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Case Report

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Remimazolam as the Primary Agent for Sedation During Cardiac Catheterization in Three Patients With Comorbid Cardiac Conduction Abnormalities

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Abstract

General anesthesia or procedural sedation may be required to ensure immobility, facilitate completion of the procedure, and ensure patient comfort during diagnostic or therapeutic procedures in the cardiac catheterization suite. Although propofol and dexmedetomidine are two of the more commonly chosen agents, concerns regarding their impact on inotropic, chronotropic or dromotropic function may limit their applicability based on underlying patient comorbid conditions. We present three patients with comorbid conditions involving pacemaker (natural or implanted) function or cardiac conduction which impacted the choice of agent for procedural sedation during procedures in the cardiac catheterization suite. Remimazolam, a novel ester-metabolized benzodiazepine, was used as the primary agent for sedation in an effort to limit detrimental effects on chronotropic and dromotropic function which may be seen with propofol or dexmedetomidine. Remimazolam's potential utility in procedural sedation is discussed, previous reports of its use are reviewed, and dosing algorithms are presented.

Keywords: Remimazolam; Cardiac catheterization; Heart block; Procedural sedation

Introduction

General anesthesia or procedural sedation may be required to ensure immobility, facilitate completion of the procedure, and ensure patient comfort during diagnostic or therapeutic procedures in the cardiac catheterization suite [1-3]. Commonly used agents include propofol, dexmedetomidine, ketamine, opioids, and benzodiazepines either alone or in combination. In addition to providing effective sedation, the ideal agent should be devoid of significant deleterious effects on hemodynamic and electrophysiologic function. In many cases, the impact of sedative agents on end-organ function is not only dose-dependent, but also related to the presence of comorbid conditions [4, 5]. Commonly used agents, such as propofol and dexmedetomidine, may be associated with negative chronotropic or dromotropic effects making them relatively contraindicated in patients with conduction defects. We present clinical experience in three patients with comorbid conditions impacting pacemaker or dromotropic function with theoretical contraindications to the use of propofol or dexmedetomidine for sedation. Remimazolam, a novel ester-metabolized benzodiazepine that received initial approval by the FDA in July 2020 for sedation of adult patients during invasive medical procedures, was used as the primary agent for sedation in an effort to avoid detrimental effects on inotropic, chronotropic, and dromotropic function. Remimazolam's potential utility in procedural sedation is discussed, previous reports of its use are reviewed, and dosing algorithms are presented.

Case Reports

This retrospective review was approved by the Institutional Review Board of Nationwide Children's Hospital (Columbus, Ohio). This study was conducted in compliance with the ethical standards of Nationwide Children's Hospital for research involving human subjects as well as with the Helsinki Declaration. As a retrospective study, the need for individual written informed consent was waived. From a larger database of patients receiving remimazolam for sedation in the cardiac catheterization suite, three patients were identified with underlying conduction delays or mechanical pacemaker dysfunction who required anesthetic care or procedural sedation. Demographic data obtained included age, weight, comorbid conditions, and gender. Information regarding the sedation regimen included the agents and doses used. Remimazolam dosing information included the dose, dosing changes during the procedure, mode of administration (bolus or continuous infusion), and duration of infusion. Intraoperative and postoperative adverse effects including hypotension, bradycardia, respiratory arrest, apnea, or hypoventilation were identified. Additionally, the use of rescue

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Table 1. Clinical Patient Data and Remimazolam Dosing

