Opioid “Holiday” Following Antagonist Supported Detoxification during General Anesthesia Improves Opioid Agonist Response in a Cancer Patient with Opioid Addiction

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TREATMENT of chronic pain in patients with a history of opioid addiction is difficult since tolerance to the opioid agonist effects may require extremely large opioid doses for pain control. Furthermore, insufficient pain control may be hard to discern from craving for more opioids. Although drug-free periods, also called “drug holiday,” can reestablish sensitivity to drugs used to treat Parkinson disease and schizophrenia, this strategy has not been described for patients with chronic pain presenting with tolerance to opioids.

We report an opioid addicted patient with intractable cancer pain during methadone substitution therapy in whom antagonist supported opioid detoxification and a drug holiday reestablished sensitivity to opioids and improved cancer pain.

Case Report

A 35-yr-old man with a history of hemipelvectomy 2 yr ago for treatment of chondrosarcoma was admitted because of unbearable pain in the right leg (dermatomes L3–S2) described as burning and stabbing with a pain score of 9–10 on an 11 point (0–10) numeric rating scale (NRS). Examination also revealed paralysis of the right leg caused by extended tumor infiltration of the right lumbosacral plexus.

The patient had a history of heroin addiction and had been treated with L-methadone (120 mg/day) as a substitution therapy to avoid withdrawal symptoms. Therapy was started with sustained-release morphine (60 mg/day p.o.) but had to be increased during 24 h to 300 mg/day intravenous morphine hydrochloride without amelioration of pain.

To discriminate between craving for opioids and insufficient control of neuropathic pain a lumbar epidural catheter was inserted (interspace: L3/L4) and bupivacaine (0.25%, 10 ml) injected every 4–6 h of neuropathic pain a lumbar epidural catheter was inserted (interspace: L3/L4) and bupivacaine (0.25%, 10 ml) injected every 4–6 h.

After 4 weeks of epidural treatment, however, pain increased despite increasing dosages of epidural bupivacaine. Therefore, a short and unsuccessful attempt with high dose (1368 mg/day) intravenous morphine therapy was made but changed to epidural morphine injection, while oral therapy with L-methadone, dipyrone, amitriptyline, dexamethasone, and carbamazepine was continued. As much as 30 mg/h of epidural morphine was required for moderate pain relief.

Since long-term administration of these large opioid dosages is not feasible as a long-term home therapy, we performed an antagonist-supported detoxification procedure during general anesthesia so as to reestablish the opioid receptor system.

The L-methadone administration was stopped 7 days before detoxification without evoking withdrawal symptoms. Following anesthesia with propofol, tracheal intubation, and mechanical ventilation, the opioid receptor blockade was performed by intravenous administration of the opioid receptor antagonist naltrexone (12.4 mg naltrexone intravenous within 1 h), as described previously. Opioid receptor blockade was maintained by naloxone (0.8 mg/h intravenous for 24 h), and followed by the orally active opioid receptor antagonist naltrexone (50 mg/day p.o.) for 1 week. Withdrawal symptoms were minimized by administration of the α2-adrenoceptor antagonist clonidine (10 μg/kg + 2–5 μg/kg × h intravenous) and the patient was extubated 6 h after induction of general anesthesia. After completion of the procedure, the patient had moderate withdrawal symptoms treated by titrating doses of clonidine and amitriptyline per os until the symptoms were controlled. No significant episodes of nausea, vomiting, or diarrhea occurred. Cancer pain following opioid receptor blockade was completely relieved by epidural bupivacaine (0.25%, 5 ml/h) via a newly inserted lumbar epidural catheter (interspace: L3/L4) allowing a drug holiday of 3 weeks (fig. 1).

Subsequently, the epidural catheter was removed and sufficient pain relief (NRS ≤ 3) was achieved by a moderate dose of sustained-release morphine (90 mg p.o.) combined with dipyrone (3 g/day p.o.), dexamethasone (12 mg/day p.o.), amitriptyline (125 mg/day p.o.), carbamazepine (1200 mg/day p.o.), and clonidine (900 μg/day p.o.).

Palliative fractionated radiotherapy was started after 2 weeks of drug holiday. When treatment had been switched completely to oral medications and the epidural catheter was extracted after 3 weeks of drug holiday the patient had received 9.0 Gy of a total dose of 59.4 Gy. Unfortunately, radiation did not decrease the tumor size nor prevent tumor progression.

The patient was fully active and remained pain free under oral medications on discharge and no complications due to detoxification and analgesic treatments were observed. Pain control with sustained release morphine (≤1.5 g/day) was effective for another 8 months despite extensive tumor progression leading to a large ulcer involving his leg and gluteal region. Eight months after the end of opioid holiday subcutaneous morphine (~600 mg/day), therapy was started one week before the patient’s death.

Discussion

After long-term opioid administration, the vanishing analgesic effect of opioids in patients with intractable pain may be overcome by an opioid free period (drug...
holiday) following antagonist supported detoxification from opioids.

Neuropathic pain caused by tumor invasion of a plexus or peripheral nerve may be refractory to therapy. In our patient, tricyclic antidepressants considered to be most effective in neuropathic pain were ineffective. Although the effectiveness of opioid therapy is still controversial, opioid treatment has been recommended in patients with severe chronic neuropathic pain. However, in patients with a history of opioid abuse pain therapy may require much higher opioid dosages to achieve any analgesic effect.

Opioid tolerance is suspected when increasing opioid dosages are required to obtain a given effect. While its underlying pharmacokinetic and pharmacodynamic mechanisms are not yet fully understood chronic opioid administration decreases μ-opioid receptor density in several brain regions and uncouples opioid receptors from their second messenger system. Tolerance to analgesic effects of opioids develops in at least 15% of cancer patients receiving opioids parenterally and cross tolerance between systemic and epidural morphine can occur. Of interest, in patients receiving long term oral opioid therapy, three times higher doses of epidural opioids are required for postoperative pain therapy compared to opioid naive patients. We did not establish continuous intrathecal or epidural opioid infusion with an implanted pump system, since this was not considered feasible given a short life expectancy, a difficult social background, and little compliance. We also did not consider a L3-S2 neurolytic spinal block since the risk of side effects such as lower extremity paralysis or loss of bowel or bladder control was considered inappropriate.

