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Coma After Droperidol Administration: A Case Report

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In Switzerland, approximately 32,000 patients are hospitalized annually due to adverse drug reactions (ADRs), representing 2.3% of all hospitalizations. During the perioperative period, the administration of a variety of drugs from different classes over a relatively short period of time increases the risk of ADR. Here, we describe the case of a 32-year-old woman who was administered droperidol to treat nausea in the recovery room after a myomectomy and who subsequently became comatose. Correctable metabolic, respiratory, and cerebrovascular disorders were ruled out. Six hours after the event, she was extubated without residual effects. We discuss potential ADR for droperidol. (A&A Practice. 2024;18:e01831.)

Multiple drugs are typically coadministered to induce and maintain anesthesia during a surgical procedure. Drug-drug interactions can occur when 2 or more drugs are administered and affect each other. While these interactions can alter the effectiveness of a drug, cause unwanted side effects, or affect patient safety, the pharmacodynamic and pharmacokinetic influences of each individual drug as well as their synergistic, additive, or antagonistic interactions are often not taken into account. Adverse drug reactions (ADRs) are often minor or can be treated with supportive therapy, but in extremely rare cases, further diagnostic steps or intensive care treatment are necessary.

Our patient provided written informed consent for publication, and this article adheres to the applicable Enhancing the QUAlity and Transparency Of Health Research (EQUATOR) guidelines.

CASE DESCRIPTION

The case involved a 32-year-old female patient (65 kg, 160 cm, body mass index 25.4 kg/m^2) who was not taking any outpatient medication and was in good health. The patient's medical history was unremarkable, with regard to the intake of medication for psychiatric or neurological disorders, acute or chronic kidney dysfunction (creatinine clearance >90 ml/min), or liver disease. The preoperative electrocardiogram showed no arrhythmia or prolongation of the frequency-corrected QT interval (QTc, Figure).

The patient underwent a hysteroscopic myomectomy under total intravenous anesthesia using a supraglottic airway. Intraoperatively, she received fentanyl 150 µg as a bolus, with cumulative doses of propofol 701 mg and remifentanil 223 µg, in addition to prophylactic antiemetic doses of dexamethasone 8 mg and ondansetron 4 mg. Finally, the patient was administered metamizole 1 g and hydromorphone 0.4 mg for analgesia. After an uneventful emergence, she was transferred to the recovery room in an awake, alert, and oriented state.

During her stay in the recovery room, the patient complained of nausea, and droperidol 0.5 mg was administered once as a bolus. However, 2 minutes after the administration of droperidol the patient developed bradycardia (lowest heart rate: 43 beats/min) and hypotension (lowest blood pressure: 54/40 mm Hg), necessitating the administration of atropine 1 mg and a Ringer's lactate bolus of 500 ml over 5 minutes. These measures led to normotensive values. Over the following 5 minutes, the patient's Glasgow Coma Scale (GCS) score decreased from 15 (eye: 4, verbal: 5, motor: 6) to 3 (eye: 1, verbal: 1, motor: 1). As the GCS score decreased, hypopnea progressed to apnea over the course of 2 minutes, and bag-mask ventilation was provided. Because the intravenous administration of nalbuphine 10 mg and naloxone 200 µg produced no improvement in the patient's condition, intubated the patient 5 minutes later. To clarify the situation and establish a diagnosis, the patient was sedated with a continuous infusion of propofol at a rate of 200 to 400 mg/h (total: 633 mg over ≈ 2 hours), and fentanyl 100 µg was administered.

During the perioperative care, the patient's cardiac rhythm did not exhibit arrhythmias or signs of QT_c prolongation. A venous blood gas analysis, which was performed to rule out reversible causes such as electrolyte imbalances, revealed moderate hypercapnia, normoglycemia, and normal electrolyte concentrations. The tympanic temperature was 37.0 °C. Throughout the recovery period, no muscle rigidity or extrapyramidal signs were observed. Cranial computed tomography and magnetic resonance imaging were used to rule out cerebrovascular events and they revealed no structural pathologies. In this situation, we assumed an ADR for the patient's comatose state. Since no specific antidote exists, supportive therapy was continued. Subsequently, the patient was transferred to the intensive care unit. She was extubated without residual effects 6 hours after the administration of droperidol.

