Antidepressant treatment with MAO-inhibitors during general and regional anesthesia: A review and case report of spinal anesthesia for lower extremity surgery without discontinuation of tranylcypromine

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Abstract. Monoamine oxidase-(MAO)-inhibitors are a treatment of last resort in treatment resistant depression, which is regarded as a condition of increased psychiatric risk. General and regional anesthesia for elective surgery during use of long-term MAO-inhibitors remains a matter of debate because of an increased risk of drug interactions and decreased sympathetic stability. A series of case reports and new comparative studies reveal the safety of anesthesia/analgesia in non-cardiac surgery without discontinuation of the MAO-inhibitor if best effort is made for maintenance of sympathetic homeostasis and if known drug interactions are avoided. Very few reports with severe adverse incidents have been noted. Severe cardiovascular morbidity, a contraindication of MAO-inhibitors, probably contributed to peri- and postoperative complications. An increased psychiatric risk in patients treated with MAO-inhibitors compensates for an increased, however manageable, perioperative risk.

Introduction

According to a survey in an American hospital, ~ 15% of patients admitted for elective surgery were taking antidepressant drugs [1]. An increased cardiovascular and hemodynamic risk of perioperative anesthesia and analgesia has been recognized during long-term treatment with these frequently prescribed psychotropic medications [2, 3].

Clinical applications of irreversible monoamine oxidase-(MAO)-A/B-inhibitors (e.g., tranylcypromine, phenelzine) have considerably decreased since the 1960s because of the risk of hypertensive crisis after consumption of tyramine rich foods ("cheese effect"). A diet with a low content of tyramine, a strong indirect sympathomimetic agent, is therefore mandatory and the use of MAO-inhibitors is limited today to treatment resistant depression. Elective surgery or emergency treatment with anesthesia and analgesia is sometimes needed for these patients. There is therefore a need for accumulation and evaluation of medical scientific knowledge and clinical experience of anesthesia and analgesia in patients treated with MAO-inhibitors. The current data is limited in the area of regional anesthetic techniques such as spinal anesthesia, for instance. Therefore, a review of continuous MAO-inhibitor treat-
Review of MAO-inhibitors and anesthesia/analgesia

Antidepressant drugs and anesthesia/analgesia

The perioperative risk of antidepressant drugs is caused mainly by a higher peripheral and central tonus of amine neurotransmitters. One or more pathways of amine neurotransmission (serotonin, norepinephrine, dopamine) are affected by the different antidepressant classes. In addition, tricyclic antidepressants (TCA) also display anticholinergic, antihistaminergic and alpha-adrenergic activities. Selective serotonin reuptake inhibitors (SSRI) may cause increased bleeding and hyponatremia [2, 4, 5]. However, SSRI are generally regarded as the safest antidepressants in anesthesia because of the lack of norepinephrinergetic activity. Pharmacodynamic drug interactions with anesthetic and analgesic drugs have to be considered, in particular the risk of serotonin toxicity with MAO-inhibitors [6] and SSRI [2, 7, 8, 9], which has also been described as excitatory syndrome (Type I excitatory reaction: hypertension, hyperpyrexia, seizures) in anesthesia [10, 11, 12]. Hypertensive crisis is a risk associated with MAO-inhibitors and indirect sympathomimetics used in anesthesia for the treatment of perioperative hypotonia [12]. The relevance of pharmacokinetic SSRI-interactions is still unknown for anesthesia despite the fact that strong inhibition of microsomal cytochrome P450 (CYP) enzymes is well known for paroxetine, fluoxetine and fluvoxamine [2, 13, 14]. In the past, pharmacokinetic drug interactions were also suspected for irreversible MAO-A/B-inhibitors such as phenelzine [6]. More recent studies have shown that tranylcypromine, in contrast to phenelzine, may be devoid of significant inhibition of CYP enzymes at therapeutic doses [15, 16]. Increased plasma concentrations of opioid analgesics because of pharmacokinetic drug interactions may result in a depressant syndrome (Type II depressive reaction: sedation, hypotension, respiratory depression and coma) [10, 11, 13]. Enzymes determining the metabolism of opioids are CYP enzymes (e.g., fentanyl, sufentanil, propoxyphene, tramadol) and uridine 5'-diphospho-(UDP)-glucuronyltransferases (e.g., morphine) [13, 17, 18]. Depressant syndrome may also arise as an additive pharmacodynamic interaction, e.g., more severe hypotension by opioids with TCA or MAO-inhibitors, or as a potentiation of the narcotic effect of morphine, for example.

