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TITLE: Are we overdosing older patients?

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One of the most fundamental tasks of the anaesthesiologist is to ensure hypnosis during general anaesthesia, for patients of all ages. Yet, we know remarkably little about individual patients' anaesthetic requirements, using instead population-based metrics like the minimum alveolar concentration of volatile anaesthetic required to prevent movement to surgical incision for 50% of the population (MAC) – an index of movement, not consciousness or recall. It was apparent early on in the life of MAC that older patients' MAC value was lower than younger patients', yielding the concept of age-adjusted MAC (aaMAC): the proportion of the minimum alveolar concentration of volatile anaesthetic required to prevent movement to surgical incision for 50% of the population *of that age*. So 0.7 MAC for a 40-year-old may represent a relative overdose for an 80-year-old.

This is a canonical teaching in modern anaesthesia training, and yet, only within the last decade, the widespread availability of intraoperative electroencephalography (EEG) and processed "depth of anaesthesia" indices have finally made possible the empirical testing of age adjustment, and also the documentation of how aaMAC is actually used in routine clinical practice when an alternative metric of anesthetic depth is available. Ni and colleagues[1] present a single-center study of the latter question, built upon a meta-regression of previous work addressing fundamental tenets underlying the former.

The study, ambitiously, attempts to answer three questions: 1, is the accepted age adjustment factor actually supported by a review and meta-regression of published MAC studies in a range of adults; 2, are older adults receiving what we would consider “appropriately” age-adjusted concentrations of volatile anaesthetics in a largely unselected single-center academic population; and 3, does a processed EEG-based measure of anaesthetic depth (here, the Bispectral Index, or BIS) behave as we would expect, in response to the administered concentrations of volatile anaesthetics in an older population?

The answers are, intriguingly, *yes* (the canonized adjustment factor of ~6-7% per decade seems to be appropriate), *no* (older adults are administered more volatile anaesthetic than their aaMAC indicates they should require), and *no* (older adults paradoxically display higher BIS values even in the presence of a presumed relative anaesthetic overdose). These latter two conclusions require unpacking, since they have important implications for how we do – and how we should – provide care to this unique, and potentially vulnerable, population.

At the academic center where this work was performed, anaesthesia machines do not routinely generate an aaMAC; rather, an end-tidal percent is displayed, with the option to display MAC fraction (without age adjustment). The explanation for the authors’ finding – that older adults receive a greater aaMAC than younger – may be more due to human engineering than any other factor. When attention is divided among many competing tasks, it is cognitively easier to just empirically tweak the volatile anaesthetic delivery in relation to the MAC of a 40 year old patient, rather than properly calculate a true aaMAC (or equivalent end-tidal volatile gas percent) for each individual patient’s age. The increasing availability of aaMAC automatically computed by the gas analyzer or anaesthesia machine’s software may fix this tidily.

But what if that *isn’t* the reason for administering what we would consider a relative overdose? Roughly 30% of patients – particularly older patients – in this study underwent concurrent BIS

monitoring. We might assume that in those patients, anaesthesia providers were attempting to titrate to *individual requirements* for hypnosis, rather than a population-based MAC. And here, the authors find, sometimes either BIS misleads, or aaMAC misleads, for older adults.

The authors confirm that the BIS is relatively invariant at MAC fractions of 1.0 MAC and greater, though interestingly demonstrate a negative correlation between MAC and BIS in the range of 0.75-1.0 MAC (interesting largely because, while this is how it *ought* to work, BIS has been criticized many times before for being insensitive to clinically-relevant changes in aaMAC[2]). In comparison to prior work, Ni et al do not restrict to pharmacokinetically censored data (i.e., their findings may reflect a stronger correlation due to acute changes in volatile anaesthetic administration), so relevance to the maintenance phase of anaesthesia is somewhat unclear. Perhaps appropriately, then, this finding is not emphasized in favor of the hypothesis-driven, and titular, result that older adults show a paradoxically higher BIS value at equivalent aaMAC values.

That older adults show different EEG signatures at adequate levels of hypnosis, compared with younger adults, is also well known.[3] Slow waves and alpha waves decrease with age, and high-frequency activity is relatively more predominant, even at high doses of volatile anaesthetic. Burst suppression is also more common in older adults. While burst suppression will tend to *de*crease the BIS number, the other age-dependent features – lower alpha power relative to higher-frequency bands – will tend to *increase* the BIS number, at equi-hypnotic doses of volatile anaesthetic compared with younger adults. Importantly, while it is assumed that processed EEG indices are calibrated using loss of responsiveness as a meaningful change in clinical status which should be reflected in the index value, it is not clear how transition to burst suppression is used by manufacturers; the effect-site concentration of different anaesthetics varies so widely at the point of EEG suppression as to be incomparable with traditional ideas of MAC or its correlate for intravenous anaesthetics.[4]

Thus, there are two competing explanations for Ni et al's finding of higher aaMAC in older ages. The most likely one is the "convenience hypothesis" (mentioned earlier), which suggests anaesthesia providers are using a one-size-fits-all approach when, clearly, one size does not fit all. However, another explanation is that, faced with a black box algorithm accusing the provider of delivering a barely-adequate anaesthetic depth – the patient is showing an inappropriately high BIS number for the aaMAC being administered, resulting from known EEG characteristics of older adults – the provider attentively and "therapeutically" increases volatile anaesthetic administration. This explanation is less likely because, on average, the age-related decrease in volatile delivery was the same for the BIS-guided and non-BIS groups. Nevertheless it is a salutary warning that we should be aware of, and perhaps tolerate, higher BIS values in individual older patients.

This reflects a grander issue in medicine: that the complex, older, multimorbid, inhomogeneous population that we routinely care for has their care extrapolated from studies of simple, middle-age, healthy, homogeneous adults. BIS may perform perfectly well in a young population, but – based on this work by Ni and colleagues, and by others – its utility in the complex population of older adults is suspect. Ni and colleagues, therefore, have performed a valuable "post-marketing surveillance" task with this publication. Furthermore, their finding also suggests that it may be particularly difficult to justify *decreasing* anaesthetic administration to older adults on the basis of BIS number or EEG characteristics (in the absence of burst suppression). Since some older adults show a systematically higher BIS value and corresponding EEG characteristics while receiving a relative overdose of anaesthetic (greater than that needed to ensure hypnosis), how can an anaesthetic provider confidently reduce anaesthetic dose while a relatively high-frequency, low-amplitude EEG trace scrolls past their eyes?

It is important to remember that the mathematical model used by Ni and colleagues accounts for only about a third of the variation in drug delivery. Some patients may be driving these trends, while other older adults respond as expected to rising anaesthetic doses. A quick glance at

figure 2 shows some patients getting 0.25MAC and some getting 1.5MAC. What were those management decisions based upon? Obviously, other (undefined) factors are driving this variability in hypnotic drug titration. The key to future individualized patient care will lie in the further understanding and unpacking of these factors.

Far from replacing anaesthesia provider judgment regarding anaesthetic dosing, Ni and colleagues provide persuasive evidence that when using a BIS, or raw EEG, in older adults, providers must maintain an even more careful consideration of bias and cognitive availability, clinical scenario, vital signs, and – of course – the EEG, as yet another piece of information to refine our understanding of how our care affects body *and* brain.

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