When managing pain refractory to high-dose opioid therapy, changing the route of drug administration or switching to another opioid with a different structure may be useful. In our patient, we had already used two opioids (methadone and morphine) without success and also had temporarily changed from enteral to epidural application. Therefore, we could not switch therapy from 720 mg/day epidural morphine to oral administration, since this epidural dose is equivalent to approximately 21 g/day oral morphine, which is not successfully applicable in this dose.

To reestablish sensitivity to opioids, we performed an antagonist supported detoxification from opioids during general anesthesia followed by an opioid-free interval recommended as an alternative to conventional opioid withdrawal treatment in addicts. Gold et al. mentioned

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Fig. 1. Chart for opioid holiday following antagonist-supported detoxification to improve opioid agonist response in opioid addiction.
antagonist supported detoxification from opioids in two chronic pain patients with a reduction in the opioid dose observed after detoxification. Unfortunately, detailed information was not provided.

In our patient, anesthesia-supported detoxification from opioids combined with analgesia provided by epidural bupivacaine allowed control of his otherwise untreatable pain and reestablished sensitivity to orally administered opioids, allowing the patient's discharge. Thereafter, escalation of the opioid dose was only moderate during the eight months following opioid holiday.

It is not clear whether it is necessary to perform, during general anesthesia, antagonist-supported detoxification from opioids, since it may be the abstinence from opioids for a certain time rather than the presence of opioid antagonists that is critical to reestablish responsiveness to opioids. However, given the history of opioid addiction in our patient, ultra-rapid detoxification believed to be associated with a high rate of completed withdrawals and referrals for further treatment may have been the preferable withdrawal procedure.

After 2 weeks of drug holiday, radiotherapy was started but without any effects on tumor size or its progression. Although we cannot exclude that the rather small and apparently ineffective dose of radiotherapy may have contributed to analgesia following opioid holiday, it is unlikely to account for the excellent long-term pain reduction persisting for more than eight months despite extensive tumor progression.

In summary, therefore, when the analgesic effects of opioids decrease after long-term opioid administration resulting in insufficient treatment options, sensitivity of the opioid receptor system may be reestablished by antagonist supported detoxification from opioids and a drug holiday. Although rapid detoxification is not risk free, this technique may also be considered in selected patients with chronic pain who have become exceptionally tolerant to opioids but who do not have a history of drug addiction.

References


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Suxamethonium and Donepezil: A Cause of Prolonged Paralysis


**CASE REPORT**

A 72-yr-old woman (weight, 52 kg) was admitted for open reduction and internal fixation of her left wrist following a fall. Her current medical history included symptomatic hiatus hernia, osteoarthritis and Alzheimer disease. She had a history of depression and a bleeding duodenal ulcer.

Her medications consisted of fluoxetine 20 mg, donepezil hydrochloride 10 mg, nimesulide 12.5 mg, and omeprazole 20 mg all taken once a day. She had no drug allergies and had no history of adverse reactions to anesthetic medications. Clinical examination of the patient was normal.

A rapid sequence induction of anesthesia was carried out, following institution of routine monitoring and intravenous cannulation. Propofol 2 Smg/kg was administered followed by suxamethonium 1 mg/kg. Tracheal intubation was performed, and the patient’s lungs were manually ventilated via a circle system.

Anesthesia was maintained using isoflurane in oxygen and nitrous oxide, 60/40. A nerve stimulator was applied over the distribution of the right facial nerve. Six minutes postinduction, there were no twitches in response to a train-of-four stimulation.

Twenty minutes after the start of the anesthetic induction, there was still no twitch response and no spontaneous respiratory effort. The nerve stimulator was checked and proved to be in working order. The position over the facial nerve was reviewed and adjusted slightly. Thirty minutes into the procedure, there were two twitches of diminishing height. After 50 minutes of anesthetic administration, there were four twitches with fade. The patient began to breathe spontaneously, and ventilation was changed to manual mode. The surgical procedure finished 10 min later. No further medications were administered, and the patient’s lungs were extubated uneventfully. She was transferred to the recovery room. Observations of vital signs remained within normal limits.

Neurologic examination carried out in the recovery room did not detect any deficits. The patient and her husband did not agree to have a pseudocholinesterase assay carried out postoperatively. The patient was discharged to the ward and went home three days later. Five years earlier, the patient underwent a laparotomy and oversewing of a perforated duodenal ulcer. Anesthetic notes for this procedure were obtained. A rapid sequence induction of anesthesia had been carried out. Medications employed included sodium thiopentone, suxamethonium, and atracurium besylate. There was no documentation of prolonged duration of paralysis following suxamethonium. Atracurium was administered to the patient 4 min after induction. There was no reported prolongation of action of the nondepolarizing agent, atracurium besylate. Neostigmine was administered at the end of the procedure, followed by uneventful emergence from anesthesia. The patient’s medications at that time were fluoxetine 20 mg, ranitidine 150 mg once daily, and diclofenac 50 mg three times daily.

**Discussion**

Prolonged paralysis is an unusual perioperative complication, most commonly medication induced. Large doses of nondepolarizing neuromuscular agents, particularly in an elderly population, may account for motor impairment, especially in the recovery room. This may be further complicated by inadequate reversal. Inherited deficiencies in the pseudocholinesterase enzyme may cause marked prolongation of drug effect.

Putative interaction with neuromuscular antagonists is included in the product insert of donepezil. Donepezil is a reversible, noncompetitive, piperidine-type cholinesterase inhibitor. It is more selective for acetylcholinesterase than pseudocholinesterase. A previous report from Sprung et al. suggested that inhibition would not occur unless patient levels of pseudocholinesterase were 64% of normal levels. However, interaction with suxamethonium appeared to occur in the case described above.

Suxamethonium is generally short acting, as it is rapidly hydrolyzed by plasma pseudocholinesterase. Similar to suxamethonium, there have been reports of muscle weakness and fasciculations occurring while taking donepezil.