Reports of continuous MAO-inhibitors during anesthesia/analgesia

Several case reports were published which described in more detail general anesthesia during long-term treatment with tranylcypromine without peri- or postoperative complications, e.g., non-cardiac surgery with diazepam, thiopental, succinylcholine, pancuronium, N2O/halothane, N2O/enflurane or N2O/isoflurane as well as morphine or fentanyl (n = 11) [19]. Another case was with lorazepam, propofol, N2O/enflurane, and fentanyl/morphine for non-cardiac surgery (n = 1) [20]. Conscious sedation with diazepam, methohexital, and lidocaine/epinephrine (n = 1) during long-term tranylcypromine and lithium was described for periodontal surgery [21]. Anesthesia with lorazepam, thiopental, sufentanil, isoflurane/ N2O, and vecuronium (n = 1) was used for elective gastric surgery in a patient taking 60 mg/day tranylcypromine and a TCA [22]. Reports are also available for anesthesia during phenelzine treatment, e.g., with remifentanil (pharyngolaryngectomy and free jejunal flap repair) [23], propofol (mandible surgery) [24], and ketorolac (coloscopy and polypectomy) [25]. A retrospective study of 46 general anesthesias for joint replacement surgery during continuous isocarboxazid showed no difference to the comparison group in perioperative hypotension and hypertension. The percentages of hypo- and hypertension were 10% and 2%, respectively, in the isocarboxazid group. No postoperative complications were attributed to the MAO-inhibitor [26]. A letter in the British Medical Journal in 1975 estimated that thousands of general anes-
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Thesias were used in patients taking MAO-inhibitors and undergoing electroconvulsive therapy (ECT) [27]. More recent reports of ECT are also available, e.g., with phenelzine and propofol-alfentanil anesthesia [28].

El-Ganzouri et al. [19] described three cases of spinal and epidural anesthesia during long-term treatment with MAO-inhibitors: removal of the tibial plate (12 mg tetraacaine 1%, morphine), total gastrectomy (13 ml bupivacaine 0.5%, thiopental, succinylcholine, N₂O/isoflurane, morphine), and transurethral prostate resection (10 mg tetraacaine 1%, morphine). Management of labor over 14 hours (bupivacaine 0.25%) and subsequent successful Caesarean section with epidural anesthesia (bupivacaine 0.5%, morphine) was described for a 25-year-old pregnant woman taking phenelzine [29]. Epidural anesthesia (15 ml bupivacaine 0.5%) with general anesthesia (fentanyl, thiopentone, vecuronium, isoflurane) for an abdominal hysterectomy was conducted in a 70-year-old patient during long-term moclobemide therapy, a reversible MAO-A-inhibitor [30]. Five regional anesthesia cases for joint replacement were reported using isocarboxazid [26].

