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Real-World Case Studies and Clinical Considerations for a Procedural Sedative Metabolized by Tissue Esterases

Chapter 1: Clinical Overview of a Tissue-Esterase Metabolized Procedural Sedative

Dr. Ostroff:
Hello, I'm Dr. Randy Ostroff, an anesthesiologist with forty years of clinical practice experience and nearly twenty years of experience consulting for the pharmaceutical industry. I was the lead medical consultant during the US clinical development trials of Byfavo, generic name remimazolam. The clinical development included three trials: a colonoscopy and a bronchoscopy study in ASA one to three adult patients, and a colonoscopy study in medically compromised ASA three to four adult patients.[1-4] I also helped negotiate FDA approval of Byfavo. The Important Safety Information will be covered in full. This includes the Boxed Warning for personnel and equipment for monitoring and resuscitation, as well as the risks from concomitant use with opioid analgesics and other sedative-hypnotics. Byfavo was intentionally designed to be structurally different from other benzodiazepines, as it has a carboxylic ester linkage.[1,5]

Due to the addition of this carboxylic ester linkage, Byfavo is rapidly and predictably hydrolyzed to an inactive metabolite by tissue esterases with no meaningful contributions by liver cytochrome P450 enzymes.[1,5] Because of this esterase hydrolysis, the combined pharmacokinetic and pharmacodynamic profile of Byfavo is different from our other currently available sedative options. The clinical trials demonstrated that the onset of sedative effect occurs rapidly within one to one and a half minutes, with peak sedation occurring three to three and a half minutes after an initial five mg bolus dose given over a one-minute time period.[1,6]

The trials also demonstrated an offset of eleven to fourteen minutes after the last dose and three to six minutes after completion of the procedure on average.[1,3,4,6] Therefore, one thing that is very apparent when using Byfavo is not only its rapid onset but also its rapid offset of sedative effects. Byfavo's dosing should be individualized and titrated to achieve the desired clinical response. The recommended dosing for Byfavo is an initial five mg loading dose with two-point five mg top-ups at two-minute intervals. These doses can be reduced by fifty percent for medically compromised patients, such as ASA three and four patients.[1] A patient's vital signs may not change, as we're traditionally used to, to determine if they're light or if they're inadequately sedated.[6,7] So, you need to really be on top of watching these patients. And one thing that, I've, some colleagues have used is the lack or the return of the eyelid reflex to determine when to redose because you won't see it with the patient's vital signs necessarily.[7]

Keep in mind that in the Phase three trials, patients were pretreated with twenty-five to seventy-five micrograms of fentanyl.[1-4] Since concomitant use of benzodiazepines, including Byfavo, can have a synergistic sedative effect, you should take that into consideration if you plan to administer Byfavo without an opioid.[1] If you do omit fentanyl, you're going to need more Byfavo to achieve the same effect. Personally, in my practice, I've administered Byfavo with and without fentanyl.

To familiarize yourself with the drug and to have experience in titrating to effect, I recommend that you trial Byfavo in at least five to ten patients before deciding on Byfavo's utility in your specific clinical practice. Ultimately, I believe you will find Byfavo attractive for use in medically compromised, frail, ASA III and IV adult patients due to its pharmacokinetic profile and safety profile.[1,4]

Now let's look at Byfavo's established safety profile. First, the most common adverse reactions occurring in more than ten percent of patients who received Byfavo during the clinical trials were hypotension and diastolic hypotension, hypertension, including both diastolic and systolic, and hypoxia, with most of the hypoxia cases occurring during the bronchoscopy study.[1,6] In the colonoscopy trial, more than 300 patients received Byfavo for sedation and only one patient had to require any kind of an intervention for an airway issue. And

that was a jaw lift.[6] In terms of safety, it's a benzodiazepine. It's reversible with the reversal agent flumazenil.[1] Notably, no patients in the Byfavo treatment arms required flumazenil for any medically untoward effects.[6]

