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Geriatric Anaesthesiology

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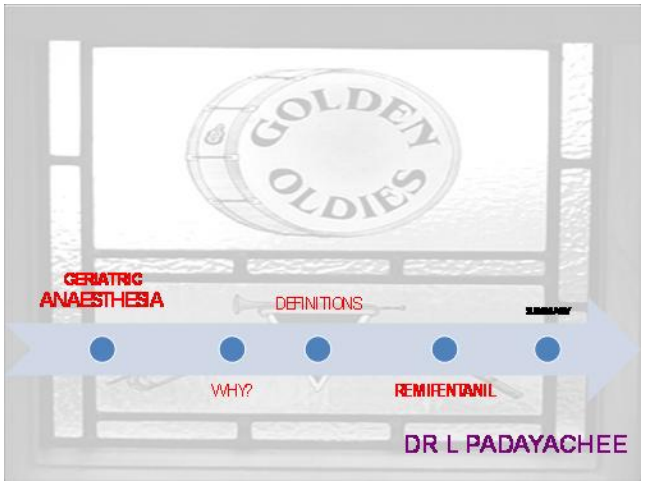

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GERONTOLOGY

Geriatric Anesthesia

Increased life expectancy and reduced mortality from chronic age-related disease continue to enlarge that fraction of the surgical patient population considered elderly. These apparently beneficial demographic changes have further amplified the societal impact of the increasing per capita health care costs that already represent a formidable fiscal burden for modern societies. As they age, adult patients also exhibit an increasingly complex array of unique physical responses to environmental and socioeconomic conditions and to concurrent disease states. Survival to adulthood and beyond permits the full expression of even the most subtle genetic differences between individuals, differences that might not be fully apparent over shorter life span intervals. People are never more alike than they are at birth, nor more different or unique than when they enter the geriatric era. Precise assessment and appropriate peri-operative management of the elderly surgical patient represents a great challenge to all medical health care providers.

Surgical procedures in the elderly will continue to require a disproportionately large share of societal and institutional health care resources. Routine postoperative hospitalization and intensive care, especially after major trauma, are frequently protracted and may be further complicated by infection, poor wound healing and by multiple organ system failure for critically ill elderly patients. Of equal concern are recent findings that postoperative cognitive dysfunction may persist at least three months after otherwise uncomplicated surgery.

Although they represent only 12 percent of the United States population, individuals 65 years of age or older undergo almost one-third of the 25 million surgical procedures performed annually, and they consume about one-third of all health expenditures and fully one-half of the $140 billion annual U.S. federal health care budget. Therefore, every anesthesiologist in contemporary practice eventually becomes a subspecialist in geriatric medicine, with a special responsibility for delivering cost-effective health care to older adults.

In its broadest sense, gerontology refers to the study of aging.[1] Biogerontologists usually limit their scope to the physiological and biochemical, rather than the socioeconomic, aspects of aging. Although many gerontologists study human aging exclusively, others have extended their interests to a cellular or subcellular level and therefore this discipline may encompass the study of nonhuman organisms. In contrast, *geriatrics*, a term with origins early in this century, is more specific because it describes the medical subspecialty that focuses upon care of the elderly patient.[2] Geriatricians are physicians who specialize in the care of the elderly patient.

Studies of human aging have been further complicated by difficulties in discriminating clearly between aging itself and the consequences of age-related disease and cohort-specific effects that make data from cross-sectional studies ambiguous. *Cross-sectional studies* measure physiologic parameters simultaneously in young and in elderly subjects. **Therefore, changes due to undiagnosed age-related disease may be erroneously attributed to age itself**. Similarly, this experimental design cannot be controlled for cohort-specific factors such as nutritional and environmental history, genetic background or prior exposure to infectious agents. Consequently, data from cross-sectional studies rarely permit unambiguous conclusions regarding the effect of age itself on any one measured physiologic parameter. Many of the "classic" cross-sectional studies of aging in the gerontologic literature must be reconsidered.

Some biogerontologists feel that processes of aging can be unequivocally identified only when a *longitudinal study* is used to supplement carefully performed cross-sectional studies. For some measurements such as glomerular filtration, data from longitudinal studies have validated the results of earlier cross-sectional investigations. However, longitudinal studies of human aging require an arbitrary chronological "starting point" for the geriatric era that may change significantly during the duration of the study itself because of increases in life expectancy. They also have intrinsic sources of error. In addition, the validity and utility of the data they generate are subject to the evolution or revision of physiologic concepts and measurement techniques over the long time period required to study human aging.

