Antidepressive Treatment With Monoamine Oxidase Inhibitors and the Occurrence of Intraoperative Hemodynamic Events: A Retrospective Observational Cohort Study

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ABSTRACT

Objective: To investigate the occurrence of intraoperative hemodynamic events when antidepressive treatment with monoamine oxidase inhibitors (MAOIs) was continued during anesthesia.

Method: A retrospective observational cohort study was conducted among patients who were admitted for elective surgery requiring anesthesia in 8 Dutch hospitals (2004–2010). The index group included current users of irreversible (tranylcypromine) and reversible (moclobemide) MAOIs. The reference group included a sample of nonusers matched to the index group on hospital, type and period of surgery, and type of anesthesia (ratio 1:3). The outcome of interest was the occurrence of the following intraoperative hemodynamic events: hypotension or hypertension and tachycardia or bradycardia.

Results: Approximately 280,000 surgical procedures were performed in the participating hospitals in the total observational period of 33 years. The index group included 26 and 25 users of tranylcypromine and moclobemide, respectively. The reference groups included 149 nonusers. Intraoperative hypotension occurred less frequently in users of tranylcypromine (46%) than in nonusers (73%) ($P = .01$). The occurrence of hypertension, bradycardia, and tachycardia during anesthesia was not different between users of tranylcypromine (27%, 50%, and 12%, respectively) and those in the reference group (35%, 61%, and 26%, respectively). The occurrence of hypotension, hypertension, bradycardia, and tachycardia was not different between users of moclobemide and the reference group.

Conclusions: Severe adverse hemodynamic events, such as hypertension and tachycardia, did not occur more frequently in users of both the irreversible MAOI tranylcypromine and the reversible MAO-A inhibitor moclobemide compared to nonusers. These findings suggest that there is no longer much justification to discontinue these MAOIs before surgery, with the considerable risk of compromising patients' psychiatric status.

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Irreversible monoamine oxidase inhibitors (MAOIs), available since the late 1950s, were the first effective antidepressant agents. They were supplanted by the tricyclic antidepressants and, later, by the selective serotonin reuptake inhibitors, which lacked the dangerous side effect of hypertensive crisis. More recently, there has been a renewed interest in the use of irreversible MAOIs, especially in the treatment of depressions resistant to other therapies. Current use of an irreversible MAOI usually indicates treatment of a patient with a severe depression with a complicated course.[1–5]

The enzyme monoamine oxidase (MAO) regulates the metabolic breakdown of several monoamines formed in the body. There are 2 subtypes: MAO-A mainly deaminates serotonin, epinephrine, and norepinephrine, and MAO-B deaminates dopamine and tyramine. The classical MAOIs, phenelzine and tranylcypromine, are nonselective and irreversible inhibitors. Moclobemide, a newer MAOI, selectively and reversibly inhibits only MAO-A.[2,6–8] Treatment with an MAOI results in accumulation of neurotransmitters in presynaptic nerve-ending store sites. Therefore, larger amounts of norepinephrine than normally expected may be released with stimulation of sympathetic nerves by (indirect-acting) sympathomimetic agents or oral ingestion of larger amounts of tyramine, a substance found in fermented foods. This outpouring of norepinephrine may cause a life-threatening hypertensive crisis.[6,8–11] MAOI use has also been associated with the occurrence of the serotonin syndrome due to the greater availability of serotonin.[2,10,12]

Although irreversible MAOIs have been available for more than 50 years, the perioperative management of patients treated with irreversible MAOIs is still under discussion. There are no evidence-based guidelines, and experts disagree whether to continue the use of irreversible MAOIs before surgery or not.[6–8,13–15] Abrupt discontinuation of irreversible MAOIs may result in severe withdrawal symptoms and the recurrence of the underlying, otherwise untreatable depression with the potential for suicide.[6,16,17] Therefore, from the point of view of appropriately treating the psychiatric illness, perioperative continuation of irreversible MAOIs is recommended. However, potentially fatal drug interactions have been reported in patients in whom irreversible MAOIs were used concurrently with opioids or sympathomimetic agents.[18–26] Although most of these reports are anecdotal, they still are the basis for the current recommendation to discontinue irreversible MAOIs before surgery.[14] In contrast, small observational studies[27–29] and several case reports[30–33] did not show hemodynamic complications when irreversible MAOIs were continued during anesthesia. The literature is also contradictory about the need to discontinue the newer reversible MAO-A inhibitor moclobemide before surgery.[6,34–36]

