HHS Public Access

Author manuscript

J Am Geriatr Soc. Author manuscript; available in PMC 2022 August 01.

Published in final edited form as:

J Am Geriatr Soc. 2021 August ; 69(8): 2106–2109. doi:10.1111/jgs.17221.

Goldilocks and Propofol Dosage in Older Adults: Too much, Too Little, or Just Right?

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"The only difference between a drug and a poison lies in the dose" wrote the Swiss physician and alchemist Paracelsus (1498-1538).[1] Nearly half a millennium later, this principle remains highly applicable to the practice of geriatric anesthesiology, particularly at the induction of general anesthesia with propofol in older adults (Fig. 1). The induction of general anesthesia aims to rapidly transform an awake, conscious patient to one who is amnestic, unconscious, and ready to undergo tracheal intubation without pain, movement, or increased blood pressure or heart rate (i.e. hemodynamic derangements). Yet, many commonly used anesthetic induction agents such as propofol can cause significant and even life-threatening reductions in blood pressure, respiratory depression, and other adverse events. The propofol dose ranges that will cause both beneficial and detrimental effects decline with increasing age, which has led the FDA to issue the recommendation that the induction dose of propofol should be reduced from 2-2.5 mg/kg to 1-1.5 mg/kg in older adults.[2] Yet, the question remains to what extent this recommendation is being followed: i.e. how much propofol are older Americans receiving for anesthesia induction? This question is addressed by a thorough study in this issue of JAGS by Schonberger and colleagues,[3] which includes propofol induction dose data from over 350,000 older Americans at 36 institutions from 2014 to 2018.

Schonberger and colleagues show that the majority of older adults received propofol induction doses above the recommended FDA range for older adults of 1-1.5 mg/kg. They also show that the percentage of older adults receiving doses above the 1.5 mg/kg FDA

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Author Contributions: Drs Devinney and Berger wrote this editorial together, and each take equal and responsibility for its full contents.

Sponsors Roles: The aforementioned grant funding agencies and professional societies had no role in the writing of this editorial, and did not review it prior to publication.

upper limit decreases with age, from ~74% in patients age 65-69 to ~46% in patients over age 80. Encouragingly, propofol doses >1.5 mg/kg also occurred at lower rates in patients presumed to be at higher risk for adverse outcomes from excessive dosage, i.e. in those with coronary disease, more severe frailty, or chronic kidney disease. These data fit well with prior reports from multiple centers across the USA and Europe showing that the majority of older adults also likely received excessive inhaled anesthetic dosage to maintain general anesthesia during surgery, i.e. older adults received relatively higher age-adjusted inhaled anesthetic doses than young and middle aged adults.[4-7] Together, these data suggest that older American and European patients are likely receiving larger doses than necessary for both the induction and maintenance of general anesthesia.

What do These Results Mean?

The answer to that question is complex and nuanced. An overdose is typically viewed as an excessive drug dose that causes adverse events. Schonberger et al and prior reports document that older adults are likely receiving excessive anesthetic drug dosage, but none of these reports have demonstrated that excessive doses are associated with adverse events. Thus, it is premature and potentially inappropriate to interpret these data to mean that the majority of older adults are receiving anesthetic “overdoses”.

In considering this issue, it is important to realize that the practice of anesthesiology is different than most other medical and geriatric specialties in several respects, including the fact that anesthesiologists titrate drug administration based on physiologic data and patient responses in real time. Unlike an internist who can gradually titrate an oral antihypertensive drug over multiple outpatient clinic visits spread across weeks to months, anesthesiologists give drugs that produce dramatic physiologic effects (i.e loss of consciousness, amnesia, and paralysis) over mere seconds to minutes. Further, despite our evolving understanding of anesthetized EEG patterns,[8,9] there is currently no ideal monitor of consciousness or amnesia in clinical use. In current practice, unconsciousness and amnesia are typically assumed to be present at anesthetic induction if there is a lack of movement and blood pressure/heart rate increases in response to tracheal intubation. Since insufficient anesthetic dosage can lead to intraoperative awareness with explicit recall, which often results in PTSD and other severe adverse mental health sequelae for patients,[10,11] anesthesiologists have an impetus to be “generous” with anesthetic dosage.