The patient was taking omeprazole, a proton pump inhibitor which is reported to have inhibitory effects on the cytochrome p450 3A4 metabolic pathway. In addition, the patient had been taking fluoxetine for the past 7 yr, commenced to aid in the management of depressive symptoms. Fluoxetine is a potent inhibitor of cytochrome 2D6.

Donepezil is metabolized by the cytochrome P450 isozymes 3A4 and 2D6 in vitro. Covalent bonding and inhibition at the same cytochrome enzyme sites by drugs such as phenytoin, omeprazole, ketoconazole, or
Dexmedetomidine to Facilitate Drug Withdrawal

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MANY patients are admitted to intensive care units (ICUs) from the emergency department for acute detoxification and withdrawal from alcohol or illicit drugs. The process of withdrawal is associated with significant psychomimetic and sympathomimetic phenomena. These patients require close cardiovascular system monitoring, intense nursing observation, and frequent interventions.

In addition, critically ill patients who receive long-term sedative–analgesic therapy in the ICU develop functional tolerance. When they improve and sedative–analgesic medications are withdrawn, they experience withdrawal symptoms similar to those of patients addicted to alcohol, narcotics, or stimulants.1–5

Herein are two reports in which dexmedetomidine was used to facilitate the withdrawal process.

Case Reports

Case 1

A 49-yr-old woman was admitted to the ICU via the emergency room with altered mental status, unusual behavior, anxiety, and agitation. Initially, she was not forthcoming with her history, but later, she admitted to daily cocaine use for at least 2 yr. Her most recent cocaine exposure was approximately 24 h before admission, and her total habit was estimated at $200.00 per week. She also reported consumption of 1 quart of beer per day, or approximately 32 g alcohol. While in the emergency room, she became progressively agitated and combative, coupled with hypertension and tachycardia.

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On arrival in the ICU, she was extremely agitated but able to answer questions at the bedside. Her blood pressure varied from 150–200/70–90 mmHg, with a heart rate between 100 and 140 beats/min. Her chest was clear to auscultation without murmur, her abdomen was soft without masses, and she appeared to be neurologically intact. As part of the diagnostic differential to assess her hyperadrenergic state, we performed urine and serum toxicology screens along with an ABG to rule out cocaine intoxication and hypoxemia. Toxicology results were positive for cocaine. Our laboratory only qualifies the presence or absence of cocaine and does not quantify the amount.

α-Adrenergic agonists, clonidine, and dexmedetomidine have been shown to alleviate withdrawal and excess sympathetic activity symptoms in animals and humans.4–7

Given the patient’s agitation and poorly controlled hypertension, we decided to use dexmedetomidine for sedation. While in the ICU, a dexmedetomidine infusion was initiated with a loading dose of 1 μg/kg infused over 20 min, followed by a maintenance rate between 0.2 and 0.7 μg·kg⁻¹·h⁻¹ to maintain a motor activity assessment score of 3, defined as calm and cooperative, no external stimulus is required to elicit movement; patient is adjusting sheets or clothes purposefully; patient follows commands.8

She remained on dexmedetomidine for approximately 36 h. Her blood pressure ranged from 110/60 to 130/70 mmHg, with a heart rate of 80–100 beats/min. Immediately after the loading dose infusion was completed, she became quite calm. Because of the risk of seizures, she also received intermittent intravenous doses of lorazepam in 1- to 2-mg aliquots. While she was sleepy, she was also readily arousable and followed vocal commands. When dexmedetomidine was discontinued, a clonidine patch was placed to continue control of her hypertension, and oral lorazepam was administered for sedation and seizure prophylaxis.

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Case 2

A 54-yr-old male was admitted for a laparoscopic repair of a massive abdominal wall incisional hernia. On the second postoperative day, he reported abdominal pain, he was febrile, and a three-position view of his abdomen revealed free intraabdominal air. He was returned to surgery to repair the leak from his terminal ileum. Postoperatively, he became bacteremic with secondary systemic inflammatory response syndrome, temperature greater than 38°C, heart rate greater than 90 beats/min, and respiratory rate greater than 20 breaths/min. During the next 4 days, he sequentially developed acute respiratory distress syndrome and multiple organ dysfunction syndrome with renal failure. Over his 6-week course in the ICU, in addition to mechanical ventilation, tracheostomy, and hemodialysis, he received continuous infusions of lorazepam and morphine. As his multiple organ dysfunction syndrome resolved and he was gradually liberated from mechanical ventilation, it became apparent that he was having symptoms of sedative-analgesic withdrawal, e.g., tachycynpa, tachycardia, and agitation. After 6 weeks of continuous benzodiazepine and opioid administration, he was given a full loading dose of dexmedetomidine (1 μg/kg over 20 min), maintained at the maximal infusion rate of 0.7 μg·kg⁻¹·h⁻¹. Over the course of 7 days, the dexmedetomidine infusion was gradually decreased according to his motor activity assessment score (target 3) and was ultimately discontinued. When he was subsequently removed from ventilatory support, he exhibited no further symptomology consistent with withdrawal phenomena.

Discussion

Physicians primarily observe withdrawal phenomena in those patients who are addicted to various drugs. However, those patients who experience multiple organ dysfunction syndrome or have prolonged courses in the ICU may also become functionally addicted or tolerant to therapeutic medications. Both conditions may result in withdrawal.

For more than 20 yr, clonidine, an α-adrenergic agonist, has been used to ameliorate central psychomimetic, sympathomimetic, and cardiovascular symptoms of withdrawal. Given the acute nature of these patients’ symptoms, dexmedetomidine was used instead of clonidine because of its advantages, specifically rapid onset and titratability. The choice of dexmedetomidine allowed us to provide sedation, comfort, and hemodynamic control with a single agent. Because dexmedetomidine has a six-fold higher affinity for the α₂ subunit than clonidine, it is an excellent sedative–hypnotic agent with limited side effects, e.g., hypotension. These two patients were gradually withdrawn over 36 h and 7 days, respectively.