Clinical Points

- Severe intraoperative events did not occur in users of the irreversible MAOI tranylcypromine or the reversible MAO-A inhibitor moclobemide who continued their antidepressant treatment in the perioperative period.
- The current observations suggest that there is no longer much justification to discontinue these MAOIs before surgery, with the considerable risk of compromising patients' psychiatric status.
- When in an individual patient there still is doubt about the continuation of an MAOI, consultation among anesthesiologist, psychiatrist, and surgeon is indicated in order to balance the potential risks of anesthesia against the psychiatric complications of drug withdrawal.

The aim of this study was to investigate the occurrence of intraoperative hemodynamic events, such as hypertension and tachycardia, when antidepressive treatment with irreversible MAOIs and the reversible MAO-A inhibitor moclobemide was continued during anesthesia.

METHOD

Setting and Study Population

This retrospective observational cohort study was conducted in 8 hospitals in the Netherlands. The medical ethics boards of the hospitals approved the study protocol and waived the need for written informed consent, as only routinely documented data were used. All patients who were admitted for elective surgery requiring anesthesia from January 2004 until June 2010 were eligible to enter the study. However, patients were included only during the years for which both computerized pharmacy databases and an electronic anesthesia record were available in a particular hospital. Patients were excluded if they were scheduled for a procedure requiring anesthesia for a time period shorter than 10 minutes (eg, electroconvulsive therapy) or if they were younger than 18 years.

The index group consisted of current users of an MAOI as an antidepressant agent. The MAOIs included both the nonselective irreversible inhibitors (tranylcypromine and phenelzine) and the selective reversible MAO-A inhibitor moclobemide. A current user of an MAOI was defined as a patient using an MAOI who continued this use during hospital admission. These patients were identified by means of computerized pharmacy databases containing information about medication of hospitalized patients. If a user of an MAOI was scheduled for more than 1 surgical procedure, each procedure was included as a separate patient with separately selected reference patients. The reference group (nonusers) was matched to the index group on hospital, type and period of surgery, and type of anesthesia in a 1:3 ratio. If a reference patient met the exclusion criteria, another suitable patient was selected in the same manner.

Outcomes and Data Collection

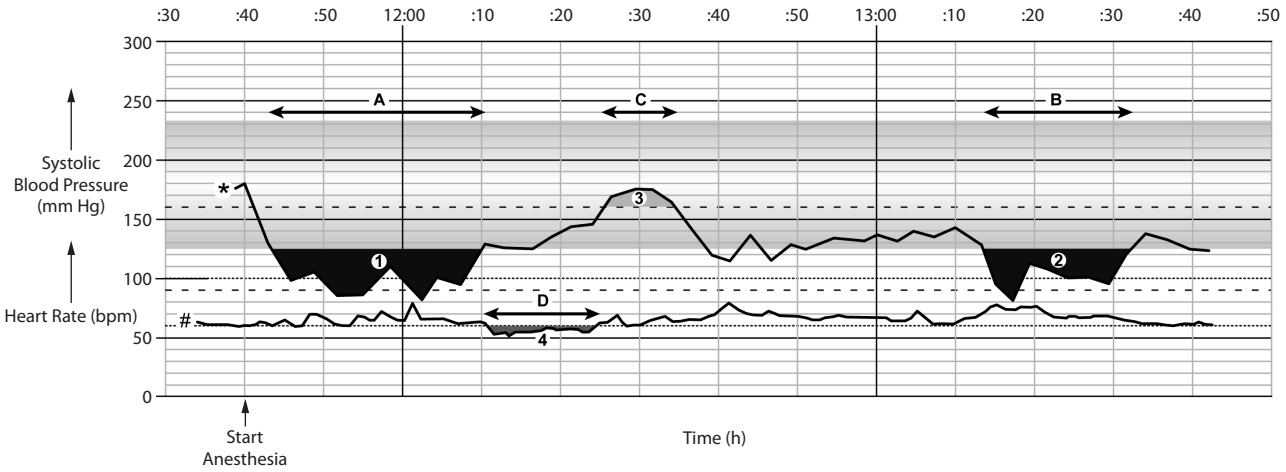
The outcome of interest was the occurrence of intraoperative hemodynamic events: hypotension or hypertension and tachycardia or bradycardia. An episode of hypotension or hypertension was defined as a decrease or increase in systolic blood pressure during anesthesia of 30% or more compared to baseline for at least 5 minutes or an episode of systolic blood pressure below 90 mm Hg or above 160 mm Hg for at least 5 minutes.[37] Baseline blood pressure was defined as the blood pressure measured at the preanesthesia evaluation clinic. When this value was not available, the mean of all systolic blood pressures before induction of anesthesia was used as baseline blood pressure.[37,38] An episode of tachycardia or bradycardia was defined as a heart rate >100 beats per minute or <60 beats per minute for at least 1 minute. In case of the occurrence of a hemodynamic event (or more than 1), the total duration of the episode(s) was measured (Figure 1). In addition, the administration of sympathomimetic drugs during anesthesia (ephedrine and phenylephrine) was registered. Finally, the occurrence of the serotonin syndrome and the need for psychiatric consultation were registered.

