Geriatric Pharmacology

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KEYWORDS

• Geriatric • Pharmacology • Anesthetics • Aging

KEY POINTS

- Anesthetizing elderly patients requires understanding of the pharmacokinetic and pharmacodynamic changes with aging.
- Practitioners need to recognize the effect of administering multiple anesthetics and their interactions with nonanesthetic medications.
- Neurologic changes with aging can affect anesthesia.
- Older patients show more hypotension and greater hemodynamic lability during anesthesia.
- Elderly patients require much less anesthetic.

INTRODUCTION

The aging process is characterized by a significant level of complexity, which makes the perioperative care of the elderly patients extremely challenging. Typically, elderly patients have multiple morbidities and are often taking multiple medications.[1–3] Polypharmacy is the norm in the elderly.[2] Effects of drug interactions are substantially magnified with advanced age. It is also well recognized that sicker patients require less anesthetic. Frequently, elderly patients also have geriatric syndromes; for example, falls, malnutrition, delirium, and mild cognitive dysfunction.[4,5] Against this background of reduced reserve (frailty), multimorbidity, and polypharmacy, geriatric patients present for surgical and anesthetic care.

Elderly patients require less anesthetic, which is often attributed to progressive pharmacokinetic and pharmacodynamic changes that occur with aging. Although pharmacokinetic changes have been well characterized, the data are typically from healthy elderly patients (American Society of Anesthesiologists [ASA] I/II) or patients who are less than 80 years old.[6] Most of the pharmacologic data are extrapolated to older octogenarians and nonagenarians.

Anesthetizing very elderly patients requires understanding of the pharmacokinetic and pharmacodynamic changes with aging. Practitioners also need to recognize the

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effect of simultaneously administering multiple anesthetics and their interactions with nonanesthetic medications. This article addresses current understanding of mechanisms of general anesthesia, neurologic changes with aging that can affect anesthesia, and commonly accepted pharmacokinetic and pharmacodynamics changes with aging. It also discusses specific commonly used drugs, the impact of combining and overdosing elderly patients, and concludes with recommendations for dosing elderly patients and future areas of research.

CEREBRAL MECHANISMS OF GENERAL ANESTHESIA

Cellular and molecular mechanisms underlying induction of general anesthesia are well understood. All anesthetic agents are similar in decreasing neuronal firing, either through the enhancement of inhibitory currents or the reduction of excitatory currents within the brain.[7,8] Gamma-aminobutyric acid type A ($GABA_A$) and *N*-methyl-D-aspartate (NMDA) receptors in the cortex, thalamus, brainstem, and striatum seem to be the most important targets of anesthesia.[9,10] Activation of these receptor targets of general anesthetics cause either enhancement of inhibitory currents mediated by GABA and glycine protein channels, or reductions of excitatory currents mediated by glutamate and acetylcholine protein channels, and enhancement of background potassium leak currents.[8] Barbiturates, etomidate, propofol, and benzodiazepines target $GABA_A$ receptors, the main inhibitory receptors in the brain, expressed in nearly one-third of all synapses.[9,11] Reduction of excitatory neurotransmitter receptors by anesthetics contributes to inactivation of large regions of the brain, thus resulting in a neurodepressive effect of anesthetics and unconsciousness.[9] Glutamate, the major excitatory neurotransmitter in the brain, activates 2 subclasses of receptors: the NMDA receptors and the non-NMDA receptors, which are further divided into a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid and kainate receptors.[12] The activation of NMDA receptors necessitates binding of glutamate and either glycine or D-serine.[13] Volatile anesthetics, xenon, and nitrous oxide inhibit NMDA receptor activity.[14–16] Xenon has a minimal or no effect on the $GABA_A$ ligand channels. Ketamine inhibits NMDA-mediated glutamatergic inputs with an excitatory activity in the cortex and limbic system, ultimately leading to unconsciousness.[13]

Given that nearly all anesthetics decrease global cerebral metabolism in a dose-dependent manner, it was generally accepted that a general (eg, nonspecific) reduction in metabolism was the common mechanism for producing anesthesia-induced loss of consciousness.[17] However, newer research using electroencephalogram (EEG), functional MRI, and other imaging techniques has shown that unconsciousness is more complicated than simple global depression.[7,13] Different regions of the brain are intricately connected to each other and are constantly communicating with each other. The human brain has a highly organized network of communication pathways between functionally related regions.[18,19] This network is also called connectivity, which executes the basic functions of the brain. Functional connectivity refers to the temporal correlations between different related regions of the brain, linked to functionally related neurophysiologic events. It is this inherent functional connectivity that sustains a conscious state. Various functional networks in the brain have been identified. The default mode network (DMN) is one such network whose function has been explored in many studies.[20] The anterior part of the DMN is the prefrontal cortex. During the process of development, the frontal lobe is the last part of the brain to get myelinated, and during senescence it is the first part where demyelination occurs. It is active in the resting state. In contrast, when a task is being performed there is a decrease in activity in the DMN. The more challenging the task, the greater is the