▼ Review Article

Management of Postoperative Analgesia in Elderly Patients

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There is a trend toward an increasingly aging population. By 2050, there are expected to be 31 million American citizens over 80 years of age.[1] In the past decade alone, the proportion of the population over 75 has increased from 5.3% to 6.1% in the United States.[1] Given that the elderly undergo surgery 4 times more often than other age groups, anesthesiologists can look to the future and see a time when the majority of our patients will be older than 65 years and many older than 80 years.[1] In a French survey of anesthesia in 1996,[2] the most important finding concerned the major increase in the level of in anesthetic activity. It was found that the number of anesthetic procedures performed annually had increased by 120% since 1980, the major changes being observed in patients over 75 years of age (>200%) and in those with an American Society of Anesthesiologists' status 3 (>270%). Although the incidences of perioperative anesthesia-related events and complications increase with age and American Society of Anesthesiologists score,[3] we still have to anesthetize these elderly patients and treat their postoperative pain.

Pain is underestimated in the postoperative period,[4] and some authors consider that elderly patients who have a higher pain threshold are more sensitive to the effects of analgesics and/or need fewer analgesics in the perioperative period. Inadequate analgesia results from the lack of assessment of the effectiveness of treatment, unfounded concerns about the risks of opioid-related adverse effects or opioid addiction, and poor education of medical and nursing staff leading to an inadequate knowledge of the drugs used. More than 30% of drugs are used by elderly patients, and only 5% of elderly patients take no drugs at home. Polypharmacy is an important problem in the elderly, and the risk of pharmacokinetic and pharmacodynamic interactions between analgesics and the intercurrent treatment of the patient is high.

Pharmacodynamic and Pharmacokinetic Changes

The number of receptors present in a given tissue and/or the affinity of these receptors for neurotransmitters decrease with aging. Thus, elderly patients are more sensitive to the effects of benzodiazepines and opioids.[5] Also, physiological and homeostatic impairments in elderly patients may affect drug responses. These include autonomic nervous system dysfunction, impaired thermoregulation, and reduced cognitive function reserve.[6] The loss of efficiency of homeostatic mechanisms puts the elderly at risk of symptomatic orthostatism, falls, or delirium after the administration of sedative drugs or regional anesthesia. Pharmacodynamic interactions may occur with synergistic effects when taking more than 1 sedative or anticholinergic agent, resulting in delirium, deep sedation, urinary retention, or constipation. Most drugs administered orally are absorbed via the process of passive diffusion, which is unchanged. A few agents require active transport for absorption, and their bioavailability may be reduced as a function of aging. Of more significance is the decrease in first-pass activity at the intestinal wall and/or hepatic extraction that occurs with aging, resulting in an enhancement in systemic bioavailability for drugs such as morphine.[7,8] The decrease in lean body mass and the increase in adipose tissue that occurs with aging can change the distribution of drugs.[8] Fat-soluble psychoactive drugs, such as diazepam or fentanyl, have an increased volume of distribution, whereas drugs that are water soluble have a decreased volume of distribution. A decrease in serum albumin concentration (which binds acidic drugs) can lead

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to a reduction in the degree of plasma protein binding of drugs and an increase in the free or unbound drug in the plasma, as in the case of naproxen.[9] Alpha-1 acid glycoprotein, which binds basic drugs like lidocaine, remains the same or rises.[10] The overall result is a reduction in the drug-free action. Drugs are metabolized by 2 types of reactions: phase 1 (oxidative reactions) and phase 2 (hydrolysis, reduction, glucuronide conjugation). There is an age-related decrease in phase 1 metabolism with reduced total body clearance and increased terminal disposition half-life of some benzodiazepines and nonsteroidal anti-inflammatory drugs (NSAIDs). On the other hand, the phase 2–type reactions are not significantly affected by the aging process.[8] Moreover, an age-associated decrease in hepatic blood flow can reduce the clearance of high hepatic extraction ratio drugs such as several opioids or lidocaine.[11] Finally, there is a reduction in renal function with age with a decline in renal mass and an associated reduction in the number of functioning nephrons.[12] The progressive reduction in the functional capabilities of the kidney with age leads to a significant decrease in the renal clearance of various agents such as opioids and their metabolites,[13] but changes in renal clearance of drugs can be both age related and because of illnesses that occur more commonly in older persons (Table 1).