The other thing I've noted and that I've also learned from colleagues who have had experience with Byfavo is patients breathe very well, and even down at low levels of sedation, we see that their vital signs are not affected by these low levels of sedation, their blood pressure, heart rate, oxygen saturation, respiratory rate, etc. stay constant, even at deep levels of sedation.[7] Additionally, a post-hoc analysis evaluating vital signs across sedation levels was conducted on the pivotal trial safety data in high-risk ASA III and IV patients who received Byfavo for colonoscopy. This analysis demonstrated no correlation between sedation level and vital signs, such as blood pressure, heart rate, oxygen saturation, partial pressure of carbon dioxide, or respiratory rate.[7]

In summary, the pharmacokinetic profile of Byfavo in combination with its established safety profile is why it is my short-acting sedative of choice for procedures lasting 30 minutes or less in medically compromised, frail ASA three and four adult patients.[1,4] Thank you for taking the time to watch this video. To learn more about Byfavo, I encourage you to watch the additional chapters where my colleagues provide further insights and share their clinical experiences.

References:

1. Byfavo [package insert]. Indianapolis, IN: Acacia Pharma Inc; 2023.
2. Rex DK, Bhandari R, Desta T, et al. A phase III study evaluating the efficacy and safety of remimazolam (CNS 7056) compared with placebo and midazolam in patients undergoing colonoscopy. *Gastrointest Endosc*. 2018;88(3):427-437.
3. Pastis NJ, Yarmus LB, Schippers F. Safety and efficacy of remimazolam compared with placebo and midazolam for moderate sedation during bronchoscopy. *Chest*. 2019;155(1);137-147.
4. Rex DK, Bhandari R, Lorch DG, et al. Safety and efficacy of remimazolam in high risk colonoscopy: a randomized trial. *Dig Liver Dis*. 2021;53(1):94-101.
5. Pambianco D, Cash B. New horizons for sedation: the ultrashort acting benzodiazepine remimazolam. *Tech Gastrointest Endosc*. 2016;18:22-28.
6. Acacia Pharma. Data on File.
7. Ostroff R, Harris D, Bichajian L, et al. Safety profile of the benzodiazepine remimazolam for procedural sedation in higher risk patients (ASA III/IV): results from a randomized trial. Poster presented at: SAMBA Annual Meeting 2022; May 11-14, Phoenix, Arizona.

Chapter 2: Clinical Considerations for First-Time Use for this Tissue-Esterase Metabolized Procedural Sedative

Dr. Henson:
Hi, I'm Kevin Henson, a CRNA practicing for 30 years as a provider and healthcare administrator. I'm here to share my clinical experience and some product information on remimazolam, brand name Byfavo. I've been administering Byfavo for over two years and over 700 adult patients for the induction and maintenance of sedation in procedures lasting 30 minutes or less.[1]

The Important Safety includes the Boxed Warning for personnel and equipment for monitoring and resuscitation, as well as the risks from concomitant use with opioid analgesics and other sedative-hypnotics. Byfavo is an injectable benzodiazepine that was intentionally designed to be short-acting. Clinical trials have demonstrated the onset of sedative effect occurs rapidly within 1.0 to 1.5 minutes, with peak sedation occurring 3.0 to 3.5 minutes after a 5 mg bolus dose given over a 1-minute time period.[1-3] Unlike other injectable benzodiazepines, Byfavo is rapidly hydrolyzed to an inactive metabolite by tissue esterases with no meaningful contribution by cytochrome P450 enzymes.[1,4] This leads to a rapid offset of Byfavo's sedative effect, which was demonstrated in clinical trials by a median time to fully alert of 11.0 to 14.0 minutes after the last dose and 3.0 to 6.0 minutes after the end of the procedure.[1,6,7]

We were introduced for the release of remimazolam a couple of years ago. Theoretically, it sounded promising. We were always worried in the past about using benzodiazepines. They had a prolonged effect, so we couldn't use them very heavily with the patients we wanted to use them on for the safety profile: the geriatrics, the hypoxic patients. All of those considerations, we had to use other medications. We were approached to use this. We had a great relationship with our administration and how we get medications into our organization. We had a box within a week or two.