In contrast to these complication-free surgeries, a case of severe postoperative complications and fatal outcome was reported for a 64-year-old patient with severe cardiac morbidity, including a recent myocardial infarction, and coronary arterial bypass grafting. The patient received multiple medications including continuous 60 mg/day tranylcypromine for depression. Anesthetic/analgesic medication consisted of fentanyl, midazolam and pancuronium. The causal relationship of the incident with the MAO-inhibitor was weak, however, the authors suggested that the MAO-inhibitor may have hindered successful management of the cardiovascular system. It is important to note the difference here from the previous reports because severe cardiac morbidity is a contraindication of tranylcypromine, and cardiac surgery was still performed. The authors concluded that surgery without such stress to the cardiovascular system may be safe in the presence of MAO-inhibitors [31]. A similar case was reported for a multi-morbid patient one week after myocardial infarction and with continuous treatment with phenelzine (30 mg/day) in coronary arterial bypass grafting (premedication scopolamine/morphine, general anesthesia with fentanyl/midazolam, vecuronium). Perioperative hypertension and supraventricular tachycardia occurred and subsided only after substitution of fentanyl/midazolam infusion with enfurane/ketorolac. The total dose of fentanyl was 78 mg/kg and the authors suggested that fentanyl may not be safe for cardiac surgery patients at high doses [32]. However, they did not consider differences in pharmacokinetic interactions of phenelzine and tranylcypromine as known from more recent studies [15, 16, 17, 18]. Increased plasma levels of fentanyl may be possible with phenelzine but not with tranylcypromine.

Irreversible MAO-A/B-inhibitors and their perioperative risk

Irreversible MAO-A/B-inhibitors, such as tranylcypromine, decrease the metabolism of monoamine neurotransmitters, including norepinephrine, and considerably increase their availability in presynaptic storage vesicles of the peripheral and central nervous system. Because of this modification of sympathetic homeostasis and the risk of interactions with indirect sympathomimetic drugs, management of perioperative hemodynamic instability may be more complicated in anesthesia during long-term MAO-inhibitor treatment. In addition, drug interactions with opioids and, for instance, serotonergic opioids (meperidine, tramadol, dextromethorphan) have to be considered [33]. Discontinuation of irreversible MAO-inhibitors usually two weeks before elective surgery has therefore been recommended to provide the time needed for regeneration of MAO activity [3]. This recommendation received the lowest evidence level in a guideline of the European Society of Anesthesiology [34]. However, prolonged cardiovascular collapse with blood pressure 40/20 mmHg (recovered) occurred during combined general anesthesia and epidural administration of 10 mg bupivacaine in partial colorectal surgery still three weeks after discontinuation of tranylcypromine [35]. The patient was a multimorbid 79-year-old woman (including recent congestive heart failure) treated continuously with a calcium...
blocker (verapamil) and an inhalative β2-sympathomimetic (metaproterenol). Reports of severe incidents and death are available for continuous calcium blockers during anesthesia [10]. Disregarding a possible role of the calcium blocker and the general physical risk in this patient, the authors discussed down-regulation of adrenoceptors, which developed during MAO-inhibitor treatment as a possible reason. They also suggest, that recovery of receptor hyposensitivity requires additional time. Two or 3 weeks of discontinuation of MAO-inhibitors may be too short for some patients to achieve full sympathetic homeostasis. In a similar case, tranylcypromine treatment of 10 mg/day was suspended 8 days before non-cardiac surgery. No data on concomitant morbidity and medications was provided for this 75-year-old female patient. Severe complications (hypotension, bradycardia, cyanosis, cardiac arrest) emerged 10 minutes after induction of general anesthesia with thiopental, succinylcholine, N₂O and isoflurane. Reanimation was needed and the patient recovered [36]. Consequently, it is thought that a recent discontinuation may not decrease the risk of shock or may even increase it. Four weeks of MAO-inhibitor discontinuation is discussed as a minimum [35]. This is confirmed by a prospective and randomized study of three days of preoperative TCA-discontinuation in 80 chronically depressed patients undergoing orthopedic surgery. The 3 days of TCA-discontinuation are equivalent to 8 to 14 (21) days of MAO-inhibitor discontinuation because the primary pharmacologic effect in the norepinephrinergic and serotoninergic systems is vanished (reuptake or MAO-inhibition) along with, however, enduring changes of sympathetic homeostasis due to reduced receptor density. After a duration of anesthesia of 141.1 ± 42.4 min and 146.0 ± 47.1 min (mean ± standard deviation), respectively, postoperative delirium or confusion occurred in five patients (13%) of a group who continued, and in 12 patients (30%) who discontinued the antidepressant (p = 0.05). The incidence of hypotension and arrhythmias during anesthesia was equal in both groups (5 and 6%, respectively) [37]. A recent observational cohort study of 51 patients in 8 Dutch hospitals investigated the occurrence of intraoperative hemodynamic events without stopping MAO-inhibitors (index group: tranylcypromine (n = 26) and moclobemide (n = 25), reference group: no MAO-inhibitors (n = 149)) during anesthesia and non-cardiac surgery [38] and is in agreement with the TCA data [37]. The tranylcypromine group was comprised of 17 cases of general anesthesia, 7 cases of regional anesthesia, and 2 cases of combined general and regional anesthesia. The median duration of anesthesia in the tranylcypromine group was 79 minutes (interquartile range 85 minutes). Intraoperative hypotension occurred less frequently in tranylcypromine users than non-users. Hypertension/bradycardia/tachycardia did not occur more frequently in users of both the irreversible MAO-A/B- and reversible MAO-A inhibitor compared to nonusers. No excitatory syndromes were found. The authors concluded that, “These findings suggest that there is no longer much justification to discontinue these MAO-inhibitors before surgery.”