Processes of aging are usually distinguishable from age-related disease by the fact that they are universally present in all members of an elderly population and, in longitudinal studies of aging subjects, become progressively more apparent with increasing chronological age. Aging is a *universal and progressive* physiologic phenomenon characterized by degenerative changes in both the structure and the functional reserve of organs and tissues. It produces many physical manifestations due to reduced connective tissue flexibility and elasticity or the degeneration of highly structured molecular arrangements within specialized tissues. At the tissue level, cross-linking, glycosylation, or similar dysfunctional interactions occur. The difference between maximum capacity and basal levels of function is *organ system functional reserve*, a "safety margin" available to meet the additional demands imposed by trauma or disease, or by surgery, healing and convalescence. Cardiopulmonary functional reserve, for example, can be quantified and assessed clinically using various exercise or maximal stress tests. However, there is at present no comparable approach to assessment of renal, hepatic, immune, or nervous system functional reserve. It is simply assumed that the functional reserve of these organ systems is reduced in elderly patients and that this is the mechanism by which the obvious susceptibility of elderly patients to stress- and disease-induced organ system decompensation occurs.

CONCEPTS OF AGING

Life span is an idealized, species-specific biologic parameter that quantifies maximum attainable age under optimal environmental conditions. Historical anecdote suggests that human life span has remained constant at 110 to 115 years for at least the past 20 centuries.[7] In contrast, *life expectancy* describes an empirical estimate of typical longevity under prevailing or predicted circumstances. Advances in medical science and health care have improved life expectancy dramatically in industrialized societies and increased their relative "agedness" but do not appear to have altered human life span. The mechanisms that control the aging process and determine life span remain unknown. Perhaps because gerontology is a relatively new discipline, theories of aging have been presented from various individual perspectives, many without any logical interconnection or relationship.

In general, however, theories of aging fall into two major categories. One group can be described as stochastic because it is essentially time- and probability-dependent. The nonstochastic group includes those theories proposing that there are programmed or predetermined mechanisms that explain aging. Nonstochastic theories of aging share a common theme of a "biological clock" or "life pacemaker" for each species.[8] In order to effect processes of aging throughout the organism, the pacemaker tissue or organ must itself have widespread interaction with all other organ systems. Therefore, this type of theory usually involves a neuroendocrine or immune mechanism.

The "error-catastrophe" theory of aging is a stochastic concept. It postulates that random errors of protein synthesis due to faulty nucleic acid transcription or translation eventually accumulate to compromise cellular function and produce the physical signs of aging. However, there is little evidence that the individual cells of older subjects contain more defective protein than do young cells. This theory also fails to explain the dramatically different patterns of aging that are seen in various animal species that share a common ecosystem and are exposed to similar catabolic environmental forces such as ionizing radiation. Similarly, a "genetic wear and tear" theory of aging proposes that recurrent damage to nuclear deoxyribonucleic acid (nDNA) eventually exhausts intrinsic intracellular capacity for nuclear chromosomal repair, leading to a critical loss of functioning cellular and tissue elements. Although there is a general correlation between species longevity and DNA repair capacity, there is no firm evidence that the ability to recover from random nDNA damage is, in fact, progressively or universally compromised in older human subjects.[9]

However, investigations of oxidative phosphorylation in aging mitochondria suggest that progressive increases in the incidence of defects within mitochondrial DNA (mDNA) may lead to a decline in bioenergetic capacity and a progressive reduction in the efficiency with which free radical species such as superoxide, routinely produced in the mitochondria during aerobic metabolism, are scavenged from the cytosol of aging cells.[10] Free radicals damage the unsaturated fatty acid and nucleic acid components of cells and cross-link protein molecules, eventually damaging cellular microarchitecture.[11] Superoxide dismutase appears to be the most important endogenous enzymatic scavenger of free radical species and, in

fact, it is present in higher concentrations within human cells than in the cells of species with a shorter life span. A relatively recent proposal suggests that cellular aging is due to a "vicious cycle" of diffuse bioenergetic failure in the mitochondria of metabolically-active tissues.[12] This mechanism, which may be thought of as progressive failure of a genetically-determined capacity to clear random damage to mDNA by free-radicals, is compatible with both stochastic and nonstochastic theories and falls within the larger evolving concept that aging is a consequence of a lifetime of "oxidative stress."

PHARMACOKINETIC AND PHARMACODYNAMIC DIFFERENCES IN THE ELDERLY

Pharmacokinetic variables determine the relationship between the dose of a drug administered and the concentration delivered to the site of action. Pharmacodynamic variables determine the relationship between the concentration of the drug at the site of action and the intensity of the effect produced. Physiologic changes occur during aging that impact on the pharmacokinetic and pharmacodynamic responses of elderly patients to administered drugs. For example, changes occur in plasma protein binding, the percentage of body content that is lipid or lean, the efficiency of metabolism and elimination of drugs and in the elderly patient's sensitivity to administered drugs, an effect due to pharmacodynamic changes. Each of these physiologic changes will be discussed.