We started with our medical director and our staff narrowing down where we are going to use this, how we're going to select the patients. And we did exactly what the package insert said. We followed it on-label to the T. We used it for, basically everybody though, that we thought was over the age of 18 that it could possibly be considered on.[1] Very quickly, though, we titrate it into that patient

population that were the most vulnerable, the geriatrics, the advanced age.[1,7] We went through several doses with several providers, not restricting them too much. And we all kind of congealed and went towards the center on this intentionally manufactured fragile drug was ideal for our most fragile individuals. So, a metabolically fragile drug and a biologically frail patient.[1,2,7] This has been mirrored in my clinical practice where remimazolam is used predominantly for those ASA III-IV patients.[1,7]

Due to the rapid onset and offset of Byfavo,[1,3] it did take me some time to get accustomed to how the drug performs and how to dose it appropriately. First time using remimazolam, an important thing to keep in mind is that initial dose. You need to come in at the recommended dose of 5 mg unless you have a very strong reason not to because of advanced comorbidities.[1] Byfavo was studied with bolus dosing. The recommended dosing is a 5 mg load with a 2.5 mg top-off at 2-minute intervals, with the recommended 50% reduction for ASA III and IV patients.[1] The most important thing is the initial bolus of 5 mg, and you watch it really closely and stay on top of redosing and redosing. It's cleared quickly, has a low volume of distribution, and you're going to need to watch the patient's level of sedation closely, titrate to, based on the recommendations of 5 followed by 2.5, 2.5 to get them in the place where you want them for sedation. The procedure will take place and then you can see the rapid recovery.[1]

Clinicians may be inclined to start lower than the labeled dosing when using a new drug for the first time. To start low and go slow. In my experience, when I started low and slow, we did not get the therapeutic level of sedation necessary for the procedure to start at an expected time. When I dosed at recommended doses, we achieved a level of sedation required to perform the procedure safely and in a timely manner. Depending on the procedure and other factors, I've administered Byfavo with and without an opioid. When using an opioid with a benzodiazepine, including Byfavo, there is a risk for profound sedation, respiratory depression, coma, and death. Therefore, you should take into account the synergistic sedative effect when dosing patients with or without concomitant opioid use to achieve the desired effect.[1]

In clinical trials, Byfavo was administered with the opioid, fentanyl, with a pre-treatment dose of 25 to 75 micrograms and supplemental doses of up to 200 micrograms for analgesia during the procedure. It is important to remember that the label dosing was established from trials in which the drug was studied with concomitant opioid use.[1,5-7] Byfavo has been studied in specific patient populations, and has been found to be appropriate for use in these populations, including individuals that are medically compromised, such as ASA III and IV status, advanced age patients, and patients with renal failure.[1,5-7]

From a patient selection perspective, when we started this two years ago, we didn't know exactly which patient population this would be ideal for. Then when we started using it, we used it on a broad range of patients. Patients that were over the age of 18 getting an assortment of different procedural sedation.[1] So, it was me giving you a recommendation from probably one, if not the, most used site in the United States of using Byfavo. I would say patient selection are those that are biologically fragile, predominantly for those ASA III or IV patients. So those men and women that are coming in for maybe outpatient procedures that want to have quick recovery and a smooth transition through recovery post-op.[1,5-7] That's the ideal patient population. For the first time user, however, I would recommend using it on a broader patient population, so you understand based on your practice environment where you get the benefits of the PK and PD specifics for remimazolam, Byfavo.[1]

In my opinion, Byfavo is another tool to add to our armamentarium when selecting the appropriate sedative for a patient to achieve an adequate depth of sedation for the procedure being performed and maintain hemodynamic stability based on the patient's health status, the procedure being performed, the location of the procedure and the anticipated adverse outcomes.[1,8] Thank you for taking the time to watch this video. To obtain more information about Byfavo, I encourage you to watch the additional videos on this page.