Physiological Changes

Aging is characterized by a failure to maintain homeostasis under conditions of physiological stress. This failure is associated with a decrease in viability and an increase in vulnerability. Physiologic changes associated with aging are progressive, but concomitant injury or diseases may rapidly worsen the health status of the patient (Table 1).

Peripheral and Central Nervous System. Aging decreases neuronal and neurotransmitter density and activity (within active nuclei of the cholinergic and dopaminergic systems) and decreases the number of neurotransmitter receptor sites. There is a decline in sympathetic response secondary to a significant decrease in the rate of synthesis of neurotransmitters. There is an age-dependent reduction in β-endorphin content and GABA synthesis in the lateral thalamus[14] and a decline in the concentration of gamma-aminobutyric and serotonin receptors.[15] Moreover, aging induces changes in all forms of perception, including vision, hearing, touch, sense, and proprioception. These changes result in difficulty in understanding, such as pain management methods like patient-controlled analgesia (PCA), communication such as pain assessment, and sensory and motor function such as perception of regional anesthesia. Cognitive impairment increases with aging and may be aggravated by pain or pain medications. Moreover, other causes like uncorrected anemia, lack of hearing aid in case of a hearing loss, retention of urine, or bladder dysfunction may be responsible for cognitive dysfunction in the postoperative period. Nerve conduction secondary to neurogenic atrophy and loss of peripheral nerve fibers is slowed. There is an age-related decrease in the capacity or speed of processing of nociceptive stimuli. C and Aδ fiber function decreases with age.[16,17] A corresponding deterioration of electrical conduction occurs along motor pathways. Peripheral motor nerve conduction velocity decreases by approximately 0.15 m/s/y.[13] Although neurons in sympathoadrenal pathways undergo attrition and fibrosis, plasma levels of catecholamines are higher in the elderly patient. However, this situation may not be clinically apparent because they are masked by the decreases in the age-related autonomic responsiveness. The autonomic nervous system is less tightly self-regulated. Anesthetic techniques such as spinal or epidural anesthesia that induce a rapid loss of sympathetic activity are more likely to produce hypotension in elderly surgical patients than in young patients.[13]

Many studies have focused on the age-related pain threshold changes.[18-25] The majority of these studies suggests that there is an increase in pain perception threshold, but most of the work has been methodologically weak.[26] Moreover, age differences in pain may be dependent on the pain sale used.[27] Aging has been reported to be associated with an increased heat pain threshold[28] or not,[29-31] with an increased mechanical pain threshold[32] or not,[22,24] and an increased electrical pain threshold[33] or not.[34,35] According to Gibson et al.,[14] the threshold for pain seems to be increased in older people when stimuli are briefer, of a lesser spatial extent, and at peripheral cutaneous or visceral sites. Helme et al.[36] assessed the methodological factors contributing to variations in experimental pain threshold and found that the elderly have an increased threshold for thermal and electrically induced pain if the stimulus duration is kept short.[36] At the opposite, age-related increases in pain report may be more apparent when stimuli are very intense and/or persist for longer periods.[14]

Cardiovascular Function. Fifty percent to 65% of elderly patients have cardiovascular disease, and coronary artery disease has been found in completely symptom-free septagenarians.[26] The biggest change in the cardiovascular system is the decline in cardiac output of about 1% per year after the age of 30 years.[37] Aging makes the patient's heart volume dependent and volume tolerant. Small

Table 1. General Considerations of Pharmacologic Changes and Their Consequences in the Elderly