Concurrent medications and doses	Procedure and diagnosis	Treatment	Outcomes and follow-up
Furosemide 20 mg q. AM. Mycophenolate 720 mg BID. Omeprazole 20 mg q. day. Trimethorpirim-sulfamethoxazole 160 mg q. MWF. Tacrolimus 3.5 mg BID. Tadalafil 20 mg q. day. Drosprenone 4 mg q. day. Valganciclovir 400 mg q. day. Insulin pump - regular insulin.	Cardiac catheterization and myocardial biopsy. ECG with new onset second degree (Mobitz type I) heart block. Echocardiogram with depressed myocardial function and moderate size pericardial effusion with no tamponade. Mostly posterior and around the right atrium. History of cardiomyopathy, status post heart transplantation and AICD placement.	Sedation initiated with remimazolam bolus (4 mg) followed by a remimazolam infusion at 20 µg/kg/min. The infusion was supplemented by four bolus doses of ketamine (10 mg each). After 45 min, the infusion was decreased to 15 µg/kg/min for 30 min, then to 10 µg/kg/min for 15 min followed by 5 µg/kg/min for 15 min. There were no adverse intraoperative events during the 120-min procedure.	PACU recovery for 58 min. Uncomplicated postoperative course. Postoperative echocardiogram showed resolution of diastolic dysfunction and decreased ventricular filling pressures. Repeat endomyocardial biopsy performed one month later with similar sedation regimen.
Metoprolol 25 mg q. day. Lisinopril 5 mg day. Furosemide 20 mg q. day. Ferrous sulfate 325 mg q. day. Aspirin 81 mg q. day. Nicotine transdermal patch.	AICD battery change. Complete heart block with no ventricular escape rhythm, status post placement of epicardial dual chamber pacemaker and AICD. Rhythm was sinus with ventricular pacing with RBBB. History of Ebstein's anomaly status post tricuspid valve replacement.	Premedication with midazolam (2 mg). Sedation initiated with a remimazolam bolus (2.5 mg) followed by a remimazolam infusion at 10 µg/kg/min for 15 min. The remimazolam infusion was increased to 15 µg/kg/min for 15 min and then decreased to 10 µg/kg/min for the remainder of the procedure (45 min). Supplemental sedation included four bolus doses of fentanyl (25 µg each) and one bolus dose of propofol (10 mg) prior to infiltration of the surgical site with local anesthetic by the cardiologist. There were no adverse intraoperative events during the 72-min procedure.	Uncomplicated postoperative course with discharge from PACU in 25 min. Successful replacement of a dual-chamber cardioverter defibrillator. The pacing and sensing threshold were satisfactory.
Buprenorphine 8 mg BID. Omeprazole 40 mg q. day. Metoprolol 25 mg BID. Aspirin 81 mg q. day. Cariprazine 0.2 mg q. day. Gabapentin 600 mg TID. Venlafaxine 75 mg BID.	AICD battery change. History of sick sinus syndrome, RBBB, tetralogy of Fallot status post repair.	Sedation initiated with a remimazolam bolus (2.5 mg) followed by a remimazolam infusion at 10 µg/kg/min. After 15 min, the infusion was increased to 15 µg/kg/min for 30 min and then decreased to 10 µg/kg/min for the remainder of the case. Supplemental sedation included three bolus doses of fentanyl (25 µg) and one bolus dose of propofol (10 mg).	PACU recovery for 36 min. Uncomplicated postoperative course with discharge from PACU in 36 min.

ECG: electrocardiogram; AICD: automatic implantable cardiac defibrillator; PACU: post-anesthesia care unit; RBBB: right bundle branch block.

medications including anticholinergic or vasoactive agents (epinephrine, phenylephrine, vasopressin, or ephedrine) was noted.

Investigations and diagnosis

There were three patients (one adolescent female and two adult females) weighing, 57.2, 63.8, and 73.4 kg, respectively. Additional patient and procedure information including medications, remimazolam dosing, and use of supplemental analgesic and sedative agents are outlined in Table 1. All three patients had cardiac conduction concerns including first degree heart block in one and pacemaker dependency with right bundle branch block in the other two.