References:

1. Byfavo [package insert]. Indianapolis, IN: Acacia Pharma Inc; 2023.
2. Pambianco D, Cash B. New horizons for sedation: the ultrashort acting benzodiazepine remimazolam. *Tech Gastrointest Endosc*. 2016;18:22-28.
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4. Midazolam Injection [package insert]. Lake Forest, IL: Hospira, Inc.; 2018.
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8. Ostroff R, Harris D, Bichajian L, et al. Safety profile of the benzodiazepine remimazolam for procedural sedation in higher risk patients (ASA III/IV): results from a randomized trial. Poster presented at: SAMBA Annual Meeting 2022; May 11-14, Phoenix, Arizona.

Chapter 3: Important Safety Information with Boxed Warning

Byfavo is a benzodiazepine indicated for the induction and maintenance of procedural sedation in adults undergoing procedures lasting 30 minutes or less. Byfavo has a benzodiazepine-class boxed warning regarding the need for personnel and equipment for monitoring and resuscitation, and the risks from concomitant use with opioid analgesics and other sedative-hypnotics.

Byfavo has been associated with hypoxia, bradycardia, and hypotension. Continuously monitor vital signs during sedation and through the recovery period. Only personnel trained in the administration of procedural sedation, and not involved in the conduct of the diagnostic or therapeutic procedure, should administer Byfavo. Administering personnel must be trained in the detection and management of airway obstruction, hypoventilation, and apnea, including the maintenance of a patent airway, supportive ventilation, and cardiovascular resuscitation.

Resuscitative drugs, and age- and size-appropriate equipment for bag/valve/mask-assisted ventilation must be immediately available during administration of Byfavo. Supplemental oxygen should be administered to sedated patients through the recovery period. A benzodiazepine reversal agent (like flumazenil) should be immediately available during administration of Byfavo.

Concomitant use of Byfavo and opioid analgesics may result in profound sedation, respiratory depression, coma, and death. The sedative effect of IV Byfavo can be accentuated when administered with other CNS depressant medications (such as, other benzodiazepines and propofol). Titrate the dose of Byfavo when administered with opioid analgesics and sedative-hypnotics to the desired clinical response. Continuously monitor sedated patients for hypotension, airway obstruction, hypoventilation, apnea, and oxygen desaturation. These cardiorespiratory effects may be more likely to occur in patients with obstructive sleep apnea, the elderly, and ASA III or IV patients.

Byfavo contains dextran 40, which can cause hypersensitivity reactions, including rash, urticaria, pruritus, and anaphylaxis, in patients with allergies to dextran 40 or products containing dextran 40. Receiving benzodiazepines late in pregnancy can result in sedation and/or withdrawal symptoms in the neonate. Monitor neonates exposed to Byfavo during pregnancy or labor for signs of sedation, and monitor for signs of withdrawal and manage these neonates accordingly. If anesthetic and sedation drugs are a necessary part of the care of children needing surgery, other procedures, or tests that cannot be delayed, and no specific medications have been shown to be safer, decisions regarding the timing of any elective procedures requiring anesthesia should take into consideration the benefits of the procedure weighed against the potential risks, including pediatric neurotoxicity.

The most common adverse reactions reported in >10% of 630 patients who received Byfavo were: hypotension, hypertension, diastolic hypertension, systolic hypertension, hypoxia, and diastolic hypotension. Infants exposed to Byfavo through breast milk should be monitored for sedation, poor feeding, and poor weight gain. A lactating woman may consider interrupting breastfeeding and pumping and discarding breast milk during treatment and for 5 hours after Byfavo administration. As a reminder, Byfavo is not indicated in patients younger than 18 years. Observe elderly patients closely as sedating drugs, such as Byfavo, may cause confusion and over-sedation. In patients with severe hepatic impairment, the dose of Byfavo should be carefully titrated to effect as reduced doses might be indicated depending on the patient's overall status. Remimazolam has the potential for abuse and physical dependence, therefore, Byfavo is a controlled (C-IV) substance.

Please refer to the full Prescribing Information for additional information.