Characteristics	Elderly Versus Young Patients	Consequences/Recommendations
Pharmacokinetic changes	Main changes	
Oral absorption	No change except if achlorhydria (↗ absorption) or prolonged gastric residence (↗ delay of absorption)	
Distribution	Increased Vd (lipophilic agents) decreased Vd (hydrophilic agents) alterations in protein binding	Increased risk of drug accumulation. Vulnerability to cumulative drug effects, drug adverse effects, interactions between drugs
Metabolism	Decreased hepatic clearance: drugs undergoing phase I-type reactions (hepatic microsomal oxidation)	Assess risks of drug interactions (polypharmacy)
	Phase II-type reactions (hydrolysis, reduction, glucuronide conjugaison) are not affected	Reduce doses and/or lengthen time intervals between drug administration
Renal elimination	Reduction of renal function	
	Prolonged t1/2β of drugs and/or metabolites	
Physiological and pharmacodynamic changes		
Nervous system	Cognitive function impairment. Changes in all forms of perception	Difficulties in understanding and communication.
	Decrease in the autonomic responsiveness	Increased risk of hypotension after spinal or epidural anesthesia
		Assess pain (notably to the demented), prevent and treat (without delay) hypotension (spinal and epidural anesthesia)
Cardiovascular system	Increased vascular resistances and arrhythmic propensity, decline in cardiac output and sympathetic response	Increased risk of cardiovascular instability
		Use a slower injection rate and prevent hypovolemia (epidural analgesia)
Hepatic digestive function	Normal physiological functioning of the gastrointestinal tract. Partial change in hepatic metabolism	Reduction in hepatic metabolism for drugs with a high hepatic extraction ratio (opioids, lidocaine)
		Reduce the dose of morphine
Respiratory function	Reduction in total lung capacity, vital capacity, response to hypoxia/hypercarbia	Increased risk of hypoxemia, apnea, and airway obstruction
	Increased ventilation/perfusion mismatch	Morphine titration in PACU and postoperative oxygen if opioid required
Renal function	Decreased in glomerular filtration, tubular excretion, and tubular reabsorption	Reduction in renal metabolism and clearance of analgesics and metabolites (morphine ++)
		Calculate the Cr Cl before prescription of drugs (NSAIDs)
Postoperative pain assessment	Underestimation of pain	Undertreatment of pain with physiologic, quality of life, and economic consequences
	Difficulties in pain assessment	Self-assessment methods +++ (NRS, VRS, or VAS). FPS or other behavioral scales (Doloplus2) in confusional states

NOTE. Some examples of physiologic changes, consequences, and recommendations for postoperative pain management in elderly versus young patients.
Abbreviations: Vd, volume of distribution; T1/2β, half life elimination; PACU, postanesthesia care unit; Cr Cl, clearance of creatinine; NSAIDs, nonsteroidal anti-inflammatory drugs; NRS, numerical rating scales; VRS, verbal rating scales; VAS, visual analog scales; FPS, facial pain scales.

changes in intravascular volume or venous capacitance may induce cardiovascular instability. Hypovolemia or a decrease in sympathetic response following epidural anesthesia may have severe deleterious consequences. In addition, the decrease in cardiac output induces a decrease in hepatic blood flow. Most drugs like opioids have relatively high extraction ratios across the liver. Clearances of opioids would be relatively unaffected by the activity of hepatic enzymes but sensitive to hepatic blood flow. Thus, a 25% to 40% reduction in clearance could be expected secondary to reduced hepatic blood flow in the elderly patient.[38-49] Finally, cardiac output is an important pharmacokinetic parameter, notably after injection of analgesics, for example, with morphine titration in the postanesthesia care unit (PACU). The initial high arterial concentration observed in the first few minutes after injection of an intravenous (IV) bolus dose is a function of this dilution with cardiac output and the kinetics of the first pass of the drug through the lungs. Thus, a 0% to 20% reduction in cardiac output would lead to higher peak arterial concentrations after intravenous administration. The strategy for administration of intravenous medications therefore is to reduce the initial dose and to use a slower injection rate in elderly patients.[40-43]