Treatment

Successful sedation was achieved in all three patients using a remimazolam-based sedation regimen without impact on hemodynamic or conduction function. Two of the three patients received premedication with midazolam (2 mg) intravenously prior to the initiation of the procedural sedation. This was followed by a remimazolam bolus dose (2.5 mg in two patients and 4 mg in one patient) and an infusion at 10 to 15 µg/kg/min. Supplemental sedation included small bolus doses of ketamine in one patient and fentanyl (50 - 100 µg) plus a single bolus of propofol (10 mg) in the other two patients. The propofol bolus doses of 10 mg were administered in patients 2 and 3 prior to the subcutaneous infiltration with a local anesthetic agent at the surgical incision site.

Follow-up and outcomes

No intraoperative impact on hemodynamic or conduction function was noted. In all cases, recovery was rapid with discharge from the post-anesthesia care unit (PACU) in less than 60 min.

Discussion

In both adults and pediatric-aged patients, propofol and dexmedetomidine are frequently chosen to provide sedation in various clinical scenarios including the ICU setting during mechanical ventilation as well as anxiolysis and sedation for invasive and non-invasive procedures [6, 7]. However, associated patient comorbid conditions may limit the choice of agent. As both propofol and dexmedetomidine may impact chronotropic and dromotropic function, they may be relatively contraindicated in patients with underlying conduction or pacemaker dysfunction.

Propofol has been linked to a number of adverse effects on cardiac conduction and pacemaker function [8-10]. It can affect atrioventricular (AV) node conduction by reducing sympathetic outflow, increasing vagal tone, and altering baroreceptor sensitivity. It may lengthen Wenckebach cycle length and AV conduction (or stimulus-to-His bundle interval) in a concentration-dependent manner. Instead of depressing baroreceptor function, propofol can potentially lower heart rate via central sympatholytic or vagotonic processes. Clinical sequelae have been noted and postulated to be the result of the electrophysiologic effects of propofol. Anecdotal reports in both adults and children have noted the occurrence of bradycardia, asystole, and all degrees of heart block including complete heart block (AV dissociation) following the administration of propofol [11-15]. These have been noted in patients with and without pre-existing conduction defects. Further information into the specific effects of propofol on cardiac electrophysiologic function have been provided by Matsushima et al in their prospective study of 23 pediatric patients undergoing radiofrequency catheter ablation during general anesthesia with propofol [16]. The sinus node recovery time (SNRT), sinoatrial conduction time (SACT), atrial-His (AH) interval, and the His-ventricular (HV) interval were measured. Cardiac autonomic regulation was simultaneously assessed based on heart rate variability. Propofol significantly suppressed intrinsic cardiac HV conduction, but did not affect the SNRT, SACT or the AH interval. The authors noted that HV blocks, which occur below the His bundle, are often life-threatening. HV conduction delay may be the cause of severe AV blocks induced by propofol.

Dexmedetomidine has raised similar concerns, including effects on pacemaker function (natural and implanted) [17-23]. As with propofol, these effects may be dose-related, with bolus dose administration being the most common. Although the primary mechanism has not been fully defined, the primary electrophysiologic effects are thought to be mediated by decreased central sympathetic output and increased parasympathetic tone [24]. The primary electrophysiological effects of dexmedetomidine include sinus and AV node depression, including prolongation of sinus node recovery time and cycle length, as well as increased AV nodal refractory period and Wenckebach cycle length [24, 25].

In both adult and pediatric patients with comorbid cardiac disease, these effects have anecdotally been associated with clinically significant bradycardia, cardiac arrest, and progressive pacemaker dysfunction [17-23].

