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Remimazolam: Is the Sedative of the Future Here?

Dibash K. Das, PhD

Sedative and anesthetic safety is continuously reviewed as part of quality assessments. Yet, the market for sedation and anesthesia has been short on pharmaceutical development, and standard options for moderate sedation medications have not changed in three decades.

Typically, either propofol or a benzodiazepine (e.g., midazolam) with or without a narcotic (e.g., fentanyl) is used to obtain sedation for procedures. Both strategies have pros and cons. A disadvantage of propofol is the requirement of constant monitoring by an anesthesia provider due to its potential for respiratory- and cardio-depressive effects, which results in additional costs and higher risks, since there is no reversal agent available for propofol to be able to quickly stop sedation if required. For midazolam, although these side effects are less pronounced, there is a slower onset and a longer duration of action that can impact patient throughput and overall efficiency. Consequently, the search for an elusive ideal anesthetic remains.

Remimazolam (BYFAVO™), developed by PAION AG, is a novel moleculer, water-soluble, ultra-short-acting intravenous benzodiazepine that was developed to address the shortcomings of current sedation strategies. A key feature of remimazolam

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Severe Sequelae, Chronic Headache Linked to PDPH

Jessica Ansari, MD Pamela Flood, MD, MA

Post-dural puncture headache (PDPH) is a well-known complication of neuraxial anesthetic procedures resulting in an acute postural headache within five days of a dural puncture (*Minerva Anestesiol* 2019;85:543-53). Patients generally experience a severe, dull, frontal or occipital headache, often associated with neck pain, tinnitus or

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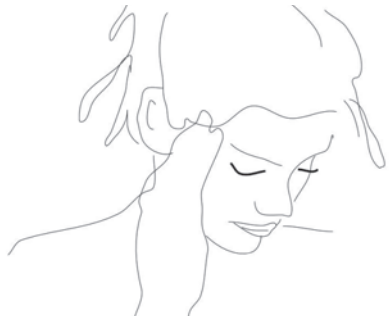

ASA Survey Results:
Commercial Fees Paid for Anesthesia Services, 2020

Stanley W. Stead, MD, MBA, FASA Sharon K. Merrick, MS, CCS-P

Summary

ASA is pleased to present the annual commercial conversion factor survey for 2020. Each summer we survey anesthesiology practices across the country. We ask them to report up to five of their largest managed care (commercial) contract conversion factors (CF) and the percentage each contract represents of their commercial population, along with some demographic information. Our objectives for the survey are to report to our members the average contractual amounts for the top five contracts and to present a view of regional trends in commercial contracting.

Based on the 2020 survey results, the national average commercial conversion factor was $82.14, ranging between $76.09 and $85.75 for the five contracts. The national median increased to $73.00, ranging between $69.00 and $77.25 for the five contracts (Figure 1, Table 1). In the 2019 survey, the mean conversion factor ranged between $73.79 and $80.76, and the median ranged between $69.00 and $78.00. In contrast, the current national Medicare conversion factor for anesthesia services is $22.2016, or about 27.03% of the

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Remimazolam

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is its rapid breakdown to an inactive metabolite by tissue esterases, rather than the hepatic pathways often involved in drug metabolism. This results in reliable and predictable sedation and recovery in patients, with very low risk of pharmacokinetic drug-drug interactions. Furthermore, remimazolam can be reversed with flumazenil to rapidly terminate sedation or anesthesia if necessary.

In clinical studies, remimazolam demonstrated efficacy and safety in approximately 2,900 volunteers and patients. The safety of remimazolam was evaluated in three pivotal studies in patients undergoing colonoscopy (two studies) or bronchoscopy (one study). Remimazolam demonstrated clear patient benefits in its extensive clinical trial programs, offering rapid onset and offset of action combined with a favorable cardio-respiratory safety profile. Patients recovered quickly after remimazolam use, and a validated scoring system demonstrated that cognition returned to baseline. Furthermore, adverse reactions were similar to that seen in patients in the placebo group.