Data on hemodynamic outcomes were obtained manually from the graphs of blood pressure and heart rate in the electronic anesthesia record keeping (ARK) systems. These systems store data recorded during anesthesia, such as blood pressure (at least every 5 minutes) and heart rate (every minute), as well as data that are entered manually, such as administration of medication and time of intubation.[37] Two investigators (H.J.D. and I.M.M.vH.) independently examined the trend graphs without knowing whether the evaluated patient was an index or reference patient. When there was an inconsistency between the 2 investigators, consensus was achieved using a third independent investigator (W.A.vK.). Preoperative data were collected at the outpatient preanesthesia evaluation clinics. If use of an MAOI was identified preoperatively by the anesthesiologist and noted as a potential risk with respect to the planned anesthesia, these data were registered. Medical records were used to assess whether a psychiatrist was consulted during admission or the serotonin syndrome was diagnosed and to obtain patient and surgery characteristics: age, gender, American Society of Anesthesiologists (ASA) classification,[39] comorbidity, comedication, and duration of anesthesia.

Data Analysis

Patient and anesthesia characteristics are described as proportions or means with standard deviations. Outcomes were described as proportions or medians with interquartile ranges. Comparisons of proportions among groups were performed using the χ^2 test or Fisher exact test when appropriate. The Student independent samples *t* test was used for 2-group comparison of continuous variables when the data satisfied assumptions for parametric analysis and Mann-Whitney *U* tests when the data did not satisfy assumptions for parametric analysis. SPSS release 14.0 (SPSS Inc, Chicago, Illinois) was used for statistical analysis.

Figure 1. Example of Blood Pressure and Heart Rate Data From Electronic Anesthesia Record Keeping System



* Systolic blood pressure (SBP)
Range of SBP from > 30% to < 30% vs baseline (179 mm Hg)
Upper (160 mm Hg) and lower (90 mm Hg) limits of SBP
Baseline systolic blood pressure before start of anesthesia = 179 mm Hg
① and ② = hypotensive episodes (≥ 5 minutes ≤ 30% baseline or < 90 mm Hg)
③ = hypertensive episode (≥ 5 minutes ≥ 30% baseline or > 160 mm Hg)
A + **B** = total duration of hypotensive episodes
C = total duration of hypertensive episode

\# Heart rate
Upper (100 bpm) and lower (60 bpm) limits of heart rate
④ = bradycardic episodes (≥ 1 min < 60 bpm)
(No tachycardic episodes [≥ 1 min > 100 bpm] are shown)
D = total duration of bradycardic episode

Table 1. Participating Hospitals[a]

Hospital	Years Contributing	Tranylcypromine, Index Group n/ Reference Group n	Moclobemide, Index Group n/ Reference Group n
University Medical Center Utrecht, Utrecht	2004–2009	5/13	5/15
Gelre Hospital, Apeldoorn	2004–2009	2/6	5/15
Jeroen Bosch Hospital, 's Hertogenbosch	2004–2010	3/9	1/3
Leiden University Medical Center, Leiden	2007–2009	4/10	4/12
Westfries Gasthuis, Hoorn	2007–2010	1/3	5/15
Onze Lieve Vrouwe Gasthuis, Amsterdam	2007–2009	2/6	3/9
Ziekenhuisgroep Twente, Almelo	2007–2009	5/15	0/0
Rijnstate Hospital, Arnhem	2009	4/12	2/6

[a]All hospitals are located in the Netherlands.