Remimazolam is an ester-metabolized benzodiazepine that received approval by the United States Food & Drug Administration in July 2020 for sedation of adult patients during invasive medical procedures lasting ≤ 30 min, such as colonoscopy or bronchoscopy. Initial clinical trials have demonstrated its efficacy for sedation of adults during invasive procedures including gastrointestinal endoscopy and bronchoscopy [26-28]. Similar to other benzodiazepines, remimazolam provides sedation, amnesia, and anxiolysis through the gamma-aminobutyric acid (GABA) system. These trials have demonstrated an efficacy that parallels that of propofol for procedural sedation as well as an acceptable safety profile with fewer effects on hemodynamic function, a lack of pain with intravenous administration, reduction of post-procedure nausea and vomiting, and a rapid return to baseline neurologic function. As an ester-based medication, it is hydrolyzed quickly with a more rapid offset than midazolam and a limited context-sensitive half-life. To date, there are limited data regarding its impact on electrophysiologic function; however, when compared to propofol in a prospective trial of 67 adult, ASA physical status III surgical patients undergoing general anesthesia, there was less hypotension with remimazolam compared to propofol when used as part of the regimen for general anesthesia [29]. Similar hemodynamic stability and safety with remimazolam has been noted during anesthetic induction in an open label trial in a cohort of 20 adult patients (ASA physical classification IV) with aortic stenosis [30]. However, as noted in our patients, supplemental analgesic and sedative agents (propofol, fentanyl, and ketamine) may be added to the primary regimen using remimazolam. In such cases, the hemodynamic and electrophysiologic effects may be impacted by the supplemental agents. In particular, ketamine has been shown to augment endogenous catecholamine release which may counteract the negative cardiovascular effects of other agents.

In adults, both intermittent bolus doses and continuous infusions have been used as the sole agent during procedural sedation and as a supplement to volatile anesthetic agents during general anesthesia [26-28, 31-35]. Bolus dosing in adults has generally included 2.5 - 5 mg doses (repeated as needed) for procedural sedation while maintaining spontaneous ventilation up to 0.2 mg/kg for the induction of general anesthesia. Infusions, titrated to effect, have varied from 1 - 2 mg/kg/h, which is similar to our dosing same range of 10 - 20 µg/kg/min. As remimazolam is a sedative hypnotic, additional agents may be needed to supplement analgesia for painful procedures.

Prior to the addition of this novel agent to our operating room formulary, departmental education was completed including discussions of the medication at a faculty and staff meeting, the dissemination of published reports regarding its clinical use, and the development of departmental guidelines for preparation by pharmacy and intraoperative anesthesia and procedural sedation dosing guidelines. Given that it is not FDA-approved for use in pediatric patients, the initial recommendations were to limit its use to patients more than 12 years of age, weighing more than 40 kg. For our cases, remimazolam was reconstituted using normal saline from a lyophilized powder to a final concentration of 20 mg/8 mL (2.5 mg/mL) according to the manufacturer's recommendations. The medication was delivered in a syringe and administered by an infusion pump during intraoperative care. Based on our usual clinical practice, dosing used µg/kg/min and not mg/kg/h.

In summary, remimazolam is an ultra-short-acting benzodiazepine that was approved by the FDA in 2020 for proce-

dural sedation in adults. Clinical trials have demonstrated a rapid onset with limited impact on hemodynamic and respiratory function, a predictable half-life with a short offset, and minimal pain on injection. It can be titrated to effect by intermittent bolus dosing or a continuous infusion. Preliminary clinical experience suggests that it may be useful as a primary agent for procedural sedation with a native airway in the cardiac catheterization suite. Anecdotal experience suggests limited impact on inotropic, dromotropic, or chronotropic function, making it a potentially useful agent in patients with comorbid electrophysiologic concerns.

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None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

This retrospective review was approved by the Institutional Review Board of Nationwide Children's Hospital (Columbus, Ohio). As a retrospective study, the need for individual written informed consent was waived.

Author Contributions

SiK reviewed the medical records and prepared the first and subsequent drafts of the manuscript; SK and CM provided clinical care for the patients and participated in manuscript preparation including the final draft; JDT reviewed the medical records, participated in the preparation of all drafts including the final manuscript, and provided oversight for the project.

Data Availability

The authors declare that data supporting the findings of this study are available within the article. Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

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