Respiratory Function. There is a decrease in sensitivity of the respiratory centers to hypoxia and hypercapnia. Furthermore, elderly patients have increased periodic breathing or apnea periods during sleep, which make them more likely to have apnea and airway obstruction in the postoperative period. There is an increased risk of hypoxemia in the PACU that requires prevention with oxygen in the elderly who need opioids. However, the higher incidence of episodic respiration observed in elderly patients given parenteral opioids is now believed to reflect the higher initial plasma concentration of these drugs rather than a true increase in sensitivity to the respiratory depressant properties of the narcotics.[4] Thus, slow intravenous morphine titration is a good way to reduce the risk of overdosage in the PACU.[44,45] Pain after thoracic or upper abdominal surgery is the most important factor responsible for regional impairment of ventilation, ineffective cough reflexes, and decreased ability to sigh and breathe deeply, resulting in atelectasis, hypoxemia, infection, and respiratory failure.[46,47]

Hepatic and Digestive Function. A 1% decline in the cardiac output per year after the age of 30 induces a 0.5% to 1% reduction in the hepatic blood flow with a decrease in the liver clearance.[48] There is also a 1% decrease in liver mass annually.[49] The changes of the hepatic mass and blood flow induce a reduction in hepatic metabolism for drugs with a high hepatic extraction ratio (see Pharmacokinetics section).

The gastrointestinal tract generally maintains normal physiological functioning in the elderly population. Nevertheless, gastric prostaglandin synthesis, bicarbonate, and nonparietal fluid secretion may diminish, making the elderly patient more prone to NSAID-induced mucosal damage. In addition, *Helicobacter pylori* infestation is common in the elderly, and these 2 factors, which seem to act synergistically, may facilitate gastroduodenal ulcer disease in this age group.[50,51]

Renal Function. Renal function is reduced with age.[52,53] There is a decrease in the glomerular filtration rate (GFR, 1%-1.5% per year after the second decade) secondary to decreased renal blood flow (related to arteriosclerotic changes within the cardiovascular system). Total renal blood flow decreases 10% per decade in the adult years.[52] Tubular excretion, tubular reabsorption, renal metabolism, and clearance of medications and metabolites are also affected by aging. However, measurements of serum creatinine remain within normal range despite impaired GFR because the marked reduction in the proportion of skeletal muscle to total body mass imposes a very small creatinine load. Because creatinine levels are based on the catabolism of muscles, the serum creatinine concentration is therefore not a sensitive measure of renal function in the elderly. Furthermore, there is a decrease in the renal elimination of creatinine. A 50% to 75% decrease in the GFR induces only a moderate increase in creatinine concentration.[54] Creatinine clearance gives the most reliable assessment of GFR.

Postoperative Pain Assessment. Pain assessment and pain relief evaluation may present problems arising from differences in reporting of pain, cognitive impairment, and difficulties in measurement. Anxiety; depression; cognitive, visual, or hearing impairment; and social or family isolation associated with aging may also result in differences in the reporting of pain.[40] The elderly patient may see pain as a normal part of aging,[55] and several studies have suggested that elderly patients report lower pain intensity than younger patients.[56,57] Cognitively impaired patients are known to be at greater risk of undertreatment of acute pain.[58] In patients with hip fracture, the authors showed that the cognitively impaired patients received one third the amount of opioid analgesia as compared to cognitively intact patients. The majority of dementia patients were in severe pain postoperatively.[59] Unrelieved pain is a risk factor for the development or aggravation not only of delirium[60] but also respiratory and renal and cardiac dysfunction or failure.[61]

The visual analog scale (VAS) is considered as the

gold standard method for the assessment of chronic and acute pain.[62] Elderly patients have been reported to experience more difficulties with the VAS.[62-64] Using a chronic pain model, Jensen et al.[62] observed that there was a significant correlation between age and incorrect response to the VAS. Using an acute pain model, Berthier et al.[64] showed that patients more than 65 years of age were more likely than younger patients to be unable to give pain scale responses (36% vs 14%, $P < .001$). Success was less frequent with the VAS compared with the numerical rating scale (NRS) or verbal rating scale (VRS).[62,65] However, most of these studies were performed in patients with chronic or perioperative pain but not for the immediate postoperative pain assessment when morphine titration is required because of severe pain.[62,66] Even if the VAS is the most frequently used method, the NRS and the VRS seem to be the preferred scales.[27,62,63,65] In addition, Gagliese et al.[27] observed that age differences in pain scores depend on the scale used. Men undergoing radical prostatectomy were assessed in the postoperative period using 3 pain scales: the McGill Pain Questionnaire, the Present Pain Intensity with 6 words between 0 = none and 5 = excruciating, and the VAS. Scores on the McGill Pain Questionnaire and the Present Pain Intensity suggested decreased pain or improved analgesia with age, whereas the VAS scores was not sufficiently sensitive to detect age differences.[27] Age differences in the postoperative period were better captured by verbal descriptions of pain qualities than nonverbal measures of intensity.[27]