RESULTS

Approximately 280,000 surgical procedures were performed in the participating hospitals in the total observational period of 33 years. Forty-two users of MAOIs with a total of 51 surgical procedures requiring anesthesia were identified, resulting in 51 index patients. Of these patients, 26 (51%) used tranylcypromine, and 25 (49%) used moclobemide (Table 1). No users of phenelzine were identified. For 3 index patients, only 1 or 2 (instead of 3) reference patient(s) could be identified, resulting in a total of 149 reference patients.

Table 2 summarizes the characteristics of all study patients. Users of tranylcypromine were more often female. Nine users of tranylcypromine (35%), 7 users of moclobemide (28%), and 17 (23%) and 11 (15%) of the corresponding nonusers were preoperatively classified as being in a higher risk group, as reflected by an ASA score of 3 or higher. Most patients (83%) received general anesthesia. Users of tranylcypromine and moclobemide and corresponding nonusers did not differ with respect to duration of anesthesia or length of hospital stay.

Intraoperative hypotension occurred less frequently in users of tranylcypromine (46% [12/26]) than in nonusers (73% [54/74]) ($P = .01$). The occurrence of hypertension, bradycardia, and tachycardia during anesthesia was not different between users of tranylcypromine (27% [7/26], 50% [13/26], and 12% [3/26], respectively) and those in the reference group (35% [26/74], 61% [45/74], and 26% [19/74], respectively). The occurrence of hypotension, hypertension, bradycardia, and tachycardia was not different between users of moclobemide and the reference group. The total durations of the episode(s) of hypotension or hypertension and bradycardia or tachycardia in users of tranylcypromine and moclobemide did not differ from those in the corresponding reference groups (Table 3).

Twelve users of tranylcypromine (46%) and moclobemide (48%) and 47 (65%) and 42 (56%) patients in the reference groups were treated with sympathomimetic drugs during anesthesia. A subgroup analysis of the 42 different patients (24 users of tranylcypromine and 18 users of moclobemide) showed no differences in outcomes compared to the total of 51 surgical procedures in users of an MAOI.

In none of the study patients was the serotonin syndrome diagnosed. In 2 users of tranylcypromine, a psychiatrist was consulted during admission. These consultations were not

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Table 2. Characteristics of Study Patients

	Tranylcypromine			Moclobemide		
	Index Group (n = 26)	Reference Group (n = 74)	*P* Value	Index Group (n = 25)	Reference Group (n = 75)	*P* Value
Demographic and clinical characteristics						
Male gender, n (%)	4 (15)	28 (38)	.04	9 (36)	36 (48)	.30
Age, mean (SD), y	64 (16)	63 (10)	.86	59 (17)	57 (16)	.53
Body mass index, mean (SD), kg/m^2	24.6 (4.8)	26.6 (4.5)	.08	27.7 (5.2)	26.0 (4.5)	.17
ASA classification, n (%)						
1	0 (0)	16 (22)		2 (8)	18 (24)	
2	15 (57)	36 (48)		13 (52)	36 (48)	
3	8 (31)	17 (23)	.02	7 (28)	11 (15)	.04
4	1 (4)	0 (0)		0 (0)	0 (0)	
Unknown	2 (8)	5 (7)		3 (12)	10 (13)	
Systolic blood pressure at the preanesthesia evaluation clinic, mean (SD), mm Hg	134 (23)	140 (24)	.29	137 (18)	137 (21)	1.00
Comorbidity, n (%)						
Heart failure	0 (0)	2 (3)	1.00	0 (0)	3 (4)	.57
Hypertension	6 (23)	30 (41)	.11	8 (32)	21 (28)	.70
Arrhythmia	4 (15)	6 (8)	.28	2 (8)	5 (7)	1.00
Angina pectoris	1 (4)	3 (4)	1.00	2 (8)	5 (7)	1.00
History of myocardial infarction	1 (4)	7 (10)	.68	3 (12)	5 (7)	.41
Diabetes	3 (12)	13 (18)	.55	6 (24)	11 (15)	.36
Renal disease	0 (0)	4 (5)	.57	1 (4)	1 (1)	.44
Comedication, n (%)						
Calcium antagonists	3 (12)	6 (8)	.69	3 (12)	8 (11)	1.00
β-Sympatholytics	4 (15)	19 (26)	.28	7 (28)	17 (23)	.59
RAAS inhibitors	4 (15)	21 (28)	.19	10 (40)	14 (19)	.03
Analgesics	1 (4)	6 (8)	.67	3 (12)	8 (11)	1.00
Antiarrhythmic drugs	1 (4)	1 (1)	.45	0 (0)	0 (0)	…
Diuretics	5 (19)	22 (30)	.30	7 (28)	8 (11)	.05
SSRIs	0 (0)	6 (8)	.34	0 (0)	2 (3)	1.00
Other antidepressants	1 (4)	3 (4)	1.00	1 (4)	0 (0)	.25
Anesthesia and surgery characteristics						
Type of anesthesia, n (%)						
General	17 (65)	51 (69)		19 (76)	57 (76)	
Regional[a]	7 (27)	19 (26)		1 (4)	6 (8)	
General + regional[a]	2 (8)	4 (5)		5 (20)	11 (15)	
Local	0 (0)	0 (0)		0 (0)	1 (1)	
Type of surgery, n (%)						
General	15 (58)	42 (57)		15 (60)	45 (60)	
Orthopedic	8 (31)	24 (32)		1 (4)	3 (4)	
Gynecologic	2 (8)	5 (7)		3 (12)	9 (12)	
Other	1 (4)	3 (4)		6 (24)	18 (24)	
Duration of anesthesia and length of hospital stay						
Duration of anesthesia, median (IQR), min	79 (85)	105 (100)	.13	83 (109)	90 (95)	.62
Length of hospital stay, median (IQR), d	4 (7)	4 (6)	.81	4 (9)	4 (9)	.93