Chapter 4: Real-World Case Studies of this Tissue-Esterase Metabolized Procedural Sedative

Mitch Markins:
My name is Mitch Markins. I am a certified registered nurse anesthetist. I am also the facility administrator, also director of anesthesia. It's probably been over a year and a half now since I got introduced to Byfavo. Like other benzodiazepines Byfavo has a box warning, so be sure to have the proper personnel and equipment for monitoring and resuscitation and be aware of other risks from concomitant use with opioid analgesics and other sedatives or hypnotics.[1]

Our patients are not the healthiest of patients. You know, I deal mainly with an ASA III/IV clientele. You know, we're looking for

something with rapid onset. We're looking for something with rapid offset. We're also looking for a drug that has a wide safety margin. You're always looking at respiratory rate. You're always looking at blood pressure. You're looking at pulse rate. And you're looking to see how well the patient is tolerating the procedure as well. Sometimes, you know, the patient might become hemodynamically unstable or their respiratory rate has been compromised, then you have to use interventions. I might have to do bag mask, ventilation, might eventually have to go to an LMA or even intubate the patient. If their blood pressure become unstable, I have to give medications to bring up the blood pressure. I have to look at all those other interventions also as an administrator, because all these have cost to the facility. So, when you start adding some of these medications to intervene and help these patients, you know, you're adding a significant cost to the care.

For those who are first using it, don't use it sparingly. Give the five milligrams, you know, IV push, wait a little bit, then go with two and a half milligrams. You'll see the rapid recovery, the rapid onset. Within 90 seconds to 5 minutes, it's pretty much hits its peak.[1,2] I think if you're too conservative, you're going to find that you're not happy with the drug, you're not going to achieve the levels of sedation that you're adequate with. And that's where your clinical judgment as an anesthesia provider comes in. I mean, you have to be vigilant of the level of sedation of your patient. I'm able to achieve, you know, a rapid onset of sedation with these patients, and you're able to recognize conditions that would be masked. That you are able to identify the situations like maybe they're not breathing so well. Is that because I gave them too much of the medication or is it because they've got something else going on? You know, all I have do is hold off for another minute or two on Byfavo and talk to the patient. And these patients wake up immediately. I'm able to talk to them during the procedure and they're totally unaware that the procedure is going on.[1] When they talk to you, it's kind of like that sedated talk. It's almost like a mumble or a whisper, but they're able to respond, you know, mildly. Whereas if they're starting to lift their heads up or/and move around a little bit, you know, you need to probably give a little bit more medication.[1,2] Byfavo gives me that safety margin that I feel comfortable.[1-4]

This lady presented to us, she was 93 years old.[5] She suffered from dementia. She also had some slight renal insufficiency.[1] And these are the kind of cases where you're like me, and I don't feel comfortable, you know, sedating the 93-year-old. And more often the surgeon goes. "Well, I can probably do this under local." But when you have a patient with dementia, it's hard to keep them reoriented. It's a fairly short procedure, usually around 30 minutes. The patient came into the room. I gave her, I think, three milligrams of Byfavo, and I gave her 25 mcg of fentanyl. Within 3 to 5 minutes, she was adequately sedated.[1] We did local injection without any response. I think I gave this lady a total of ten milligrams of Byfavo over a 30-minute period and she received no more fentanyl.[1] At the end of the case, she was able to mentate properly. We took her to the recovery room. Her recovery lasted all of one hour. She was able to walk out of here.

We had another ideal patient. He's been a frequent flier for our facility. This man is a very sick individual. He has an ejection fraction of 10%, defibrillator, severe cardiomyopathy, has been three days since his last dialysis, severe respiratory hypoxia failure.[3] He only needed to receive a total of ten milligrams of Byfavo. And he only got 12 and a half mcgs of fentanyl.[1] He was able to converse with me throughout the whole process. And then at the end when I told him we were done, he's like, what do you mean we're done? So once again I mean, these are procedures that, you know, three years ago I wouldn't even think about doing here. But I'm able to and feel very confident about sedating this man.

References:

1. Byfavo [package insert]. Indianapolis, IN: Acacia Pharma Inc; 2023.
2. Acacia Pharma. Data on File.
3. Rex DK, Bhandari R, Lorch DG, et al. Safety and efficacy of remimazolam in high risk colonoscopy: a randomized trial. *Dig Liver Dis*. 2021;53(1):94-101.
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