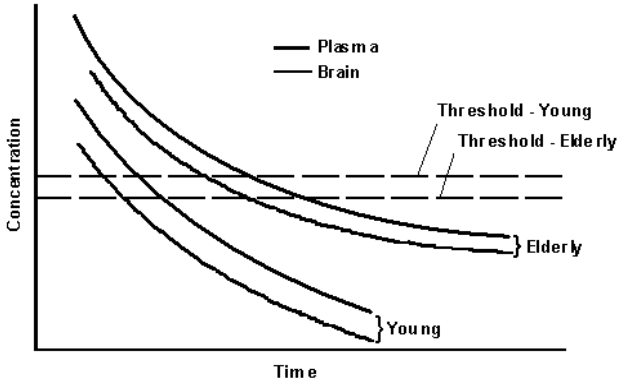


Figure 1. Hypothetical response of young and elderly subjects to a bolus administration of a drug.

The figure illustrates higher blood levels in the elderly, initially due to a smaller volume of distribution, and later due to a slower drug metabolism. Furthermore, in this example, the brain is more sensitive to the drug in the elderly. All these effects conspire to increase the length of time that the drug is active in the elderly patient.

Protein Binding

All anesthetic agents are to some extent protein-bound to plasma proteins. The portion of the drug that is bound to protein is unable to cross membranes to produce the desired drug effect. On the other hand, the portion that remains free in plasma is able to cross membranes, including the blood brain barrier, and is responsible for drug effect. In the elderly, protein binding of anesthetic drugs is less efficient resulting in an exaggerated pharmacologic effect.

Four factors may explain the reduced drug-binding to serum protein in elderly individuals. First, with aging, the circulating level of serum protein, especially albumin, decreases in quantity, reducing available protein-

binding sites for a variety of anesthetic drugs. Second, qualitative changes may occur in circulating protein that reduces the binding effectiveness of the available protein. Third, co-administered drugs may interfere with the ability of anesthetic agents to bind to available serum protein binding sites. Fourth, certain disease states exaggerate this phenomenon. Thus, anesthetic agents that are highly protein bound should be delivered to an elderly individual with the expectation that reduced protein binding will lead to higher free drug levels and an enhanced delivery of the drug to the brain. Figure 1 illustrates the effect of decreased plasma protein binding as a smaller difference between brain and plasma drug levels in the elderly than in young adults.

Change in Body Compartments

Important age-related changes in body composition include a loss of skeletal muscle (lean body mass) and an increase in percentage of body fat. These changes are more exaggerated in women. In addition, it has been suggested that a 20-30 percent reduction in blood volume occurs by age 75. Therefore, injection of anesthetic drugs will initially be dispersed in a contracted blood volume in the elderly patient producing a higher than expected initial plasma drug concentration. (See Fig. 1)

The increase in percentage of body fat that occurs with age results in an increased availability of lipid storage sites and a greater reservoir for deposition of lipid-soluble anesthetic drugs. The greater sequestration of anesthetic agents in the lipid storage tissues of the elderly allows for a more gradual and protracted elution of anesthetic agents from these storage sites, increasing the time period required for their elimination and resulting in greater residual plasma concentrations of drugs that contribute to prolonged anesthetic effects.

Hepatic and Renal Function

Hepatic and renal function are reduced about one percent per year beyond age 30. The age-related reduction in renal blood flow is accompanied by a gradual loss of functioning glomeruli. The combination of these changes produces a predictable decline in glomerular filtration rate that in old age is only 60 percent of that found in younger individuals. These renal changes result in a reduced ability of an elderly patient to excrete administered drugs and their metabolites. The combination of reduced hepatic and renal elimination and more protracted elution of drug from lipid stores contribute to the more gradual fall in plasma-drug concentration in the elderly depicted in Figure 1, and reflected in the table below as an age-related change in the beta elimination half-life of many of our administered anesthetic agents.

T 1/2 b ö Elimination Half-life

Drug	Young Adults	Old Adults
Fentanyl	250 min	925 min
Alfentanil	90 min	130 min
Diazepam	24 hrs	72 hrs
Midazolam	2.8 hrs	4.3 hrs
Vecuronium	16 min	45 min

(Return of twitch height from 25 percent to 75 percent of control)

Central Nervous System (CNS)