For the second patient, the utilization of dexmedetomidine was advantageous compared to a gradual tapering of benzodiazepines or opioids for three reasons. First, with the known benzodiazepine–opioid ventilatory effects of increasing the slope of the carbon dioxide response curve, the potential for additional ventilatory depression was not warranted in this patient with severely compromised respiratory function.9 Second, dexmedetomidine, with its pharmacodynamic properties, facilitated a more thorough neurologic examination. Third, the use of dexmedetomidine ameliorated the hemodynamic withdrawal phenomena associated with opioid withdrawal.10 Although propofol infusions could possibly be used in a fashion similar to that described for dexmedetomidine, this agent is not utilized in our ICUs. Furthermore, given the hyperadrenergic state of these patients, we believe the sympatholytic properties of dexmedetomidine make it a more suitable agent than propofol.

At present, dexmedetomidine is only approved for 24 h of continuous infusion and for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting. Other investigators, however, have reported more prolonged infusions of the drug, with good clinical outcomes and an absence of side effects.11 In the absence of pharmacokinetic and pharmacodynamic data, we titrated the infusion dose rate to a motor activity assessment score of 3. We observed no evidence of withdrawal from the effects of dexmedetomidine in either case. Despite highly dissimilar circumstances and medical histories, both patients remained calm, cooperative, and arousable while receiving dexmedetomidine. In addition, their vital signs remained stable.

In summary, these reports illustrate the potential benefit of dexmedetomidine for sedation of patients during withdrawal from illicit drugs or the iatrogenic-induced tolerance that develops from extended treatment with...
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A Combustive Destruction of Expiration Valve in an Anesthetic Circuit
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DEFLAGRATION occurring in a respiratory circuit can be fatal to the patient directly connected to the system. Although the circuit is often filled with oxygen at a high concentration, lack of an igniting source and fuel make combustion impossible. Therefore, it is extremely rare to see combustion around an anesthetic machine in the absence of flammable anesthetics. Here we report a combustive accident, in which an expiration valve in an anesthetic machine was destroyed and flame was observed inside the expiratory limb of the circuit.

Case Report
An 18-yr-old man was anesthetized with sevoflurane-nitrous oxide during orthopedic surgery on his left clavicle. Anesthesia was induced with propofol (2 mg/kg), and tracheal intubation was facilitated with vecuronium (120 μg/kg). Anesthesia was maintained with 1.5–2.0% sevoflurane, nitrous oxide, and oxygen. The lungs were ventilated using the ventilator incorporated in the anesthetic machine (Cato; Draeger Inc., Lubeck, Germany).

Immediately after the completion of the surgery, administration of sevoflurane and nitrous oxide was discontinued. Oxygen was delivered to the respiratory circuit at 6 l/min. Seven minutes after the start of ventilation with 100% oxygen, exudate trapped in the endotracheal tube was suctioned. At that time, the anesthetist sprayed Xylocaine® pump spray (AstraZeneca, London, UK) twice (approximately 0.2–0.3 ml) to lubricate the internal surface of the tube. The patient was ventilated again with 100% oxygen under intermittent positive pressure ventilation mode. Three minutes after suctioning, the patient opened his eyes in response to verbal command and started breathing spontaneously. The ventilation mode of the anesthetic machine was then changed from intermittent positive pressure ventilation to "MAN./SPONT."

Immediately after this action, the anesthetist and a circulating nurse heard a moderately loud explosive sound. They looked at the origin of the sound, a connecting port between the anesthetic machine and the respiratory circuit, and found that a disc valve in the expiratory limb had been destroyed (fig 1). The dome cover was intact, and there was no gas leakage from the circuit. Approximately 10 s after the explosive sound, an orange, ring-shaped flame ran up from the destroyed valve toward the endotracheal tube for approximately 15 cm. The flame stopped 10 cm from the air filter (ARNK F001; Draeger Inc.) inserted between the anesthetic machine and the respiratory circuit and disappeared. The anesthetist disconnected the circuit from the endotracheal tube immediately. The anesthetist and the nurse smelled a scorched odor originating from the circuit. Since the patient was awake and breathing normally, the endotracheal tube was extubated. The patient had no airway problems and did not complain of dyspnea or chest discomfort. The machine and the circuit were left as they were to be subjected to a technical inspection by the manufacturer.

Inspection by the Manufacturer
Three components are required for fires and explosions to occur: an oxidizing gas to support combustion, a flammable material, and a source of ignition. In the current case, the gas that supported combustion was unquestionably the 100% oxygen flowing in the respiratory circuit. The laboratory of the manufacturer scrutinized the respiratory circuit for a possible source of ignition and the material that was burned in this accident. In the respiratory circuit, there was only one part that was acting at high temperature, a platinum wire in the flow

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sensor. During normal operation, the temperature of this sensor is 140°C. When the wire becomes worn out after long use, it is possible for it to reach temperatures greater than 900°C; however, the wire itself will not start burning even in an atmosphere of 100% oxygen. Although the fact that the wire is incombustible was confirmed in an experiment in a Draeger laboratory, the condition of the wire before the accident could not be revealed by examination of the machine.

The burnt parts taken from the machine were investigated. Flow sensor and air filter set in the expiratory limb were deformed, probably by high temperature. The inside of the air filter was scorched and tainted with ash. Examinations with gas chromatography and mass spectrography revealed silicone oil (maybe used on O-ring) and d-t-butyl-phenol (an antioxidant for plastics). However, no residue of the burnt material could be identified. It was considered possible that the material was completely burned out, leaving no residue. Analyzing the sequence of events, inspectors suspected that Xylocaine pump spray was the inflammable material present at the scene of this accident. The solution in Xylocaine pump spray contains 241 mg/ml ethanol. Explosive limits for ethanol in air at 1 atm is 3.5–15%, and the ignition temperature is 363°C. Flash point is 13°C. During an oxygen-rich condition, ethanol is more flammable than under air atmosphere. Platinum can act as a catalyst and decrease the ignition temperature of ethanol. Accordingly, the ethanol contained in Xylocaine pump spray can be ignited when the vapor mixes with oxygen at a concentration between the specified limits and makes contact with an ignition source.

Discussion

From the analysis of the sequence of events and the results of the manufacturer’s laboratory investigations, a possible scenario of the accident was proposed as follows:

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1. Ethanol contained in Xylocaine pump spray was vaporized in the warm expiratory gas from the patient, which consisted mainly of oxygen.