[a]Regional anesthesia = spinal or epidural anesthesia or a nerve block.
Abbreviations: ASA = American Society of Anesthesiologists, IQR = interquartile range, RAAS = renin angiotensin aldosterone system, SSRIs = selective serotonin reuptake inhibitors.

Table 3. Intraoperative Hemodynamic Events With Continuation of MAOI Treatment During Anesthesia

	Tranylcypromine			Moclobemide		
Outcome	Index Group (n = 26)	Reference Group (n = 74)	*P* Value	Index Group (n = 25)	Reference Group (n = 75)	*P* Value
At least 1 intraoperative episode, n (%)						
Hypotension	12 (46)	54 (73)	.01	13 (52)	49 (65)	.23
Hypertension	7 (27)	26 (35)	.44	7 (28)	12 (16)	.24
Bradycardia	13 (50)	45 (61)	.34	16 (64)	38 (51)	.25
Tachycardia	3 (12)	19 (26)	.13	7 (28)	20 (27)	.90
Administration of sympathomimetics, n (%)						
Total	12 (46)	47 (65)	.12	12 (48)	42 (56)	.49
Ephedrine	9 (35)	38 (51)	.14	10 (40)	31 (41)	.91
Phenylephrine	5 (20)	23 (31)	.25	5 (20)	22 (29)	.36
Total duration, median (IQR), min[a]						
Hypotension	19 (16)	28 (39)	.24	31 (44)	24 (31)	.49
Hypertension	18 (39)	12 (20)	.13	12 (20)	11 (35)	.77
Bradycardia	41 (71)	24 (57)	.55	32 (51)	28 (60)	.48
Tachycardia	3 (…)	2 (20)	.23	2 (23)	2 (10)	.69

[a]Total duration in those cases in which at least 1 episode of intraoperative hypotension, hypertension, bradycardia, or tachycardia occurred.
Abbreviations: IQR = interquartile range, MAOI = monoamine oxidase inhibitor.

related to complications due to the perioperative use of tranylcypromine.

DISCUSSION

This cohort study investigated the occurrence of intraoperative hemodynamic events in patients who continued their antidepressant treatment with an MAOI in the perioperative period. Adverse hemodynamic events, such as hypertension and tachycardia, did not occur more frequently in users of either the irreversible MAOI tranylcypromine or the reversible MAO-A inhibitor moclobemide compared to nonusers. Moreover, intraoperative hypotension occurred even less frequently in users of tranylcypromine than in nonusers. In none of the patients in the index or reference groups was the serotonin syndrome diagnosed.