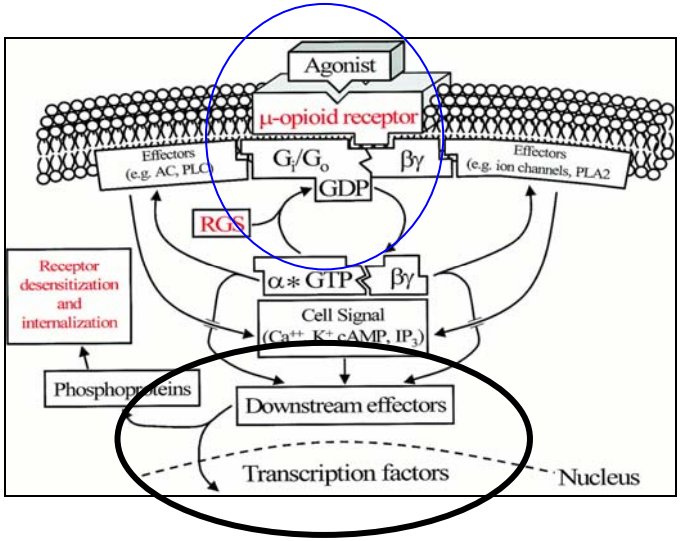
Classically, it has been thought that the physiologic function of most organs, including the central nervous system, undergoes a gradual decline during the aging process. There is a continual loss of neuronal substance with advancing age. On average, a daily attrition of perhaps as many as 50,000 neurons from an initial neuron pool of approximately 10 billion occurs during the life span of an individual. The reduction in neuronal density that occurs

with age is accompanied by a parallel reduction in cerebral blood flow and cerebral oxygen consumption ($CMRO_2$).[1]

Regional cerebral blood flow remains as tightly coupled to cerebral metabolic activity in the healthy elderly individual as it does in young adults. The absence of a quantitative relationship between age-related brain atrophy (accompanied by reduced cerebral blood flow) and general level of mental function, however, suggests that at the time of maximum brain weight there is considerable redundancy of neuronal function within each cortical, subcortical and spinal region. Although an obligatory age-induced decline in cerebral cognitive function remains controversial, it is generally agreed that geriatric patients have a reduced requirement for anesthetic agents. This may not be distinguishable in any given patient but is observed in cross-sectional studies comparing elderly to younger individuals and is believed to be due, at least in part, to a reduction in pre-existent CNS activity.

A classic example of age-related reduced anesthetic requirement is the reduced minimum alveolar concentration (MAC) necessary in elderly patients to produce anesthesia with either cyclopropane, halothane, isoflurane or desflurane.[2] The requirement for these inhalational agents decreases linearly with patient age. The reduced anesthetic requirement for geriatric patients applies not only to inhalational anesthetics but also to local anesthetics, narcotics, barbiturates, benzodiazepines and other intravenous anesthetic agents. Elderly patients achieve a comparable level of sedation at diazepam plasma concentrations significantly lower than that required in young adults. Equivalent EEG suppression occurs at lower plasma concentrations of both fentanyl and alfentanil in the aged.[3] Similar to narcotics, the induction dose of barbiturates required in 70 year old adults is approximately 30 percent less than that required for individuals four to five decades younger. However, it has been suggested that the greater sensitivity of the elderly to the same dose of thiopental is dependent upon the basis of a reduced initial volume of distribution resulting in a higher plasma concentration following the same administered dose.

OPIATES



Opiates were primarily used as analgesics until approximately 20 years ago, when it became known that larger doses of some agents caused loss of consciousness (more reliably so in the elderly as opposed to young patients). The potent and rapid-acting opiates (fentanyl, sufentanil, alfentanil) can be used as the sole induction agents in cardiovascular surgery where hemodynamic stability is critical. High doses of these analgesics not only produce loss of consciousness, they effectively blunt the blood pressure and heart rate responses to laryngoscopy and intubation. Opioids can be administered in lower doses by intermittent intravenous injections or continuous infusion for maintenance of anesthesia or as adjuvants to inhaled anesthetics.

Fentanyl in doses of 50 to 150 mcg/kg IV are usually necessary to induce unconsciousness. Because the elimination half-life of fentanyl is significantly longer in elderly patients compared to young patients (roughly 945 min and 265 min, respectively), such a dose will produce respiratory depression and analgesia for a long time in the elderly. Transdermal fentanyl has been used for postoperative analgesia; however, because of the increased sensitivity to the depressant effects of opioids in the elderly, the occurrence of respiratory depression with the usual 50-75 mcg/hr dose makes the transdermal patch method of pain control unsuitable in opioid-

naïve elderly patients. Administering 25 mcg of fentanyl with bupivacaine during spinal anesthesia in the elderly significantly decreases pain intensity in the post operative period. The only significant side effect of this was pruritus; respiratory depression occurred only if benzodiazepines were used in conjunction with the spinal fentanyl.

Alfentanil is a very rapid, short-acting synthetic derivative of fentanyl. It has a low pK_a, so much of the drug exists in the nonionized form at physiologic pH and thus readily crosses the blood brain barrier. It has a smaller volume of distribution and shorter elimination half-time in comparison to fentanyl. Alfentanil can be used as the sole induction anesthetic (150 to 300 mcg/kg IV produces unconsciousness in approximately 45 seconds) and, at a continuous infusion of 25 to 150 mcg/kg/hr IV, for anesthetic maintenance in combination with volatile anesthetics. Alfentanil is a good choice for short operative procedures in the elderly because it does not produce sustained postoperative sedation and respiratory depression.