2. The gas—oxygen-rich and containing ethanol within explosion limits—reached the expiration gas analysis unit equipped with a hot platinum wire as a part of the flow sensor.

3. At the time of contact, the gas was ignited by the high temperature and catalyzing action of the platinum wire.

4. High temperature during the deflagration damaged the expiratory port valve made of incombustible ceramic. During the patient’s spontaneous breathing, a flame of burning ethanol ran backward to the endotracheal tube because the expiratory valve was not functioning.

5. Under high-flow gas, temperature decreased quickly, and the damage was limited near the part of ignition.

Although the aforementioned scenario is a reasonable sequence of events, there is some uncertainty. Could the two pumps of Xylocaine pump spray (approximately 0.1 ml × 2) supply enough fuel for the deflagration? How was the concentration of ethanol in the oxygen-rich expiration gas set between the explosion limits? It is plausible that a large volume of expiration gas should quickly dilute the inflammable ethanol to a very low concentration below the lower limit of explosion. However, we could not deny the possibility that a gas deposit containing ethanol (highly volatile and relatively heavy; vapor pressure at 20°C is 5.8 kPa, and relative density of air mixture is 1.03) within the explosive limits (3.5–15%) was composed accidentally in a part of respiratory circuit.

The anesthetic machine presented in this report does not meet the criteria of an APG machine, which can be used with inflammable gas, such as ether or cyclopropane. The User Instruction Manual clearly prohibited use with any inflammable gases. The Xylocaine pump spray, which was speculated as a source of fuel in this accident, contains ethanol at a high concentration. The label attached to the bottle clearly noted that the solution is inflammable and prohibited use under flammable conditions. The anesthetist working in this case knew of these warnings; however, he did not consider that Xylocaine pump spray solution sprayed into the endotracheal tube could flow into the machine with minimal dilution and make contact with an ignition source. Although ether or cyclopropane not commonly used in modern operation rooms, there are still several risks of fire relating to anesthesia practice. Recently, Barker and Polson reported a fire in the operating room, in which isopropyl alcohol used for surgical preparation was suspected as a fuel.

It is impossible to eliminate all sources of ignition and inflammable materials from anesthesia practice. Anesthesiists should be cautious of deflagration accidents even in sophisticated modern operating rooms. Although the patient in this case did not suffer an injury from the accident, fires around an anesthetic machine and the respiratory circuit tend to cause serious injury or have mortal consequences.

References


Transient Cross-Resistance to Neuromuscular Blocking Agents in a Patient with Tetanus

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RESISTANCE to nondepolarizing neuromuscular blocking agents (NMBAs) occurs in many clinical diseases and drug interactions. This phenomenon is attributed to changes in pharmacokinetic and pharmacodynamic characteristics. In this case report, we present a transient loss of response to three different NMBAs in a patient suffered from tetanus.

Case Report

A 49-yr-old woman (weight, 55 kg; height, 156 cm) was referred to our medical center in October 2000 because of trismus and nuchal rigidity. Tetanus toxoid had been given to her in a local clinic a week prior to this admission because of general malaise and masseter rigidity. When hospitalized, she presented with tachycardia, hypertension, tachypnea, profuse sweating, copious saliva, trismus, nuchal rigidity, and hyperreactivity to noise. Past history was unremarkable except...
chronic onychomycosis with paronychia over right thumb. She worked in rice fields and made a recent trip to southeast Asia 40 days prior to this episode. Physical examination revealed no obvious skin wound. Laboratory findings showed only leukocytosis (12,600/m\(^3\)). Cerebrospinal fluid examination was unremarkable. Due to intractable trismus, dribbling, and impending respiratory failure, she was scheduled to receive emergent tracheostomy under general anesthesia. Before induction of anesthesia, a train-of-four (TOF) electromyography was installed in order to monitor neuromuscular function during operation. Anesthesia was induced with glycopyrrolate 0.2 mg, propofol 200 mg, and fentanyl 50 \(\mu\)g. Anesthesia was maintained with isoflurane 1.5\% and oxygen. Short-acting neuromuscular blocking agent (NMBA), mivacurium (11 \(mg\)), was administered to facilitate tracheal intubation. Surprisingly, the full dose of mivacurium did not provide an adequate muscle relaxation measured by TOF and was accompanied by undesirable spontaneous movement (fig. 1, M). Additional doses of 4 mg mivacurium (fig. 1, M), 25 mg atracurium (fig. 1, A), and 5 mg vecuronium (fig. 1, V) still did not suppress the TOF value to zero. The patient was sent to intensive care unit after tracheostomy was completed.

In the quiet, isolated room of the intensive care unit, antibiotics with penicillin (3 million units every 6 h for 5 days) were prescribed and later was replaced by metronidazole (500 mg every 6 h for 15 days). Muscle spasm was controlled with atracurium (0.6–0.8 mg · kg\(^{-1}\) · h\(^{-1}\)) and propofol (0.02 to 0.03 mg · kg\(^{-1}\) · min\(^{-1}\) for 7 days). Propofol was later replaced by midazolam (0.3 mg · kg\(^{-1}\) · h\(^{-1}\) for 7 days). An electromyography and a nerve conduction study were performed 16 h after surgery at bedside. The nerve conduction study (NCS) revealed only mild suppression of amplitude of compound muscle action potentials (CMAP). Nerve conduction velocity and sensory nerve conduction study were within normal range. The needle electromyography studies revealed reflex spasms with persistent electromyographic activity in the masseter muscle. A follow-up of TOF revealed a normal twitch suppression following atracurium 40 h after surgery (fig. 2). The patient was weaned from the ventilator and artificial airway 21 days after initiation of artificial ventilation. No significant sequela was ever noted and the patient was discharged from our hospital uneventfully.

**Discussion**

Resistance to nondepolarizing NMBA has been noted in patients with burns,\(^1\) hepatic disease, sepsis, cerebral palsy,\(^2\) immobilization,\(^3\) and in patients taking anticonvulsants.\(^4\) The potential contributing factors to the resistance are altered pharmacokinetics,\(^5\) resulting from escape of drug \(t_{1/2}\) wounds, increased protein binding, altered volume of distribution, depressed plasma cholinesterase activity and enhanced hepatic or renal elimination. As a receptor-mediated potential for resistance, the nicotinic receptor (AChRs) characteristics can be altered at the level of number, functions and localization by thermal injury.\(^6,7\) However, the cellular mechanism responsible for, e.g., up-regulation of AChRs, remains unclear.