Our results confirm the findings from small observational studies[27–29] involving users of irreversible MAOIs who continued to use these medications during surgery without the occurrence of severe hemodynamic instability. There are no previous studies with respect to the use of the reversible MAO-A inhibitor moclobemide during anesthesia. Current recommendations to discontinue irreversible MAOIs 2 or 3 weeks before surgery[6] appear to contradict daily clinical practice, for we found that the irreversible MAOI tranylcypromine and also the reversible MAO-A inhibitor moclobemide are generally continued during anesthesia. However, the use of an MAOI was in 41 cases (80%) documented in the medical record before surgery and in only 21 cases (41%) accompanied by an explicit warning of the possible risk with respect to the planned anesthesia. Therefore, we cannot conclude that in all cases the anesthesiologist deliberately decided to continue the MAOI during anesthesia. It is likely that continuation often also occurred "by accident." In the literature, it was also suggested to exchange irreversible MAOI therapy for the reversible MAOI moclobemide 2 weeks before surgery.[14] Restoration of the depleted neurotransmitters requires the discontinuation of moclobemide for only 24 hours.[6,7] In daily clinical practice, however, this method does not seem to have gained widespread acceptance, possibly because switching antidepressants may endanger the psychiatric treatment. In our study, tranylcypromine was not exchanged for moclobemide in any patients. (The patients we studied did not discontinue the use of moclobemide.)

The occurrence of some comorbidities seemed somewhat higher in the reference group (Table 2). However, we did not find any significant differences in the occurrence of comorbidity between users of MAOIs and the reference groups. Furthermore, the percentage of patients with an ASA score of at least 3 was higher in users of an MAOI. We assume that some anesthesiologists qualify users of an MAOI as having an ASA classification of 3, as recommended by Huyse et al,[6] apart from the presence of other morbidities.

Both intraoperative hypotension and hypertension have been reported to be associated with adverse outcomes. Besides absolute or relative blood pressure thresholds, the duration of low blood pressure is equally important in the possible association with adverse outcomes. Anesthesia (regional and general) normally leads to a reduction in blood pressure.[38,40] In our study, intraoperative hypotension occurred in fewer users of tranylcypromine when compared to the reference group. However, among patients in whom intraoperative hypotension occurred, the total duration of the episode(s) was not different between users of an MAOI and reference patients. As the enzyme monoamine oxidase regulates the metabolic breakdown of serotonin, MAOIs may possibly have an influence on changes in intraoperative blood pressure. The exact mechanism is not clear, but it has been suggested that serotonin plays a role in the regulation of vascular tone and/or in buffering blood pressure response to stress.[41] In a recent study,[41] we found an association between treatment with selective serotonin reuptake inhibitors and duration of intraoperative hypotension.

Two seriously hazardous interactions between agents used during anesthesia and irreversible MAOIs have been described. These interactions may—although less severe and frequently—also occur in users of moclobemide.[7,18,20] First, the administration of indirect-acting sympathomimetic drugs, such as ephedrine, can result in the release of accumulated norepinephrine from presynaptic nerve-ending store sites. Such release may be augmented by an MAOI. Therefore, the use of direct-acting sympathomimetic agents, such as phenylephrine, has been recommended to treat intraoperative hypotension, if necessary. The higher the risk of unstable blood pressure, the higher the risk of interactions between MAOIs and indirect-acting sympathomimetics.[6] However, apart from case reports, there are no controlled studies that contribute to the evidence that concurrent use of indirect-acting sympathomimetics and MAOIs leads to the development of severe hypertensive episodes. In our study, both phenylephrine and ephedrine were administered to users of an MAOI (Table 3). We did not find a higher incidence of intraoperative hypertension in patients treated with ephedrine compared to phenylephrine. Furthermore, a subgroup analysis showed no differences in hemodynamic outcomes between users of an MAOI who were intraoperatively treated with ephedrine and the corresponding reference patients (data not shown). None of the study patients showed a hypertensive crisis. Three users of irreversible MAOIs in Wong's study[29] were also treated with ephedrine without the occurrence of severe events.

Second, the interaction between meperidine and an MAOI has been described.[22,24–26] The interaction has a depressive and a potentially fatal excitatory form. It has been postulated that the excitatory response is caused by an elevation of the cerebral concentration of serotonin. This increase is the result of the inhibitory effect of an MAOI and may be intensified by meperidine or other serotonin-enhancing analgesic drugs.[6,8,20] Although the reports are anecdotal and no controlled studies are available, it is generally accepted that the use of meperidine in users of MAOIs is hazardous. In our study, meperidine was administered to 1 user of moclobemide in the recovery room, which resulted in agitation

without further complications. With respect to other opioids, such as sufentanil or morphine, interactions appear to be much less common and severe. Sufentanil and morphine were administered to 27 and 13 users of an MAOI, respectively, without the occurrence of severe adverse reactions.