Postoperative Confusional States, Dementia, and Pain Assessment

Postoperative cognitive dysfunction is a common complication after cardiac and major noncardiac surgery in the elderly. Delirium occurs in 5% to 45% of cases.[67-69] The main predisposing factors are older age,[68,70-73] cognitive impairment and preexisting cerebrovascular or other brain diseases,[70-74] depression,[72] low educational level,[68,72] postoperative complications,[68] use of psychopharmacologic drugs,[70] narcotic analgesics just before admission,[71] and hip surgery.[70,72,73] In the same way, dementia affects up to 20% to 30% of patients above 80 years old and represents a major impediment to the evaluation and the management of pain.

In nonverbal patients, the report of pain may be affected by memory impairment of limited communication skills. Patients manifest their pain or other discomfort through nonverbal means including facial expressions, restlessness, agitation, hostility, aggression, body movements, postures, gestures, and vocalizations.[75] According to numerous authors, mildly to moderately cognitively impaired older adults can complete selected pain scales, including the NRS, VRS, and Facial Pain Scale.[76-78] Herr et al.[79] showed initial psychometric properties of the Facial Pain Scale with an elderly sample and suggest that this method was an alternate approach to assess pain intensity in this population. This tool has strong ordinal properties and strong test-retest reliability.[79] Severe cognitively impaired older adults like demented patients may be assessed using behavioral scales. Many behavioral scales are specific of pain (e.g., rubbing the back) and may not be suitable for general postoperative pain assessment. Postoperatively, an observer may assess patients using pictures of different facial expressions but also sleeping disturbance, somatic complaint, psychomotor, and psychosocial impact. Doloplus is a reliable and validated behavioral French scale in the postoperative period in the elderly population.[59,80,81]

Inadequate Pain Relief and Consequences in the Elderly Patient

Pain is treated poorly in older postoperative patients. Approximately 50% to 75% of elderly patients report inadequate postoperative pain relief.[82] Postoperative pain or medications used to treat pain may cause or aggravate postoperative confusion in the elderly.[83,84] Cognitive impairment and age strongly influence the amount of analgesic that nurses administer to older patients after trauma or in the postoperative period.[85-87] Inadequate analgesia can produce unnecessary distress and emotion, depression,[88] and sleep disturbance. Postoperative pain may produce suboptimal mobilization and medical complications (hypercoagulation, development of ileus, respiratory impairment) because of immobility. Cardiovascular consequences of unrelieved pain are an increased heart rate, blood pressure, and myocardial oxygen demand with an increased risk of myocardial infarction. These factors are likely to delay rehabilitation and to increase duration of hospital stay, health care use, and costs.[89,90]

Analgesic Drugs in the Elderly

Morphine and Other Opioids. The mean elimination half life for morphine is 4.5 hours in older patients, significantly longer than the 2.9 hours observed in younger patients (Tables 1and 2). There is a decreased volume of distribution, a 50% reduction in clearance, and a reduction of protein binding.[91] After IV morphine injection, the calculated peripheral compartment morphine concentra-

Table 2. Main Characteristics of Analgesics in the Elderly Compared With Young Patients (Consequences of the Differences and Main Recommendations)