The diagnosis of tetanus in this patient was favored because of her typical symptoms and signs, and clinical progress under standard treatment against tetanus.\(^8,9\) Although no obvious deep penetrating wounds were identified, this occurred in 30% of patients with tetanus. The differential diagnosis of tetanus includes orofacial infection, drug-induced dystonic reactions and other neurologic diseases, which were all excluded in this patient. The characteristic electrophysiological findings of tetanus include a short or absent silent period, an exaggerated F-response, and persisted electromyography activity.\(^10\) The mild suppressed CMAP amplitude noted in this patient might be due to tetanus toxin itself or due to effect of atracurium when the patient had recovered from resistance.

Effects of clostridial neurotoxins on synaptic neurotransmission have been well documented.\(^11-13\) In contrast to botulism, Clostridium tetani binds to the presynaptic membrane of the neuromuscular junction (NMJ), is internalized and transported retrogradely to the spinal cord. The toxin-induced inhibition of neurotransmitter release from spinal inhibitory interneurons results in spastic paralysis.\(^14\) In various animal species (including human beings), direct blocking action of C. tetani at NMJ has been reported. The toxin lowers the presynaptic resting membrane potential, decreases both...
evoked and spontaneous transmitter release at NMJ. Whether the binding efficacy of nondepolarizing NMBAs onto postsynaptic nicotinic receptors is therefore indirectly changed by toxin remains unknown. It is worthy to note that the tolerance in this patient was crossing over 3 different competitive NMBAs, although the conventional doses we used were only approximately 2 to 3 times the ED$_{95}$ and so would not block all receptors at the NMJ. Interestingly, similar resistance to NMBAs has also been reported in the early phase of tetanus, while NMBAs have been widely used in patients with tetanus. Failure to detect any transient loss of response to NMBAs in early phase of tetanus might be caused either by a lack of opportunity of using TOF monitoring or being masked by heavy intravenous sedation without notice. The exact cellular mechanisms for the resistance to NMBAs and its recovery in tetanus still need further exploration.

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References


PERIPHERAL nerve block has emerged as an attractive anesthetic option when postoperative anticoagulation is planned and concern regarding spinal hematoma might preclude continuous epidural anesthesia. When the patient undergoes anticoagulation at the time of block placement, neuraxial block is contraindicated, and investigators have also recommended avoidance of deep blocks (such as lumbar plexus block) in anticoagulated patients out of concern for incompressible arterial bleeding. In our practice, we have routinely employed lumbar plexus blockade (LPB) instead of neuraxial blockade when patients with normal coagulation have postoperative anticoagulation planned. We now report two cases of major, delayed retroperitoneal hemorrhage following LPB in patients with normal coagulation at the time of needle placement, who received anticoagulants postoperatively for thromboprophylaxis.

Case Reports

Case 1

An active 85-yr-old woman (weight, 66 kg) presented for unicompartmental right knee arthroplasty. Her history included osteoarthritis, depression, and hypothyroidism, and her medications were mirtazapine, levothyroxine, omeprazole, zolpidem, and calcium. Laboratory data included hemoglobin level 14.4 g/dl (normal, 12-16), platelet count 225 × 10³ (normal, 160-360 × 10³), prothrombin time (PT) of 12 sec (normal, 10.8-13.9 sec), and activated partial thromboplastin time (aPTT) of 24.5 sec (normal, <31 sec).

Sciatic and continuous LPB via the posterior approach were performed with a peripheral nerve stimulator (PNS) in the preoperative...
holding area. A 90-mm, pencil-point, 21-gauge needle/catheter assembly (Polymedic®, Temena SARL, Bondy, France) was used for the LPB. After contact with the transverse process (presumed L4) at the level of the iliac crests on the first pass, the needle was redirected caudad and a quadriceps twitch was elicited at 0.4 mA (0.1 ms pulse width). After negative aspiration, 25 ml of 0.5% ropivacaine with 1/300,000 epinephrine and clonidine 50 μg was incrementally injected. The 18-gauge over-the-needle catheter was left in place, and a 20-gauge stimulating catheter threaded easily through it. A quadriceps twitch was again elicited at 2 mA and was maintained as the catheter was threaded 9–10 cm. A single-shot sciatic block was then performed via the Labat approach, and 25 ml of the same local anesthetic injected incrementally after eliciting a sciatic motor response. The lumbar plexus catheter was then fitted with a Tuohy-Borst adaptor, at which point blood could be steadily aspirated. The catheter was withdrawn 2–3 cm, flushed with saline, and after negative aspiration a test dose of 3 ml of 1% lidocaine with 1/200,000 epinephrine was negative. The patient was unable to lift her leg or feel pinprick on the thigh and calf after 45 min, but she still had sensation in the anteromedial leg and some dorsiflexion of her foot. A supplemental sciatic block at the midpoint of the line between ischial tuberosity and greater trochanter, and femoral block at the groin were performed with PNS and 15 ml and 7 ml, respectively of ropivacaine 0.5% with 1/300,000 epinephrine. The 1.5 h surgery then proceeded uneventfully with propofol 1%, ketamine 0.1% infusion for sedation. The hemoglobin level in the postanesthesia care unit (PACU) was 14.1. The lumbar plexus infusion was initiated in the PACU with 8 ml/h of 0.2% ropivacaine/0.0002% clonidine. The patient had excellent postoperative analgesia and easily participated in physical therapy.