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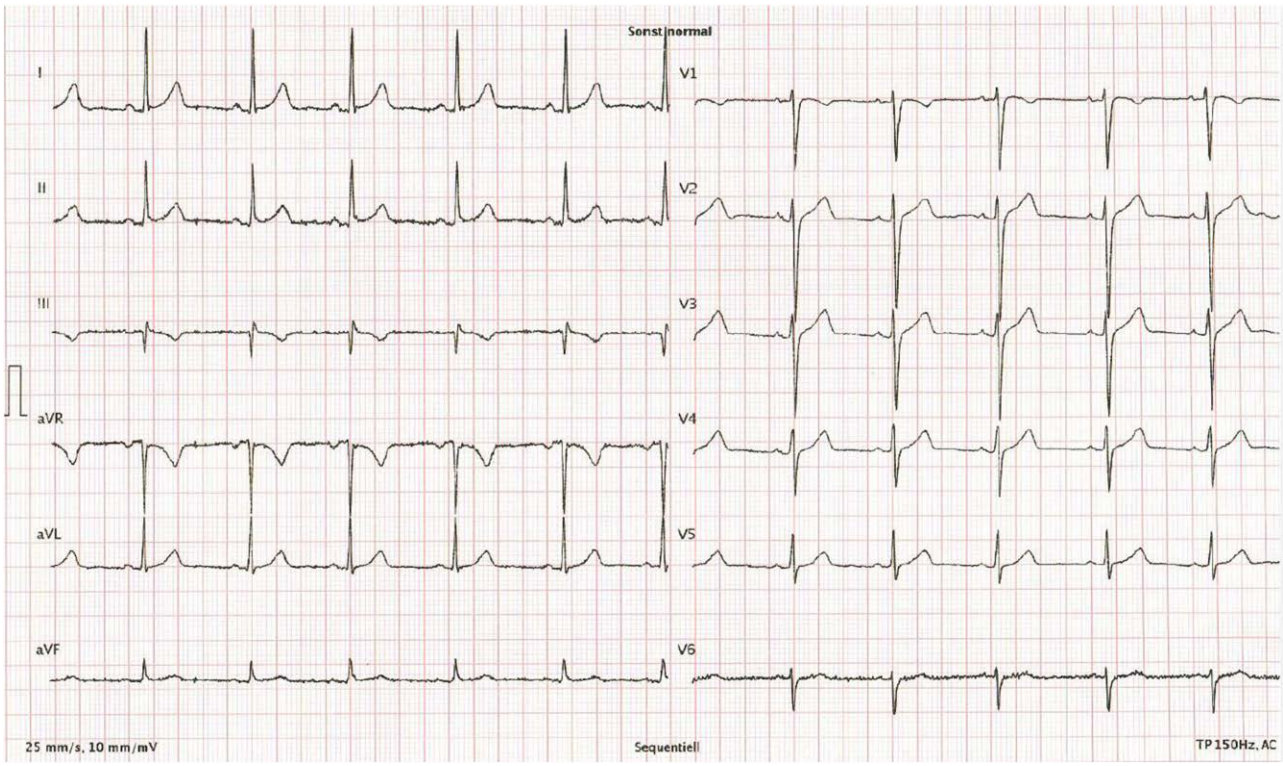

Figure. Patient's preoperative electrocoardiogram.

DISCUSSION

Anesthesia involves the administration of a variety of drugs from different classes over a relatively short period of time, which significantly increases the risk of ADR.[1] Interactions among various medications, including analgesics, antiepileptics, antifungals, antiretroviral therapy, and grapefruit juice, are possible and can affect the pharmacokinetics or potentiate the effects of opioids.[2] In Switzerland, approximately 32,000 patients are hospitalized each year for ADR, representing 2.3% of all hospitalizations, although significant underreporting exists. The in-hospital mortality rate for ADR is 2.2%.[3] In 2022, more than 14,000 ADR cases were reported to SWISSMEDIC, the Swiss national authority responsible for the authorization and supervision of for drugs and medical products, the Swiss national authority responsible for the authorization and supervision of therapeutic products, but none of these were related to droperidol.

Postoperative nausea and vomiting prophylaxis is currently a standard treatment during anesthesia. Dexamethasone, 5-hydroxytryptamine receptor (5-HT_3 receptor) inhibitors, and dopamine D_2-receptor (D_2-receptor) antagonists, such as droperidol, are the cornerstones of this treatment.[4] Droperidol is further indicated for use as a sedative in agitated patients and as a premedication.[5,6]

Droperidol, a butyrophenone derivative, exhibits a high affinity for D_2 receptors and a slightly lower affinity for α_{1A}-adrenergic receptors. In adults, the half-life of droperidol is 134 ± 13 minutes, although it may be longer in geriatric patients. After intravenous administration, the plasma concentration rapidly decreases within the first 15 minutes. Its plasma protein-binding capacity is 85% to 90%.[7] In volunteers, metabolites of droperidol are observed 8 to 12 hours after drug administration.[7,8] Droperidol is rapidly metabolized in the liver and undergoes oxidation, dealkylation, demethylation, and hydroxylation by cytochrome P (CYP) isozymes 1A2 and 3A4 and, to a lesser extent, by 2C19.