Type of Analgesic	Elderly Versus Young Patients	Consequences and Recommendations
Opioids	Increased brain sensitivity to the effects of opioids	Special care of the medical staff to the analgesic and adverse effects
Morphine	50% decreased Vd and Cl	To encourage titration in the PACU with the same protocol as the youngest (loading dose concept)
	Increase in the free or unbound drug	
	Longer t1/2β	To decrease the total dose of SC morphine in the wards ($-$40% to $-$50%) and to encourage analgesia on request
		No contraindication to PCA (greater pain relief) except refusal, confusion, or inability to understand
		Maximum dose of IT morphine: 100 μg
		Maximum dose of epidural morphine: 3–4 mg
Fentanyl	Increased Vd and delayed Cl	To decrease the dose of fentanyl
	Risk of accumulation and slow release into the blood	Given epidurally, to encourage combination with local anesthetic to reduce the dose of both drugs
Tramadol	Longer t1/2β	To reduce the dose and to increase the interval between doses (>75 years old)
	Increased absolute bioavailability	
Paracetamol	No change in bioavailability and in clearance	No need to reduce the dose
NSAIDs	Increased t1/2β	To reduce the dose ($-$25% to $-$50%) and to increase the interval between doses
	Decreased Cl	
	Increased sensitivity to the effects of NSAIDs	Use depends on the CrCl: contraindication if CrCl $<$ 50 mL/min^{-1}
COX-2 inhibitors	Decrease of apparent oral Cl of valdecoxib (40% higher plasma exposure to valdecoxib)	Dose adjustment is not necessary except if body weight >50 kg and for renal insufficiency
	Increased risk in patients with cardiovascular disease	New contraindication of parecoxib: postoperative pain management after coronary artery bypass surgery
Local anesthetics (LA)	Increased t1/2β	Longer duration of blocks (central and peripheral)
	Decreased Cl	Increased risk of hypotension
	Increased sensitivity to LA	To reduce the dose and the concentration (and the volume of epidural LA)
	Anatomic changes (increased spread in the epidural space)	To encourage combination between LA and opioids: improvement of analgesia and reduction in side effects

Abbreviations: Vd, volume of distribution; T1/2β, elimination half-life; Cl, clearance; CrCl, creatinine clearance; PACU, postanesthesia care unit; SC, subcutaneous; PCA, patient-controlled analgesia; IT, intrathecal; NSAIDs, nonsteroidal anti-inflammatory drugs.

tion is higher for the older group, and this difference is approximately 1.5 hours with young patients. The reported increase in analgesic potency of morphine in elderly patients might be related to this increased peripheral compartment concentration and to a longer duration of action.[92] In the same way, elderly patients have increased brain sensitivity to the effects of opioids.[56,83,93] Doses of opioids administered by all routes must be reduced to take into account the pharmacological specificities linked to age.

Morphine-6 glucuronide is the major metabolite of morphine. This metabolite is also more potent than morphine and induces analgesia and sedation. In elderly patients, notably those with impaired renal function, accumulation of morphine and morphine-6 glucuronide increases the risk of opioid-related adverse effects. Tolerance to side effects (which are common) develops more rapidly than tolerance to analgesic effects, although constipation tends to persist. In addition, age-related pharmacokinetic changes necessitate titration to reduce morphine (or other opioid) accumulation and to adapt to patient's analgesic requirements. Delayed-release opioid agents like oxycodone may be used, but care must be taken to prevent drug accumulation. Sedation should be monitored in the elderly because this is probably the best indicator of early respiratory depression.[94] Obstructive apnea rather than a decrease in respiratory rate is thought to be at least partly related to the use of opioids.[40] Although age was not significantly associated with hypoxemia, notably in the PACU,[94-96] supplemental oxygen may reduce the risk of postoperative hypoxemia and is therefore recommended for at least the first 48 to 72 hours after major surgery.[40] Opioid-induced ileus, constipation, and urinary retention in cases of preexisting prostatic hypertrophy or those undergoing spinal anesthesia are more common and problematic in the elderly and must be monitored in the postoperative period. Increased opioid-related cognitive impairment may also alter relationships between patients in pain and the nurses.