Discontinuation of MAO-inhibitors before surgery has been repeatedly described as a high risk for severe relapse of depression [39, 40]. Because a gradual decrease of the MAO-inhibitor dose is recommended, the time without MAO-inhibitor and the time at insufficient dose may add up to a period of 7 weeks of increased risk of relapse. The decision either for discontinuation for a sufficient period of time or for continuous treatment depends therefore on the comparative evaluation of the risk of relapse of severe depression during a period of several weeks and the specific MAO-inhibitor related risk of severe perioperative complications during one or two hours of anesthesia/surgery. The substitution of irreversible MAO-inhibitors by moclobemide is regarded as an unsystematic approach because irreversible MAO-inhibitors are defined as an ultima ratio in the treatment of depression. An increased number of relapses in patients after switch from tranylcypromine to moclobemide is also found in practice [41, 42].

An operationalization of the peri- and postoperative risk according to the American Society of Anesthesiologists (ASA) resulted in a general Classification III (severe systemic disease) for MAO-inhibitors, lithium,
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TCA, and clozapine in contrast to a Classification II (mild systemic disease) for SSRI. Physical risk: MAO-inhibitor = TCA > SSRI

The difficulty of such an approach is obvious when taking into account a survey in 150 American anesthesiology programs, which revealed a ratio of 51% for discontinuation of MAO-inhibitors but only 9% for TCA, despite an equal ASA-classification [3]. The authors recommended an individualized evaluation of patients which should also include their psychiatric risk. The mean psychiatric risk in recent MAO-inhibitor patients is estimated considerably higher than in SSRI-treated patients. There is an increased risk of relapse because of chronicity, treatment resistance, and residual symptoms. For instance, the complications of relapse are considerably more severe because of increased suicidality, a lower chance of psychiatric improvement after relapse, and also because of an increased physical risk.

Psychiatric risk: MAO-inhibitor > TCA > SSRI

The decision for either discontinuation of antidepressant medications or continuous perioperative treatment depends therefore on the ratio of physical and psychiatric risk which, in a consequent conclusion, may be roughly evaluated as similar for e.g., MAO-inhibitors and SSRI.

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\text{Ratio } \frac{\text{physical risk}}{\text{psychiatric risk}}: \text{MAO-inhibitor} \approx \text{SSRI}
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(■■■Author: bitte Kontrolle:) Thus, an increased psychiatric risk of 4 weeks discontinuation of MAO-inhibitors compensates for an increased perioperative risk of continuous treatment. However, some reluctance to continue MAO-inhibitor treatment may be explained by (i) negligence of the change of place in therapy of MAO-inhibitors, i.e., today’s clinical application mainly in treatment-resistant depression with increased psychiatric risk, (■■■Author: bitte Kontrolle:) (ii) negligence of the psychiatric risk at all because experience exists only with SSRI, (iii) negligence of the knowledge and chances of avoiding and reducing MAO-inhibitor related peri- and postoperative risk, and (iv) negligence of the risk of short-term MAO-inhibitor discontinuation.