As a result of these studies, Acacia Pharma, the U.S. licensee (in-licensed from Cosmo Pharmaceuticals for the U.S. market), recently announced that the FDA has approved BYFAVO for injection for the induction and maintenance of procedural sedation in adults undergoing invasive procedures lasting 30 minutes or less, such as colonoscopy and bronchoscopy. The U.S. launch of BYFAVO is planned for the second half of 2020.

The *ASA Monitor* spoke to **Shaw Sorooshian, MD, FFPM, FRCA,** Senior Vice President, Global Medical Affairs at PAION AG, to discuss PAION's vision of remimazolam with the anesthesia and perioperative community.

ASA Monitor: *Do you believe remimazolam is a game changer in the field of anesthesiology? If so, why?*

Dr. Sorooshian: We believe the clinical profile of remimazolam (BYFAVO) will prove very attractive in procedural sedation. Remimazolam has a very rapid onset and offset of sedative effect, as well as an encouraging cardio-respiratory safety profile, including in the least fit patients, and these are very important features for procedural sedation clinicians. Its very fast onset and offset of action could help health care providers to increase throughput of patients in busy clinical units.

We also believe remimazolam could have an attractive clinical profile for general anesthesia and intensive care sedation, indications which are not yet approved in the United States but are approved or under investigation in some other countries.

ASA Monitor: *What are the current developmental programs for remimazolam and what additional studies would you like to see run on remimazolam to better understand its clinical performance and role?*

Dr. Sorooshian: We are planning a comprehensive program of development in the following indications – procedural sedation, induction and maintenance of general anesthesia, and ICU sedation. Our development plan is at different stages in different geographic regions.

In the U.S., with our partner Acacia Pharma, we have already obtained approval for BYFAVO for procedural sedation in procedures lasting 30 minutes or less. We are evaluating the opportunity for BYFAVO in ICU sedation and induction and maintenance of general anesthesia.

In the European Union, we have submitted our application for Marketing Authorization in procedural sedation, and we expect a decision early 2021. We have also completed recruitment in our pivotal Phase III study in induction and maintenance of general anesthesia. We expect to publish top-line results in Q2 2021 and submit our application for Marketing Authorization in early 2020. In other territories, we are actively working with existing and future partners to develop remimazolam in all indications.

ASA Monitor: *Novel intravenous anesthetics have not been introduced into pediatric anesthesiology since the 1980s. Are you aiming to get in that space? Are you obliged to develop an indication for use in children?*

Dr. Sorooshian: Yes, we have a commitment to study remimazolam in children, and plan to embark on clinical studies as soon as next year. Our ultimate aim is to obtain approval for remimazolam in children in the same indications as in adults in as many countries as possible.

ASA Monitor: *In terms of commercialization, what is the most important market segment for remimazolam? Furthermore, what makes remimazolam a cost-efficient drug?*

Dr. Sorooshian: In the U.S., we feel that anesthesia providers will find remimazolam an important addition to their armamentarium. There are over 20 million colonoscopies and over 1 million bronchoscopies performed annually; and this is where BYFAVO can play a very important role. Its profile will help clinicians provide successful outcomes with the potential of high patient satisfaction – the goal of all anesthesia providers.

We anticipate that BYFAVO's predictability, rapid recovery profile, and high procedural success rates will help to maximize patient throughput, potentially generating economic benefits, especially in the busiest clinical settings. This is still to be confirmed by further observation in the real-world setting.

ASA Monitor: *What future clinical scenarios can you envision for remimazolam?*

Dr. Sorooshian: We believe BYFAVO will become a key component in sedation and anesthesia practice. The encouraging safety profile of BYFAVO, even in patients with ASA Physical Status scores of III and IV, should make it appropriate in a wide variety of settings and patient populations. ■

Dibash K. Das is a science and medical writer who holds a PhD in molecular, cellular, and developmental biology from the CUNY Graduate Center and an advanced certificate in clinical and translational investigation from Weill Cornell Medicine.