
The Worry That's Always With Us: Now I'm Depressed

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Benzodiazepines, opioids, propofol

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Abstract

This case discusses the pharmacodynamic interactions seen with the coadministration of propofol, opioids, and benzodiazepines.

Case

The anesthesia chief resident went to the preoperative area to talk to her first patient of the day, a 70-year-old man scheduled for foot surgery. He was accompanied by his wife and daughter and stated he was very nervous and did not like hospitals. He confirmed that he took no regular medications except for lisinopril and simvastatin. The plan was for ankle block and sedation as needed under monitored anesthesia care (MAC).

The patient remained anxious in the operating room (OR) and was given midazolam (2 mg) and fentanyl (50 mcg) before the block was performed. The patient startled with the incision and received fentanyl (50 mcg) and propofol (20 mg). He was also started on a propofol infusion. He began to breathe more slowly and became apneic despite chin lift and jaw thrust maneuvers. He was intubated after bag-mask ventilation proved difficult. The rest of the case proceeded without incident and the patient was extubated in the OR before being transported to the post-anesthesia care unit.

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Later, the anesthesia resident visited the patient in the recovery room to update him and his family about what happened during the case. The resident explained that the reason he required intubation was likely due to medication effects and, as she had explained while obtaining consent, this was a known risk of such procedures. The wife was very understanding but the daughter appeared uneasy. She approached the resident later and admitted that she gave her father one of her “alprazolams” that morning because he seemed so nervous about his surgery. The resident accompanied the daughter back to her father’s bedside and explained to both the patient and family how important it is to be up front about any and all medications taken because of the effects they have on the body, especially in combination with other medications. The resident went home that evening and discharged her frustration by recounting the whole story in minute detail to her spouse.

Discussion

This is an example of multiple synergistic pharmacodynamic interactions.

The combination of propofol, benzodiazepines, and opioids is one that is used commonly with general anesthesia and is being used increasingly more often in routine sedation. Procedures such as colonoscopy or those involving extremities lend themselves well to the combination of regional anesthesia with MAC.^{1,2} The likely reason for the popularity of this combination is that when propofol, opioids, and benzodiazepines are administered together they act synergistically to produce a hypnotic effect as well as to induce immobility.³ This means that, in addition to the decreased anxiety obtained with benzodiazepines and the pain control achieved with opioids, these drugs also work to accomplish the level of decreased awareness and decreased response to stimuli desired for surgical procedures. Several studies have demonstrated this point.

Most of the research has investigated combinations of two of these agents rather than all three at once. However, interactions between the two-drug combinations of propofol and benzodiazepines, propofol and opioids, and benzodiazepines and opioids have shown that each of these pairs exhibits synergistic activity in terms of producing hypnosis.³ Also, although opioids and benzodiazepines cannot produce immobility on their own, when each agent is combined with propofol it causes left-shifts in the propofol immobility dose response curves.³ Furthermore, giving opioids has been shown to yield higher concentrations of propofol in the blood than when the same dose of propofol is administered alone.⁴ Interestingly, although opioids enhance the hypnotic effects of propofol, this is not reflected by a change in the bispectral index.^{5,6} The synergistic effects of propofol, benzodiazepines, and opioids on awareness as well as immobility allow for the desired level of sedation to be

achieved using reduced dosages of each individual drug. Using lower doses of multiple drugs may decrease the incidence of side effects caused by any individual drug. This is suggested by studies in the intensive care setting that show increased hemodynamic stability in patients receiving a combination of these drugs for sedation versus one drug alone.^{7,8}

Even though combining these drugs has clear benefits that can be used to the anesthesiologist's advantage, it is not without risks. Propofol, benzodiazepines, and opioids all have the potential to cause respiratory depression independently and, when given together, these effects are additive and respiratory depression can occur at lower doses.⁶ Propofol alone has the potential to decrease hypoxic respiratory drive up to 80%.⁹ Under general anesthesia this is not as much of a concern until assessing for readiness to extubate. It is not surprising that depressive effects on ventilation become more significant in situations where it is desirable to have the patient breathe spontaneously. One retrospective study on sedation for gastrointestinal endoscopy cites the need for intubation during these procedures as occurring in 0.07%-0.1% of cases.¹ The effects on respiratory depression are dose-dependent for each agent as well as being additive when combining agents.

The cumulative nature of respiratory depression in response to these drugs may be more apparent in certain patient populations that are more sensitive to the effects of these drugs. This is the case in older patients who generally have reduced metabolism and/or clearance of the drug itself and may benefit from dose decreases.⁸ Another patient population that would be expected to have more profound respiratory depression at standard doses and would benefit from decreased doses is the group of patients with liver disease. Although even cirrhotic liver changes do not affect the clinically relevant actions of propofol, the normal metabolism of both benzodiazepines and opioids occur in the liver and are highly impacted by decreased liver function.^{8,9} The potential for the combination of these drugs to cause increased respiratory depression may be the reason why some studies show an increase in weaning time from the ventilator with a combination regimen as compared with a single drug regimen.^{7,8}

Take-Home Points

- In combination, propofol, opioids, and benzodiazepines work synergistically to produce hypnotic and immobilizing effects and therefore allow decreased doses of each drug when they are used together. The decreased doses may lead to more hemodynamic stability and decreased incidence of side effects from each individual drug.
- Propofol, opioids, and benzodiazepines all have the potential to cause respiratory depression, and when these drugs are used in combination,

their effects on respiratory depression are additive. These effects are especially pronounced in older patients and patients with liver disease.

- The importance of an accurate and complete history and physical cannot be overemphasized.

Summary

Interaction: pharmacodynamic

Substrates: propofol, opioids, benzodiazepines

Mechanism/sites of action: multiple central nervous system sites

Clinical effect: increased hypnosis and sedation, decreased respiratory drive

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