The lumbar plexus infusion was stopped the evening of postoperative day (POD) 1 in anticipation of discharge on POD2. The next morning (POD 2), the hemoglobin level was 12.4, platelet count 157 × 10^9, and the patient was comfortable. She was given her first dose of enoxaparin 30 mg subcutaneously at 0900, and the lumbar plexus catheter was removed intact at 1040. Four hours later, physical therapy was prevented by new, significant back pain (9/10 on VAS scale). Morphine was given, and enoxaparin was continued at 30 mg subcutaneously every 12 h. On POD 3 she was again evaluated by the acute pain management service (APS) that noted stable vital signs and right paravertebral pain, no knee pain, and no neurologic deficit. The former catheter site was unremarkable and the hemoglobin level was 9.1. The APS attending was concerned with the possibility of paravertebral bleeding and recommended computerized tomography (CT) scan if her pain persisted. Ten hours later, her pain had decreased by 50%, vital signs were stable, and hemoglobin level was 9.4 with no neurologic deficit. The next day, her pain had diminished, she was walking without assistance, and discharge was considered until the hemoglobin level was measured at 7.1, (repeat was 6.5). Her PT, aPTT, platelet count, and fibrinogen were normal, and vital signs and physical exam were unchanged. The enoxaparin was stopped, she was transfused with two units of packed red blood cells (PRBCs), and a CT scan demonstrated an extensive retroperitoneal hematoma that extended from the retrohepatic space to the pelvis and displaced the kidney anteriorly (fig. 1). She later developed hypotension, oliguria and her hemoglobin level was 8 the following morning. Her vital signs normalized and her hemoglobin level increased to 8.9 with two more units of PRBCs.

Her postoperative course was protracted with transient elevation of creatinine to 3.3, ileus requiring NG drainage, pulmonary edema, and atrial fibrillation for 24 h. She had no laboratory evidence for myocardial infarction. She never developed a neurologic deficit and was able to ambulate and participate in physical therapy, but complained of continued pain in the flank and hip and eventually developed extensive ecchymosis by POD 5 (fig. 2). She was discharged on POD 20.

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**Fig. 1.** Right retroperitoneal hematoma displacing the kidney anteriorly.

**Case 2**

A 65-yr-old man (weight, 82 kg) presented for arthroscopy of the left knee because of chronic pain from a meniscal tear and presumed anterior cruciate ligament injury. His medical history included a coronary artery bypass graft with mechanical aortic valve replacement 5 yr prior to admission (PTA) requiring chronic anticoagulation, angioplasty of two coronary grafts 1 yr PTA, and a negative dobutamine stress echocardiographic study 4 months PTA. His history also included a gunshot wound to the thoracic spine 30 yr prior with Brown-Sequard lesion: left leg numbness and right leg weakness. He had a cerebrovacular accident 15 yr PTA without residual deficit, and an innominate artery aneurysm. Medications included coumadin 5 mg/day, aspirin 81 mg twice a day, metoprolol, furosemide, ranitidine, and amitriptyline. The physical exam was notable for a systolic click/murmur, and right leg weakness. Admission laboratory data revealed PT 29.1 sec (INR 5.19), aPTT 37.5 sec, hemoglobin level of 12.8 g/dl, platelet count 204 × 10^9.

The cardiologist admitted the patient, coumadin was stopped, and heparin started in preparation for surgery. When his INR was measured at 9.27 twelve hours later, he was given 1 unit of FFP and 10 mg Vitamin K. One day before surgery his PT had corrected to 12.9 (INR

**Fig. 2.** Extensive ecchymosis evident on postoperative day 5.
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Fig. 3. Left retroperitoneal hematoma extending into pelvis.

...and the morning of surgery the PT was 11.9 sec (INR 0.92). His heparin was discontinued at 0100 on the day of surgery, and the aPTT was 23.9 sec at 0700. We felt that peripheral nerve block would provide prolonged postoperative analgesia with minimal residual sedation in a patient at risk for stroke. Single-injection LPB (posterior approach) and sciatic blocks were performed in the preoperative holding area with a PNS and a 21 g, 90-mm insulated needle (Polymedic®, Temena SARL, Bondy, France). A quadriceps twitch was readily elicited at 0.4 mA, and no blood or paresthesia was noted. Incremental injection of 25 ml of 0.3% ropivacaine/0.8% mepivacaine with 1:300,000 epinephrine was used for the LPB, and 25 ml for the sciatic block after stimulation at 0.35 mA. The patient received an additional 1 mg midazolam, 50 mcg fentanyl, and propofol at 30 mcg/kg/min for sedation during the 45 min surgery.

His immediate postoperative course was complicated and bizarre. In the PACU, he complained of long-term memory loss and chest pain radiating to his left arm. He was evaluated by the cardiologist and had emergency echocardiography that demonstrated no new wall-motion abnormalities. Because reperfusion was planned and he exhibited mental status changes, he had an emergent CT scan that showed no intracranial bleeding. He was admitted to the ICU for observation and myocardial enzymes were normal. His PACU hemoglobin level was 13.7.

His heparin infusion was reinitiated at 1200 U/h 8 h after the LPB; his aPTT on POD 1 was 77.7 and hemoglobin level was 13.4. Coumadin was restarted the evening of POD 1. Consultants from Internal Medicine and Neurology continued to assess the patient for his long-term amnesia (short-term memory was preserved), headache, chest, and arm pain, and left leg pain and numbness. His only new objective finding was left arm weakness; results from the carotid doppler and repeat finding head CT were negative. Psychiatric evaluation suggested his symptoms were consistent with a conversion reaction.

On POD 3 the hemoglobin level was 12.6, aPTT > 100, and INR 1.4. For the first time, he complained of back pain at the site of the LPB. The heparin infusion was adjusted, the hemoglobin level was 10.5 the following morning (POD 4), and the aPTT was 60.2 sec. His vital signs remained stable. Because of the continued flank pain and the decrease in hemoglobin level, an abdominal CT was performed which showed a “moderate-sized retroperitoneal hematoma that appears to originate in the left psoas muscle” (fig. 3). The hemoglobin level decreased further to 8.8 on POD 5, all anticoagulation was discontinued, and the patient received vitamin K 1 mg subcutaneously, and 2 units of PRBCs. The patient continued to complain of chest and arm pain daily without evidence of ischemia, but his other pain complaints resolved. He was discharged on POD 10 with a plan to restart anticoagulation 2 weeks after discharge. Because of the bleeding complication, the cardiologist felt a delay in restarting anticoagulation was necessary in spite of the embolic risk.