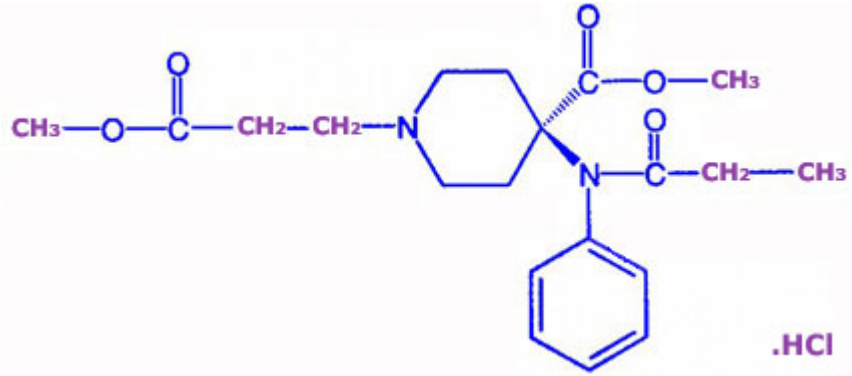
Opioids have a high lipid solubility and therefore a large volume of distribution. Recovery from a single analgesic dose of fentanyl or sufentanil may be rapid, owing to the redistribution from the brain to lean muscle and fatty tissue. However, recovery from a larger dose used for induction tends to be protracted due to the saturation of the inactive tissue sites and to the long elimination half-life of fentanyl and sufentanil (three to six hours). In spite of the high hepatic clearance rate, the elimination half-life is long due to the large volume of distribution. In the elderly, there is a decreased hepatic clearance rate, resulting in even longer half-life of elimination. Thus, a given dose would be clinically effective for a longer period of time. Another potential reason for the decreased requirement of opioids when used in the elderly is an increase in sensitivity of the brain to at least some narcotics with aging.

Lower doses of fentanyl (1 to 3ug/kg), alfentanil (10 to 20ug/kg) or sufentanil (0.125 to 0.25 mcg/kg) are effective adjuvants to thiopental (2 to 3 mg/kg) for induction of anesthesia because they decrease the need for barbiturates and diminish the cardiovascular response to laryngoscopy and intubation.

REMIFENTANIL

Chemical structure of remifentanil

A synthetic anilidopiperidine derivative.



PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Remifentanil is a selective μ-opioid agonist with a rapid onset and very short duration of action. The μ-opioid activity, of remifentanil, is antagonised by narcotic antagonists, such as naloxone. Assays of histamine in patients and normal volunteers have shown no
elevation in histamine levels after administration of remifentanil in bolus doses up to 30 microgram/kg.

Pharmacokinetic properties

Following administration of the recommended doses of remifentanil, the effective biological half-life is 3-10 minutes. The average clearance of remifentanil in young healthy adults is 40ml/min/kg, the central volume of distribution is 100ml/kg and the steady-state volume of distribution is 350ml/kg. In children aged 1 to 12 years, remifentanil clearance and volume of distribution decreases with increasing age; the values of these parameters in neonates are approximately twice those of healthy young adults. Blood concentrations of remifentanil are proportional to the dose

administered throughout the recommended dose range. For every 0.1 microgram/kg/min increase in infusion rate, the blood concentration of remifentanil will rise 2.5 nanograms/ml. Remifentanil is approximately 70% bound to plasma proteins.

Metabolism
Remifentanil is an esterase metabolised opioid that is susceptible to metabolism by non-specific blood and tissue esterases. The metabolism of remifentanil results in the formation of an essentially inactive carboxylic acid metabolite (1/4600th as potent as remifentanil). The half life of the metabolite in healthy adults is 2 hours. Approximately 95% of remifentanil is recovered in the urine as the carboxylic acid metabolite.
Remifentanil is not a substrate for plasma cholinesterase.

Cardiac anaesthesia
The clearance of remifentanil is reduced by approximately 20% during hypothermic (28°C) cardiopulmonary bypass. A decrease in body temperature lowers elimination clearance by 3% per degree centigrade.