**Recommendations for anesthesia/analgesia during continuous MAO-inhibitor treatment**

Detailed recommendations are available for general anesthesia during continuous treatment with antidepressant drugs and MAO-inhibitors [11, 12]: (i) prevention of sympathetic activation by sufficient preoperative antianxiety medications and by perioperative avoidance of pain, hypoxia, hypercapnia and hypotension, (ii) careful dosage of short-term lead-in medications, (iii) use of non-depolarizing muscle relaxants, (iv) balanced anesthesia with enflurane or isoflurane as examples of inhalation anesthetics, (v) careful and extended hemodynamic monitoring, (vi) volume supplementation and direct sympathomimetics (norepinephrine) for perioperative hypotension, (vii) vasodilator drugs for hypertension. Serotonergic opioids and indirect sympathomimetics are strictly contraindicated. Morphine and fentanyl are regarded as relatively safe as well as other fentanyl derivatives [11, 12, 22, 23, 28]. Bajwa et al. [43] deemed regional anesthesia as a safer alternative than general anesthesia for patients on psychotropic medications. No drug interactions with local anesthetic drugs have been found, but high concentrations of catecholamine supplements should be avoided. A slow sympathetic blockade, as found in epidural and continuous spinal anesthesia, is preferred.(■■■Bitte Kontrolle:) It is recommended to treat hemodynamic complications in spinal anesthesia as for general anesthesia [12, 44].

**Case report with discussion**

In February 2012, an elective surgery of the anterior of the right foot was planned in a 66-year-old female patient (170 cm, 75 kg) who had been being treated with 20 mg/day tranylcypromine (Jatrosom®) and 10 mg/day zolpidem for depression lasting 3 years. Standard laboratory data was normal before surgery including a fasting blood glucose of

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4.7 mmol/l. The electrocardiogram was unremarkable. Arterial hypertension was treated with 4 mg/day candesartan. No treatment was required for a mild case of Hashimoto thyroiditis. The patient used simeticone for meteorism and acetaminophen as needed. The patient had had local anesthesia during an ambilateral cataract surgery without discontinuation of tranylcypromine 2 years before foot surgery. She refused discontinuation of tranylcypromine for the planned foot surgery. Psychiatric consultation including psychiatric interview of the patient revealed sufficient psychic and intellectual capability and the need for continuous antidepressant treatment. Thus, it was decided to perform surgery and spinal anesthesia during long-term MAO-inhibitor treatment without discontinuation of tranylcypromine and after written informed consent.

After admission to hospital, medication consisted of 10 mg oral zolpidem, 120 mg oral etoricoxib, and 3,000 IU s.c. certoparin sodium the evening before surgery. At 7 a.m. the day of surgery, the patient received her daily doses of 20 mg tranylcypromine and 4 mg candesartan together with a small breakfast (coffee, zwieback, water). Anesthetic premedication was 7.5 mg oral midazolam at 1.30 p.m. Stable vital parameters of 160/90 mmHg blood pressure, 82 min⁻¹ heart rate, 99% oxygen saturation, and 36.8 °C body temperature as well as general physical well-being were monitored ~ 2 hours later after arrival in the operating room. The start of anesthesia and surgery was ~ 7.5 hours after taking the daily tranylcypromine dose. Volulyte® 350 ml as volume supplement and a dose of 1.5 g cefuroxime for perioperative antibiotic prophylaxis were infused. Local anesthesia at the site of lumbar puncture (L3/4) consisted of 30 mg isobar prilocaine. Spinal anesthesia was achieved by a single shot of 13.5 mg hyperbar bupivacaine at a volume of 2.7 ml (0.5%) intrathecally. After 2 minutes in a right lateral position, the patient was transferred to a supine position. Stable vital parameters were consistently found also during a subsequent 500 ml volume supplement-blood pressure of ~ 150/80 mmHg and heart rate of 75 – 82 min⁻¹. Sedation was achieved with 0.5 mg intravenous midazolam. A considerable extension of spinal anesthesia was found after an additional time of 2 minutes (right Th7, left Th9). Tilting the patient to raised upper part of the body stabilized the extension of spinal anesthesia (right Th7, however left Th5). After 35 minutes of surgery, postoperative regional analgesia was applied by peripheral nerve block (foot block) with 50 mg isobar bupivacaine in a volume of 10 ml (0.5%). Postoperative arterial hypertension with 180/105 mmHg (heart rate of 72 min⁻¹) was treated with 5 mg sublingual nifedipine. The patient was admitted to the general ward in good health, analgesia, stable blood pressure, and without an increase in body temperature.