We identified 51 procedures in which an MAOI was continued perioperatively among approximately 280,000 surgical procedures, resulting in an estimated prevalence of MAOI use among surgical patients of 1.8 per 10,000. This estimate is of the same order of magnitude as the prevalence of the usage of MAOIs in the Netherlands: roughly 3,000 users among 13.4 million adults (2.2 per 10,000).[42]

As the use of MAOIs is currently limited to a distinct group of patients, we deliberately chose to conduct this study in several hospitals. In this way, we were able to include 42 different users of an MAOI. All data on hemodynamic outcome parameters were collected from electronic anesthesia records to avoid discrepancies introduced by the use of both handwritten and computerized records.[43] Furthermore, we collected other factors that may have influenced the outcomes, such as ASA classification, comorbidity, comedication, and duration of anesthesia. Collecting these data allowed us to report on any differences between the index and reference groups. Still, some potential limitations must be addressed. First, this was a retrospective nonrandomized observational study and therefore was subject to potential bias. To prevent selection bias, we selected all index and reference patients from a well-defined population of elective surgical patients without knowledge of outcomes at the time of selection. Second, because there are no uniformly accepted definitions for intraoperative hypotension and hypertension, we used a definition that is among the most frequently found in the literature.[37] Obviously, the occurrence of outcomes depends on the definition used. However, since we used the same definition in the index and reference groups, we believe this has not affected our conclusions substantially. Third, because we derived data from daily clinical practice, there may have been some artifacts in the blood pressure data (eg, movement artifacts). However, this inaccuracy was quite likely a random or nondifferential misclassification, as blood pressure data were obtained from an electronic ARK system. Fourth, as we used computerized pharmacy databases that contain information about medication of hospitalized patients to identify users of MAOIs, we could have missed some patients whose treatment with an MAOI had been stopped before admission and was not restarted during their hospital stay. However, we assume this to be very unlikely, as, in the treatment of these psychiatric patients with a severe depression, medication will be restarted as soon as possible after surgery. Furthermore, we checked whether the anesthesiologist reported the decision to discontinue the use of the MAOI in the records of the preoperative evaluation. In the observed period, we found only 1 patient in whom an MAOI was stopped preoperatively (not included in our study). Finally, in cases of known perioperative MAOI use, the anesthesiologist could have been more alert to intraoperative hemodynamic events. However, this influence seems limited, since the most obvious preventive measure; that is, the preference to use phenylephrine instead of ephedrine in users of an MAOI, was not observed.

Our study showed no periods of severe intraoperative hemodynamic instability in a substantial group of patients treated with the irreversible MAOI tranylcypromine or the reversible MAO-A inhibitor moclobemide perioperatively. As the use of MAOIs is now limited, we doubt if there will be sufficient data to formulate a guideline based on evidence from randomized clinical trials in the near future. However, the current observations suggest that there is no longer much justification to discontinue tranylcypromine and moclobemide before surgery, with the attendant considerable risk of compromising patients' psychiatric status. Moreover, there is no consensus on the required period of discontinuation of irreversible MAOIs.[6,13,44] Currently, review of concurrent medication is an integral aspect of the preoperative anesthetic evaluation. Therefore, anesthesiologists can identify the use of an MAOI and consider the possible side effects when administering anesthesia well in advance of surgery. Although in our study the preoperative continued use of an MAOI did not always seem to have been explicitly recognized as a possible risk and MAOI use may also have been continued "by accident," severe perioperative events did not occur. However, failing to recognize the use of an MAOI during preoperative evaluation seems hazardous anyway. When in an individual patient there still is doubt about the continuation of an irreversible or reversible MAOI, consultation between anesthesiologist, psychiatrist, and surgeon is indicated in order to balance the potential risks of anesthesia against the psychiatric complications of drug withdrawal.

Drug names: meperidine (Demerol and others), phenelzine (Nardil), sufentanil (Sufenta and others), tranylcypromine (Parnate and others).

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