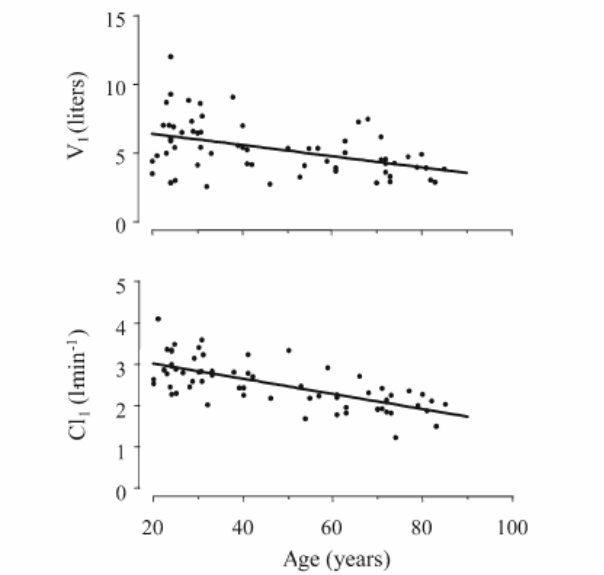
Renal impairment
The rapid recovery from remifentanil-based sedation and analgesia is unaffected by renal status. The pharmacokinetics of remifentanil are not significantly changed in
patients with varying degrees of renal impairment even after administration for up to 3 days in the intensive care setting. The clearance of the carboxylic acid metabolite is reduced in patients with renal impairment. In intensive care patients with moderate/severe renal impairment, the concentration of the carboxylic acid metabolite is expected to reach approximately 100-fold the level of remifentanil at steady-state. Clinical data demonstrate that the accumulation of the metabolite does not result in clinically relevant μ-opioid effects even after administration of remifentanil infusions for up to 3 days in these patients. There is no evidence that remifentanil is extracted during renal replacement therapy. The carboxylic acid metabolite is extracted during haemodialysis by 25 - 35 %.

Hepatic impairment
The pharmacokinetics of remifentanil are not changed in patients with severe hepatic impairment awaiting liver transplant, or during the anhepatic phase of liver transplant surgery. Patients with severe hepatic impairment may be slightly more sensitive to the respiratory depressant effects of remifentanil. These patients should be closely onitored and the dose of remifentanil should be titrated to the individual patient need. Paediatric

patients The average clearance and steady state volume of distribution of remifentanil are increased in younger children and decline to young healthy adult values by age 17. The elimination half-life of remifentanil in neonates is not significantly different from that of young healthy adults. Changes in analgesic effect after changes in infusion rate of remifentanil should be rapid and similar to those seen in young healthy adults. The pharmacokinetics of the carboxylic acid metabolite in paediatric patients 2-17 years of age are similar to those seen in adults after correcting for differences in body weight.

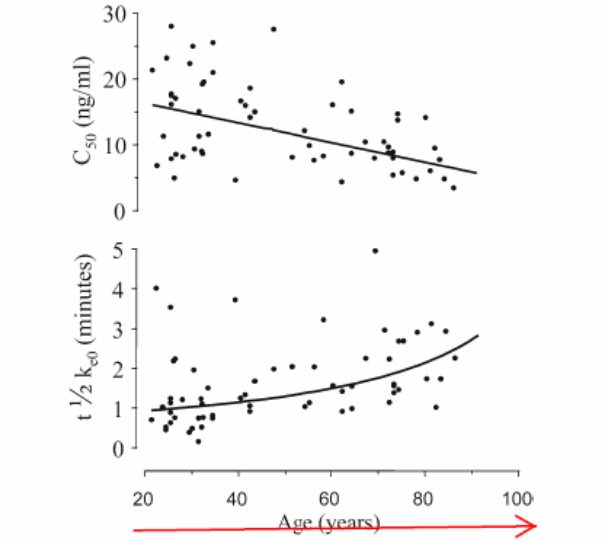
ELDERLY AND REMIFENTANIL
Remifentanil has the fastest and most predictable **metabolism** of any of the available opioids. Remifentanil was introduced into clinical practice under Food and Drug Administration guidelines that mandated explicit pharmacokinetic and pharmacodynamic analysis for special populations, including elderly subjects. Thus, the influence of age on remifentanil pharmacokinetics and pharmacodynamics was established in high-resolution trials about 3 times larger than the trials for fentanyl, alfentanil, or sufentanil. The pharmacokinetic and pharmacodynamic models for remifentanil were reported by Minto and colleagues. In a companion article, Minto et al. used computer simulation to examine the implications of the complex age-related changes on remifentanil dosing. The pharmacokinetics of remifentanil change with age, as shown in figure a.

Figure a.



The influence of age on remifentanil pharmacokinetics. With advancing age, the volume of the central compartment decreases by 50% from age 20 to age 80, and the clearance decreases by 66%. (Adapted with permission from Minto et al.[64])

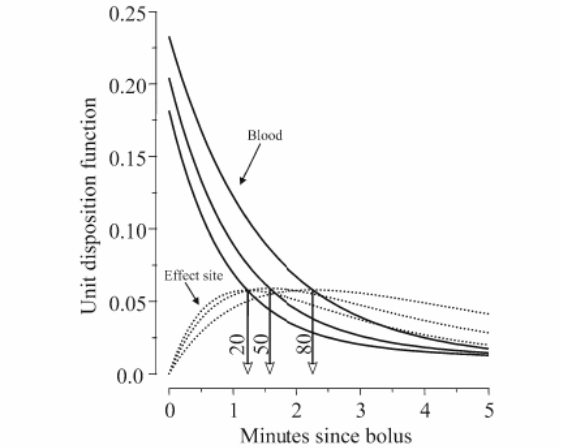
With advancing age, V1, the volume of the central compartment, decreases about 20% from age 20 to 80. Concurrently, clearance decreases about 30% from age 20 to age 80. Figure b. shows the age related changes in remifentanil pharmacodynamics.