Further postoperative analgesic treatment consisted of short infusions of acetaminophen, oral acetaminophen, 90 mg/day oral etoricoxib for 5 days, and oral oxycodone as needed. The patient had continued her antidepressant and antihypertensive medications since the first day postoperatively. No peri- or postoperative complications were observed.

Taking into account the review, it was the right decision for this patient to perform spinal anesthesia for forefoot surgery during long-term antidepressant treatment with tranylcypromine. The patient was informed in detail about the course and the risks of the intervention. Cooperation during preparation for regional and nerve blocks was regarded as a minor problem in this depressed patient. It was also important that the patient had refused discontinuation of tranylcypromine and that treatment with tranylcypromine was the ultima ratio in the clinical-psychiatric context. The individual risk of exacerbation of severe depression after discontinuation of tranylcypromine (psychiatric risk) was rated higher compared to the additional tranylcypromine-related risks of anesthesia (physical risk). Accordingly, single shot spinal anesthesia with subsequent foot block for postoperative analgesia was conducted without peri- or postoperative complications. Single shot bupivacaine was found to be safe with regard to speed of sympathetic blockade despite the fact that continuous spinal anesthesia was more recommended [44]. The single shot technique was chosen for practical reasons. Midazolam and other benzodiazepine drugs are discussed as being safe with MAO-inhibitors and this was confirmed in the present patient [12]. In agreement with the literature,
careful establishment of the block and careful intravenous fluid loading for prophylaxis of hypotension were applied [19, 29]. No direct sympathomimetics were required. Phenylephrine was used by other therapists for perioperative hypotension in epidural anesthesia [19, 30], however, it was suggested that phenylephrine exhibits partly indirect sympathomimetic activity and may be better substituted by norepinephrine [29]. An interaction of phenelzine and selegiline with indirect sympathomimetic ephedrine was reported for spinal anesthesia with blood pressure of 245/125 mmHg and 240/120 mmHg, respectively [45]. In contrast, moclobemide and ephedrine did not yield an interaction in one patient [30]. Oxycodone for postoperative analgesia is an opioid without serotonergic activity and therefore devoid of the risk of severe interactions of the excitatory type [12, 33]. Also, no interactions of the depressive type, which may occur in very rare cases [11, 12], were observed with oxycodone. The MAO-inhibitor was also safe with regard to the cyclo-oxygenase-(COX)-2 inhibitor etoricoxib. So far, no data is available for this combination in the literature, however, the COX-inhibitor etoricoxib was also safe with regard to the cyclo-oxygenase-(COX)-2 inhibitor etoricoxib. Treatment of severe serotonin toxicity following co-administration of DPH and selective serotonin reuptake inhibitors is an update on a case report of serotonin syndrome in a postoperative patient. J Psychopharmacol. 1999; 13: 1433-1438.

Conflict of interest

Dr. Adli has received grant/research support from Aristo Pharma.

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