Best Practice & Research Clinical Anaesthesiology 25 (2011) 355–365

Contents lists available at ScienceDirect

Best Practice & Research Clinical Anaesthesiology

journal homepage: www.elsevier.com/locate/bean

4

Pharmacology in the elderly and newer anaesthesia drugs

Martijn R. Kruijt Spanjer, MD [a], Nicolaas A. Bakker, MD, PhD [b], Anthony R. Absalom, MBChB, FRCA, MD [a,*]

[a] Department of Anesthesiology, University Medical Center Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands
[b] Department of Neurosurgery, University Medical Center Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands

Keywords:
PK/PD modeling
elderly
remifentanil
desflurane
ropivacaine
sugammadex

In developed countries, a growing proportion of patients presenting for anesthesia and surgery are elderly. Despite this, and the fact that aging is known to be associated with alterations in drug pharmacokinetics and dynamics, there is little detailed information about the impact of aging on the pharmacology of commonly used anesthetic agents.

In this review, we discuss existing current knowledge on the physiological changes that occur with age and the way these changes affect the pharmacokinetics and dynamics of anesthetic agents. Also, an overview of up-to-date PK-PD modeling concepts and their usefulness and limitations in modern anesthesiologic practice with respect to the elderly population is given. Finally, newer agents such as sugammadex, remifentanyl, ropivacaine and desflurane are discussed in detail with emphasis on current evidence concerning dosing, safety and efficacy of their use in the elderly.

Introduction

In industrialized countries, major advances in the treatment of common acute and chronic diseases have produced a significant increase in life expectancy. This, combined with lower birth rate figures have resulted in significant changes in population demographics. The elderly represent an increasing proportion of the population, and thus the number of patients suffering from diseases associated with aging, such as cancer and degenerative diseases, is growing rapidly. Finally the advances in medical knowledge and technology have resulted in increasing numbers of surgical and other treatment

* Corresponding author. Tel.: +31 50 3615519; Fax: +31 50 3613763.
E-mail address: a.r.absalom@anest.umcg.nl (A.R. Absalom).

1521-6896/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bpa.2011.06.002

options. These factors have together conspired to produce a significant increase in the number of elderly patients presenting for surgery over the last decades.

Because of their declining physiologic reserves and the associated risk of peri-operative complications, the elderly population presents a unique and challenging problem for the anesthesiologist seeking to provide diligent and patient tailored care. With advancing age, significant changes occur in the pharmacology of the anesthetic agents, usually resulting in significantly more profound clinical effects for any given dose. In general, there is also an increased susceptibility to the side-effects associated with these agents. The underlying reasons for this have not been fully defined. Clinical trials, especially those performed during drug development, often involve a much younger and healthier population, and thus there is a paucity of data on the effect of aging on the pharmacokinetics (PK) and pharmacodynamics (PD) of the anesthetic agents.

Over the last years, a variety of new anesthetic agents have been introduced in anesthetic practice. Sugammadex, remifentanyl, ropivacaine and desflurane are examples of these agents which are now being used more frequently, especially in the elderly. For these agents too, knowledge of the specifics of pharmacodynamics and kinetics in the elderly is scarce.

In this review, a discussion of current knowledge on physiological changes that occur with age and the way these changes affect the pharmacokinetics and dynamics of anesthetic agents is provided. Also, an overview of up-to-date PK-PD modeling concepts and their usefulness and limitations in modern anesthesiologic practice with respect to the elderly population is provided. In addition, the abovementioned newer agents are discussed in detail to summarize current evidence concerning dosing, safety and efficacy of their use in the elderly.

Pharmacology in the elderly

In general, elderly patients may be more sensitive to various agents because of changes in pharmacokinetics (i.e. what the body does to the drug) that may lead to higher concentrations for any given dose, because of changes in pharmacodynamics (i.e. what the drug does to the body) resulting in more pronounced clinical effects for a given plasma concentration, or both.

Pharmacokinetic changes associated with aging

Biometric changes

In general, the volume of distribution (Vd) of a drug, and the plasma concentration resulting from a given dose, are inversely related. When a drug is administered as a bolus or brief rapid infusion, the initial plasma concentration is inversely proportional to the initial volume of distribution (referred to as the central compartment, or V1 in compartmental models). Subsequent concentrations after a bolus, or an infusion, depend on other factors such as metabolism and re-distribution, and so here again the concentration achieved is inversely proportion to the total Vd (in compartmental models Vd is the sum of all the compartmental volumes).

With increasing age, total body water decreases and, therefore, hydrophilic drugs have a smaller Vd and thus a higher plasma concentration compared to the younger population. As a consequence, the pharmacological effect of most drugs will increase. On the other hand, elderly patients tend to have more body fat. As a result, lipophilic drugs will have a higher Vd in the elderly. This may lead to more extensive re-distribution, and a longer elimination half-life of the drug. In general, this will lead to a greater pharmacological effect, especially after repeated or continuous dosing.

Most anesthetic drugs bind to plasma proteins of which albumin constitutes a major proportion. Thus the free fraction and the overall free drug concentration are inversely related to the albumin concentration. Elderly patients often have low albumin concentrations because of their poorer nutritional state. Thus, for example, the free fraction of propofol (which is highly protein bound) can be significantly higher in the elderly. Although the free fraction of a drug is considered to be the active fraction, the overall clinical relevance of the changes in albumin concentration is unclear, and may be irrelevant, since drug elimination also increases when the free drug concentration is enhanced.