The influence of age on remifentanil pharmacodynamics. With advancing age, the 50% effective concentration (EC_{50}) declines, reflecting a nearly identical increase in intrinsic potency as seen with fentanyl and alfentanil. Additionally, half-time of blood–brain equilibration ($t_{1/2}$ k_{e0}) increases. (Adapted with permission from Minto et al.[64])

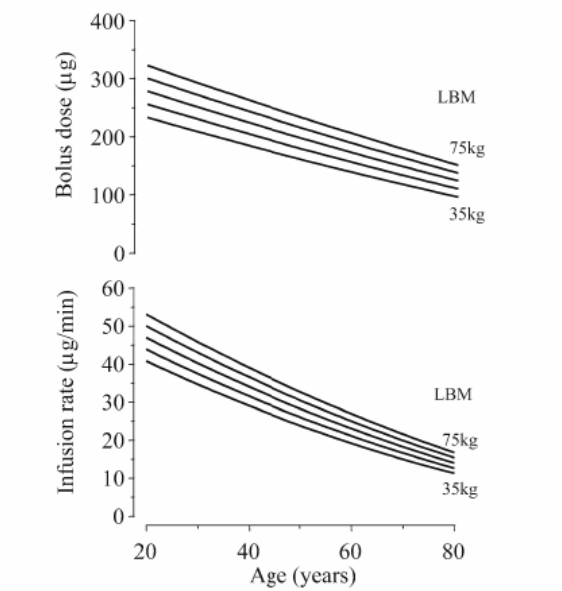
Figure b

As also observed for fentanyl and alfentanil, the C50 for EEG depression is reduced by 50% in elderly subjects, suggesting that remifentanil has about twice the intrinsic potency in elderly subjects as in younger subjects. The t1/2 *k*e0, halftime of plasma–effect-site equilibration, is also increased in elderly subjects. In the absence of other changes, this would mean that the onset and offset of remifentanil drug effect will be slower in elderly patients.



Simulations showing the effect-site concentration from identical bolus doses in a 20-, 50-, and 80-year-old subject. The concentrations are highest in the 80-year-old subject because of the reduced size of the central compartment. However, because of the slower blood–brain equilibrium in the 80-year-old subject, the peak effect-site concentration is almost identical in the three simulations. Thus, the smaller V_1 is offset by the slower plasma–effect-site equilibration. However, a bolus of remifentanil takes about a minute longer to reach peak effect-site concentrations in elderly subjects. (Adapted with permission from Minto et al.[139])

Figure c. uses computer simulations to examine the time course of blood concentration (solid lines) and effect-site concentration (dashed lines) after a unit bolus of remifentanil. The blood concentrations are higher in elderly subjects because of the smaller central compartment concentration. However, the slower t1/2 *k*e0 in elderly subjects results in less-rapid equilibration. As a result, the effect-site concentrations in elderly individuals do not increase higher than the effect-site concentrations in young individuals. However, the onset and offset are slower in elderly individuals. For example, in a young individual, the peak drug effect is expected about 90 seconds after a bolus injection. In an elderly individual, the peak effect is expected about 2–3 minutes after bolus injection.



The influence of age and weight on remifentanil bolus dose and infusion rates. Bolus doses should be reduced by 50% in elderly subjects, reflecting the increased brain sensitivity. Infusion rates should be reduced by 66%, reflecting the combined effects of increased brain sensitivity and decreased clearance. LBM = lean body mass. (Adapted with permission from Minto et al.[139])

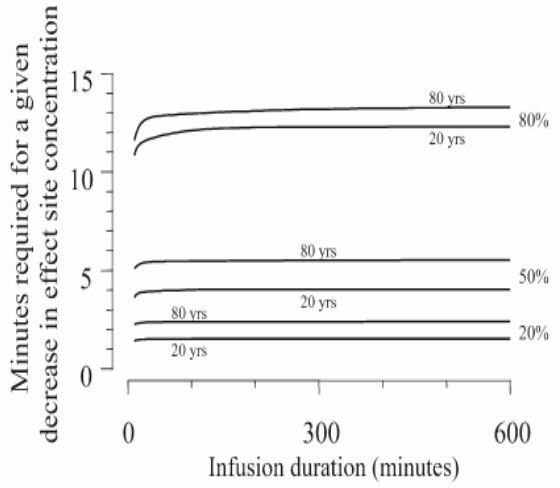
Figure d shows the influence of age and weight on remifentanil dosing. As seen in the top graph of Figure d, elderly subjects need about half of the bolus dose as younger subjects to achieve the same level of drug effect. This is not because of the change in pharmacokinetics.

