJ. Alterations in beta-adrenergic physiological response characteristics after long-term treatment with desmethylimipramine: interaction between norepinephrine and gamma-aminobutyric acid in rat cerebellum. *J Pharmacol Exper Therap* 1983;226:126-34.
 21. Ventulani J, Stawarz RJ, Sulser F. Adaptive mechanisms of the noradrenergic cyclic AMP generating system in the limbic forebrain of the rat: adaptation to persistent changes in the availability of norepinephrine (NE). *J Neurochem* 1976;27:661-6.
 22. Wolfe BB, Harden TK, Sporn JR, Molinoff PB. Presynaptic modulation of beta adrenergic receptors in rat cerebral cortex after treatment with antidepressants. *J Pharmacol Exp Therap* 1978;207:446-57.
 23. Peroutka SJ, Snyder SH. Long-term antidepressant treatment decreases spiroperidol-labeled serotonin receptor binding. *Science* 1980;210:88-90.
 24. Crews FT, Smith CB. Presynaptic alpha-receptor subsensitivity after long-term antidepressant treatment. *Science* 1978;202:322-4.
 25. Menkes DB, Kehne JH, Gallager DW, Aghajanian GK, Davis M. Functional supersensitivity of CNS alpha-adrenoceptors following chronic antidepressant treatment. *Life Sci* 1983;33:181-8.
 26. Menkes DB, Aghajanian GK, Gallager DW. Chronic antidepressant treatment enhances agonist affinity of brain alpha-adrenoceptors. *Eur J Pharmacol* 1983;87:35-41.
 27. Edwards RP, Miller RD, Roizen MF, Ham J, Way WL, Lake CR, Roderick L. Cardiac responses to imipramine and pancuronium during anesthesia with halothane or enflurane. *Anesthesiology* 1979;50:421-5.
 28. Wong KC, Puerto AX, Puerto BA, Blatnick RA. Influence of imipramine and pargyline on the arrhythmogenicity of epinephrine during halothane, enflurane, or methoxyflurane anesthesia in dogs. *Life Sci* 1980;27:2675-8.
 29. Spiss CK, Smith CM, Maze M. Halothane-epinephrine arrhythmias and adrenergic responsiveness after chronic imipramine administration in dogs. *Anesth Analg* 1984;63:825-8.
 30. Braverman B, Ivankovich AD, McCarthy R. The effects of fentanyl and vasopressors on anesthetized dogs receiving MAO inhibitors. *Anesth Analg* 1984;63:192.
 31. Veith RC, Raskind MA, Caldwell JH, Barns RF, Gumbrecht G, Ritchie JL. Cardiovascular effects of tricyclic antidepressants in depressed patients with chronic heart disease. *N Engl J Med* 1982;306:954-9.