After metabolization, approximately 75% of droperidol is excreted as metabolites in urine. Less than 1% is excreted unchanged in the urine, while 22% is excreted unchanged via the feces. Enzyme inhibitors (eg, phenobarbitone, carbamazepine, phenytoin) or metabolic polymorphisms, such as the CYP 3A subfamily, can delay or intensify the breakdown of the drug, thus prolonging its pharmacological action.[7,9] Furthermore, renal or hepatic impairment can increase the plasma drug concentration of droperidol.[7]

In 2022, the Department of Anesthesiology and Pain Medicine, Inselspital Bern, provided anesthesia to 32,670 patients. Of these, 862 (2.6%) received droperidol as a treatment for nausea and vomiting, usually in the recovery room. To date, no serious incidents have been reported. In the literature, only a single case report from 1986 describes coma after intravenous droperidol administration for agitation after electroconvulsive therapy.[10]

The side effects of droperidol include hypotension and cardiac rhythm disturbances, with a reported dose-dependent prolongation of the QT_c.[7] However, a single-blind study by Charbit et al[11] evaluated the dosage of 0.1 mg/kg droperidol and found that the mean maximal QT_c interval prolongation measurements were 17 ± 9 ms compared with predrug QT_c measurements. No cases of torsades de pointes were reported with dosages <10 mg.[12,13] Low-dose droperidol (≤1.25 mg) has been considered safe and produces comparable results to the 5-HT_3 receptor antagonist ondansetron.[12] In 2001, a black box warning about cardiovascular events related to droperidol

was published in the United States, specifically the risk that QT_c prolongation can induce torsades de pointes.[14]

Several factors may lead to a coma after droperidol administration, including higher than recommended dosage (>2.5 mg droperidol intravenous or intramuscular), rapid administration, and long-term treatment.[7,11,12] However, a meta-analysis from 76 placebo-controlled trials found that there was no difference in the level of sedation with doses of 0.25 to 0.625 mg, as compared to placebo.[15]

This specific case involved a one-time administration. The use of a higher dosage or a drug administration error can be ruled out for several reasons: Only droperidol with a concentration of 0.5 mg/mL per vial is available in our hospital. No other medications were being prepared or administered in the recovery room at the same time. A single vial of droperidol was used, and half of the drug remained in the syringe. We double-check every drug administered and ensure that the medical staff is familiar with the administration of droperidol in the recovery room.

ADR, drug-drug interactions, and individual metabolism play an important role in determining the duration of therapeutic action(s) of each administered drug.[2] In this case report, we assume a rare ADR occurred, due to the temporal proximity of the effect to the administration of droperidol. The duration of action of droperidol seemed to be extended by several hours and we did not exclude a receptor polymorphism. However, a possible explanation for this is the additional prolonged therapeutic effect of the active drug metabolites, as described by Cressmann et al.[8] Their observed rapid onset at 3 to 10 minutes after intravenous or intramuscular administration, with a peak response at approximately 30 minutes, corresponds to our observations in this case.[8] Since no specific antidote exists, the only treatment option is clinical monitoring with supportive therapy. Other pathologies were ruled out through further investigation.

CONCLUSION

We reported a rare but severe drug side effect in a 32-year-old female patient who received a single bolus of droperidol for treatment of nausea in the recovery room. Although we were unable to determine the exact cause of the coma that occurred after droperidol administration, we strongly suspect an ADR, potentially triggered by droperidol or its active metabolites, having ruled out correctable disorders or pathologies, and supportive therapy was initiated. The case underlines that even rare ADR should be considered and anticipated whenever a medication is administered.

DISCLOSURES

Name: Christian Vetter, MD.
Contribution: This author helped to prepare the article, critically revised the article, and approved the final version of the article.
Name: Carlos Biedermann, MS.
Contribution: This author helped to collect the data, draft the article preparation, and approved the final version of the article.
Name: Joana Berger-Estilita, MD, PhD.
Contribution: This author helped to critically revise the article and approved the final version of the article.
Name: Anne Bütikofer, MD.
Contribution: This author helped in the analysis and interpretation of the results, critically revised the article, and approved the final version.
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