Yet, excessive dosage for anesthesia induction (i.e. propofol) and maintenance (i.e. inhaled anesthetics) can lead to hypotension and even pulseless electrical activity (PEA) requiring advanced cardiac life support. Thus, anesthesiologists face the dilemma of needing to administer a “goldilocks” dose- not too little, and not too much, without any equation or method to *a priori* calculate the exact right propofol dose for each individual patient. This challenge forms part of the art of clinical anesthesiology; attaining this clinical judgement is partly why anesthesiology internship and residency takes four years.

Should FDA Dosing Ranges for Anesthetics be Considered Mandates?

FDA package inserts provide general guidance for drug administration: the FDA package insert for propofol simply states that most elderly patients will "require approximately 1 mg/kg to 1.5 mg/kg (approximately 20 mg every 10 seconds) of DIPRIVAN (i.e. propofol) for induction of anesthesia according to their condition and responses. A rapid bolus should not be used, as this will increase the likelihood of undesirable cardiorespiratory depression including hypotension, apnea, airway obstruction, and/or oxygen desaturation."

These FDA recommendations are just that- recommendations, not legally binding limits on drug dosage- and they explicitly recognize that the appropriate propofol induction dosage will vary across patients "according to their condition and response." In this statement, the FDA guidance recognizes a point well known to geriatricians- the heterogeneity in human physiology and functional capacity increases significantly with age.[12] While most 10 year olds can run a mile in a roughly similar time range, some older adults cannot walk while others run marathons. Similarly, some older adults need similar propofol doses to those given to healthy 40 year olds, while administering even a small fraction of these doses will cause PEA in other older adults.

Are We Overdosing Older Adults? Should Anesthesiologists Reduce Propofol Induction Doses in Older Adults?

As discussed above, we believe it is premature to conclude that the data from Schonberger *et al* demonstrate widespread "overdoses" of propofol in older adults. Nonetheless, these results and other recent reports raise the key question of whether relatively higher anesthetic induction and/or anesthetic maintenance dosage are associated with increased adverse events in older adults. If so, that would suggest the need for prospective studies to determine whether reducing anesthetic induction and/or maintenance dosage would improve outcomes in older surgical patients.

While such studies are being conducted, there are three reasons it would be premature to call for widespread reductions in anesthetic dosage for older adults. First, although "de-prescribing" is a common goal in geriatrics,[13] it does not quite apply to intraoperative anesthetic dosage in older adults. Unlike an outpatient geriatric setting in which avoiding the side effects of drugs may outweigh their potential long term benefits, the significant potential harms (including PTSD) associated with anesthetic under-dosage mean that reducing anesthetic dosage in the OR is not risk-free. Second, although other GABA-A receptors agonists like benzodiazepines are included Beers List of drugs to avoid in older adults,[14] performing surgery without administering GABA-A agonists such as propofol or inhaled anesthetics (which also act on other targets besides GABA-A receptors) is not a viable option, except during operations in which anesthesia can be provided solely by nerve blocks. Third, although some *in vitro* and animal studies have suggested neurotoxic effects of both propofol and inhaled anesthetics,[15,16] there is little evidence that these drugs have similar neurotoxicity in humans.[17] Indeed, many anesthetic drugs have been shown to produce toxic effects *in vitro* that do not occur in humans at clinically relevant doses.[18]

While it would be premature based on current data to suggest widespread changes to anesthetic dosage in older adults, this report serves two useful purposes moving forwards. First, it should serve as an impetus for anesthesiologists to carefully consider the doses of mind-altering drugs we are administering to older surgical patients, particularly since older patients are at increased risk of cognitive disturbances such as delirium following surgery.[19] Second, in order to improve clinical outcomes for older surgical patients, we first need to know exactly what our current clinical practice *is*. In this respect, Schonberger et al have provided an important step forwards in defining current geriatric anesthesia practice across 36 different hospitals; future studies will help us define the best path forwards in anesthetic drug dosage for the more than 19 million older Americans who undergo surgery each year.[20]

ACKNOWLEDGMENTS:

We thank Stanley Coffman for assistance in creating the Figure, and Drs Ken Schmader and Harvey J. Cohen for helpful discussions.