Discussion

Major bleeding complications reported following regional anesthesia and anticoagulation have almost exclusively focused on spinal and epidural anesthesia, since even modest bleeding in the noncompliant spinal canal may cause neurologic compromise. This is particularly apparent following the 1993 U.S. Food and Drug Administration approval of enoxaparin, which has been associated with 80 cases of epidural hematoma reported to the FDA. Because of the association of bleeding and neurologic complications with neuraxial anesthesia and enoxaparin, peripheral nerve blocks such as LPB have emerged as alternatives to central blocks for procedures, such as knee replacement which require intensive analgesia as well as perioperative anticoagulation. The American Society of Regional Anesthesia has published Consensus Statements with respect to neuraxial anesthesia and anticoagulation, but no such guidelines exist for peripheral nerve or plexus catheters and perioperative anticoagulation. The paucity of data in this area makes it difficult to develop recommendations. In addition, since peripheral nerve blocks are not typically performed in noncompliant tissue spaces, substantial bleeding may occur with less dramatic or no neurologic symptoms compared to epidural bleeding.

A single case report of retroperitoneal hematoma following attempted LPB was published in 1997. Unlike our cases, this patient was on enoxaparin at the time of needle placement, and the lumbar plexus could not be located “despite several attempts,” suggesting more needle passes than in our two cases. This previously reported patient developed unilateral leg paralysis, which led to a CT scan and the diagnosis. Significant retroperitoneal hematoma complicating lumbar sympathetic block was recently reported in two patients. Again in contrast to our cases, these patients were taking irreversible platelet inhibitors with residual effect at the time of needle placement, and both developed numbness in the thigh as a symptom of the bleeding.

In case 1 of our report, vascular trauma was evident from the initial blood aspiration through the lumbar plexus catheter, but it was felt the catheter had been successfully withdrawn from the vessel. Subsequent plexus stimulation and successful analgesia via the catheter indicated proper location of the catheter adjacent to the plexus. The patient was on no antiplatelet agents, and the enoxaparin was not given until 40 h after the block, but the timing of catheter removal occurred near the probable peak of anticoagulant activity of her first dose of enoxaparin. Although she had some decrease in hemoglobin level before catheter removal, the larger
hemoglobin level decrease and her back pain suggest the major bleeding occurred after removal. In an earlier review of cases of epidural hematoma following neuraxial anesthesia,7 approximately half of the cases were diagnosed after epidural catheter removal, indicating the possibility of vascular trauma with removal as well as placement of epidural catheters. In truth, it is difficult to time the onset of bleeding with continuous techniques; it is possible that slow, continued bleeding occurred after initial placement of the lumbar plexus catheter, and was only diagnosed after catheter removal. In spite of substantial retroperitoneal bleeding, this patient showed no apparent neurologic deficit.

In case 2 of our study, coagulation was normal at the time of block and there was no apparent vascular trauma. Full anticoagulation was initiated soon after the block, but the hemoglobin level remained relatively stable until POD 4. Given the precise localization of the bleeding on CT scan to the site of the LPB and the time course of pain complaints and the drop in hemoglobin level, it seems most likely that unrecognized vascular trauma occurred from successful needle placement, but that bleeding was exacerbated by excessive anticoagulation on the POD 3. The patient’s numerous somatic complaints and preop neurologic abnormalities may have obscured a new deficit from detection, but the neurology consultants diagnosed no new lower extremity deficits. Some consider neurologic disease a relative contraindication to regional anesthesia since postop deficits may be attributed to the anesthetic.8 In addition, a block may obscure or delay the diagnosis of a complication identified by neurologic symptoms.9 In this case as in our first case, however, it was back pain and anemia rather than a neurologic complaint that led to the CT scan and diagnosis.

Spontaneous retroperitoneal hematoma is a known, serious complication in patients on anticoagulants, and the risk increases with increasing intensity of anticoagulation, age greater than 70, and associated antiplatelet therapy.10 The first spontaneous retroperitoneal hematoma with therapeutic (1 mg/kg every 12 h) enoxaparin therapy for deep vein thrombosis was reported in 1999 and was fatal.11 The patient presented with hypotension and anemia.

Retroperitoneal hematoma is also a well known, potentially fatal complication following femoral arterial cannulation for angiography with a reported incidence of 0.12%.12 In a 13-month study of patients undergoing cardiac catheterization, 11 patients developed retroperitoneal hematoma requiring surgical intervention. The most common signs were falling hematocrit and hypotension, and 2 patients died. Femoral nerve palsy was evident in 6 patients. The authors recommended cessation or minimization of anticoagulation, serial CT scanning, and surgical exploration for continued bleeding or significant nerve dysfunction.13 The thromboembolic risk of discontinuing anticoagulation in a patient such as our case 2 is unknown. However, one series of 28 patients with prosthetic heart valves on coumadin who required reversal of anticoagulation when major hemorrhage occurred has been described. Anticoagulation was withheld for a mean of 15 ± 4 days, and no thromboembolic complication occurred.14

Although isolated complications such as total spinal anesthesia15 and systemic toxicity16 have been reported, LPB has been shown to provide safe and effective surgical anesthesia and analgesia for knee arthroplasty.17 Continuous femoral sheath block is an alternative to posterior LPB but is less successful in achieving surgical anesthesia of the obturator and lateral femoral cutaneous nerve unless the catheter can be advanced to the sacroiliac level.18

These two cases demonstrate the risk of significant, concealed bleeding from needle placement in an area that cannot be observed when anticoagulation is initiated after nerve block. In addition, the signs of substantial, occult bleeding from LPB in these cases were anemia and back pain without apparent new neurologic deficit. Both patients required blood transfusion and prolonged hospitalization. Since the occurrence of these two cases at our institution, we have changed our practice. We now manage patients having LPB in much the same way as we manage those having neuraxial block when thromboprophylaxis is ordered. If a patient is on prophylactic enoxaparin, we avoid LPB unless the last dose was given at least 12 h before. We do not place lumbar plexus catheters in patients who will be anticoagulated unless the catheter is removed before initiating anticoagulation, and we do not start anticoagulation until 2 h after catheter removal. We also follow patients with heightened vigilance for signs of bleeding if they have deep blocks and are anticoagulated postoperatively.

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