As shown in Figure c, the peak effect-site levels after a bolus of remifentanil are nearly identical in young and elderly subjects. Rather, the remifentanil bolus is reduced in elderly subjects because of the increased sensitivity of the elderly brain to opioid drug effect, exactly as reported for fentanyl and alfentanil. The bottom graph in Figure d shows that elderly subjects require about one third as rapid an infusion as younger subjects.

This refl ects the combined infl uences of the increased sensitivity and the decreased clearance in elderly individuals.

As seen in Figure d, the infl uence of weight on remifentanil dosing is considerably less than the infl uence of age. This is pointed out because anesthesiologists refl exively adjust remifentanil infusions to body weight,

but seem reluctant to make an adequate reduction in infusion rate for elderly individuals.



4. The 20%, 50%, and 80% effect-site decrement curves for 20- and 80-year-old subjects. Provided remifentanil dose is adequately reduced, as shown in Figure 15-13, there should be little difference in the awakening time as a function of age.

Figure e shows the time required for decreases in effect-site concentration of 20%, 50%, and 80% as a function of remifentanil infusion duration. These would be the “20% effect-site decrement time,” the “50% effect-site decrement time,” and the “80% effect-site decrement time,” respectively. For each decrement time, the expected relationship is shown for a 20-year-old patient and an 80-year-old patient. Figure e suggests that elderly patients can be expected to recover from remifentanil about as fast as younger subjects, provided the dose has been appropriately reduced (e.g., Figure d). The unique features of remifentanil are its rapid clearance and rapid *k*e0, resulting in a rapid onset and offset of drug effect. It is tempting to speculate that these characteristics will make remifentanil an easy drug to titrate and that clinicians will not need to consider patient covariates such as advanced age when choosing a dosing regimen. However, the rapid onset of drug effect may be accompanied by rapid onset of adverse events such as apnea and muscle rigidity. The rapid offset of drug effect can result in patients who are in severe pain at a time when the anesthesiologist is ill-equipped to deal with the problem, for example, when the patient is in

transit to the recovery room. It is thus important that anesthesiologists understand the proper dose adjustment required for the elderly. By adjusting the bolus and infusion doses, the anesthesiologist can hope to avoid the peaks and valleys in remifentanil concentration that might expose elderly patients to risk. When the proper adjustment is made, the variability in remifentanil pharmacokinetics is considerably less than for any other intravenous opioid. This makes remifentanil the most predictable opioid for treatment of the elderly.

Preclinical safety data
Intrathecal administration of the glycine formulation without remifentanil to dogs caused agitation, pain and hind limb dysfunction and incoordination. These effects are believed to be secondary to the glycine excipient. Glycine is a commonly used excipient in intravenous products and this finding has no relevance for intravenous administration of Ultiva.

Reproductive toxicity studies
Remifentanil has been shown to reduce fertility in male rats when administered daily by intravenous injection for at least 70 days at a dose of 0.5mg/kg, or approximately 250 times the maximum recommended human bolus dose of 2 microgram/kg. The fertility of female rats was not affected at doses up to 1mg/kg when administered for at least 15 days prior to mating. No teratogenic effects have been observed with remifentanil at doses up to 5mg/kg in rats and 0.8mg/kg in rabbits. Administration of remifentanil to rats throughout late gestation and lactation at doses up to 5mg/kg IV had no significant effect on the survival, development, or reproductive performance of the F1 generation.

Genotoxicity
Remifentanil was devoid of genotoxic activity in bacteria and in rat liver or mouse bone marrow cells in vivo. However, a positive response was seen in vitro in different mammalian cell systems in the presence of a metabolic activation system. This activity was seen only at concentrations more than three orders of magnitude higher than therapeutic blood levels.

SUMMARY

Aging is an all-encompassing, multifactorial process that results in a decreased capacity for adaptation and produces a gradual decrease in functional reserve of many of the body's organ systems. Aging itself is not a

disease process but instead serves as a reminder of the potential for development of many age-related disease states. There is no ideal anesthetic for all elderly patients. A thorough understanding of the physiological changes that occur with aging and the altered pharmacokinetic and pharmacodynamic responses of the elderly to a variety of anesthetic drugs help in the design of an optimal anesthetic technique for each elderly patient. Appropriate anesthetic management must therefore be based on a thorough medical evaluation preoperatively, with correction, if possible, of any detected abnormality. Intensity of monitoring during and following anesthesia will likely be greater than that selected for younger patients but should be determined on an individual basis taking into consideration the patient's condition and proposed surgical procedure. Because elderly patients are not only pharmacologically but also physically fragile, they require great care during positioning and moving. By offering geriatric patients the safest anesthetic possible, we can contribute to the revolutionary increase in life span of our citizenry and directly enhance their health-span -- the maintenance of full function as nearly as possible to the end of life.

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