Funding:

Dr. Berger reports grant funding from the Alzheimer's Drug Discovery Foundation and the Ruth K. Broad Foundation at Duke University, and support from NIH grants K76AG057022, P30AG028716. Dr. Devinney reports grant funding from the Foundation for Anesthesia Education and Research.

Conflicts of Interest: Dr Berger reports grant funding from the Alzheimer's Drug Discovery Foundation, and support from NIH grants K76AG057022 and P30AG028716. Dr Berger also reports serving as the liaison from the American Society of Anesthesiology to the American Geriatrics Society from 2018-2021. Dr Devinney reports grant funding from the Foundation for Anesthesia Education and Research. The authors have no other financial conflicts of interest to disclose with respect to the content of this editorial.

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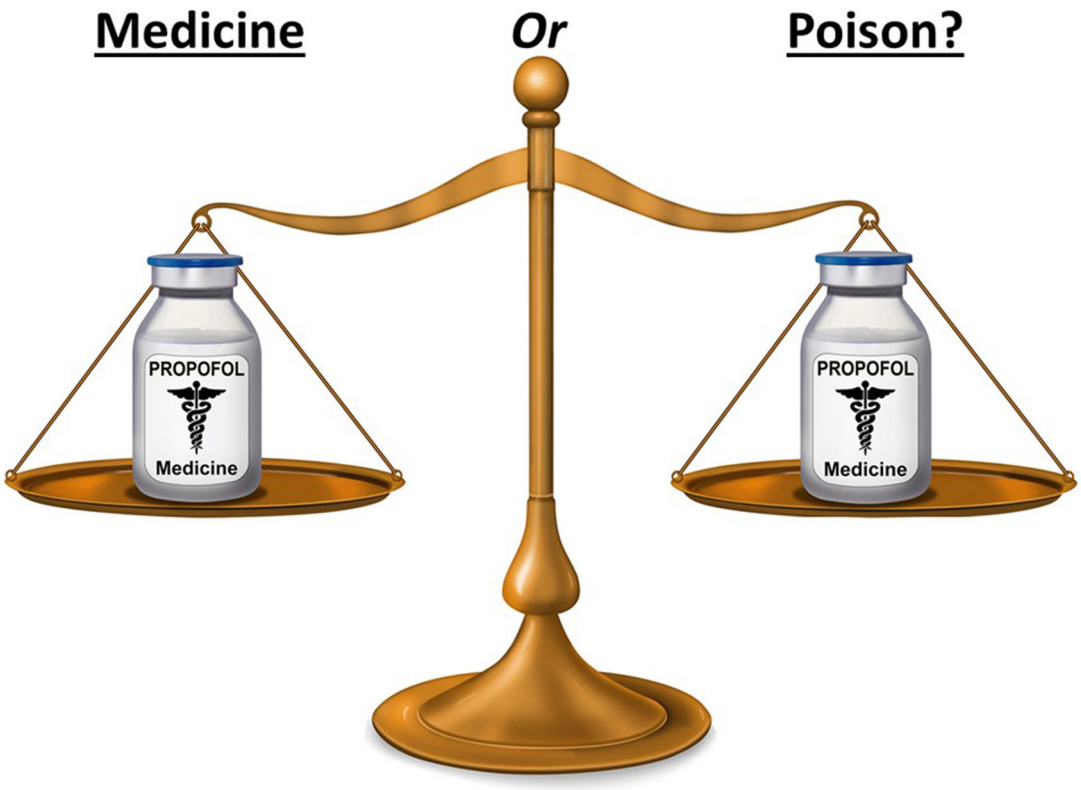

Figure 1:
Weighing the Propofol Dosage for Use as a Medicine versus as a Poison