Fentanyl is considered to have 50 to 100 times the potency of morphine.[97] PCA intravenous or transdermal systems using iontophoresis with fentanyl may provide postoperative pain control equivalent to that of standard intravenous PCA with morphine.[98-101] Moreover, PCA fentanyl seems to produce less impairment of postoperative cognitive function compared with PCA morphine among elderly patients.[69] However, fentanyl accumulates in skeletal muscle and fat[102] and then is slowly released into the blood.[103] The clearance is also delayed in elderly.

Mixed agonist-antagonist drugs should be avoided because of a higher incidence of delirium in the frail elderly patient.[104] In the same way, meperidine is not appropriate in the elderly because of the accumulation of its renally excreted active (and deleterious) metabolite, normeperidine, resulting in central nervous system excitation, tremors, and seizures. Methadone must be used with caution because of its long half-life and a risk of accumulation in elderly patients.

Tramadol. This is a centrally acting synthetic analgesic with opioid-like effects, acting through binding to the μ-opioid receptor (with a high affinity) and inhibition of noradrenaline (norepinephrine) and serotonin (5-hydroxytrypatmine) reuptake. The advantage over standard opioids in the elderly is reduced respiratory depression at analgesic dosages. Dose reduction and increased interval between doses may be required after age 75 years. In healthy volunteers over 75 years of age, the $t_{1/2}\beta$ of tramadol is longer than in younger patients and there is a trend toward increased absolute bioavailability with age.[105] Intravenous tramadol combined with morphine,[106] ketorolac,[107] or a combination between oral tramadol and acetaminophen[108] improves quality of analgesia, without additional toxicity. Tramadol is as effective as morphine but often better tolerated with more rapid psychomotor recovery.[109,110]

Paracetamol (Acetaminophen). Paracetamol is a centrally acting prostaglandin inhibitor with little peripheral effects, which unlike the NSAIDs does not affect peripheral cyclooxygenase activity. Paracetamol has no anti-inflammatory effects. It induces a morphine sparing effect (18%-46%) but does not decrease the incidence of morphine-related adverse effects during the first 24 hours after operation.[111] But elderly patients have not been specifically studied. However, in recommended therapeutic dosage, there are few contraindications and paracetamol is usually well tolerated. The most serious adverse effect of acute overdosage of paracetamol is a dose-dependent hepatic necrosis. Care must be taken if there is a preexisting liver disease or a history of heavy alcohol intake. Apart from these situations, there is no consistent evidence on the effect of aging on the clearance of paracetamol, and there may be no need to reduce the dose given in the elderly patient.[112,113]

Nonselective NSAIDs. Nonselective NSAIDs reduce pain and inflammation by diminishing peripheral and/or central prostaglandin production attributed to inhibition of both isoenzymes cyclooxygenase (COX-1 and COX-2). Nonselective NSAIDs, particularly ketorolac, diclofenac, or ketoprofen, enhance pain relief with a potent analgesic

efficacy, induce a sparing effect of morphine, and reduce morphine-induced adverse effects such as urinary retention, nausea, and vomiting and improve rehabilitation.[114,115] They are commonly used to treat postoperative pain, either as the sole agent or in combination with other drugs. However, nonselective NSAIDs cannot generally be used alone for analgesia after major and very painful surgery. They should be combined with opioids or other nonopioid analgesics to enhance analgesia and to reduce the dose of opioids, which should be titrated to the lowest efficient dose needed.[116]

Elderly patients given nonselective NSAIDs are more at risk of gastric and renal adverse effects. Risk factors for NSAID-related gastric injury notably include age >70 years and an NSAID plus aspirin, even at cardioprotective doses.[117] The incidence of gastrointestinal bleeding from NSAIDs is nearly twice as high in patients over 65 as in younger patients,[118] and the use of nonselective NSAIDs is accompanied by a 2- to 5-fold risk of serious complications of peptic ulcer disease, such as hemorrhage or perforation, which increases in the elderly, particularly in women.[119-122] Moreover, the number of medications used increases in proportion to the incidence of illness and disease that occurs with advancing age. NSAIDs can cause pharmacokinetic and pharmacodynamic interactions with other drugs, such as warfarin and low–molecular-weight heparin.[123]

The incidence of their adverse effects depends on the half-life of the agent, which is prolonged in patients with decreased renal function and in the elderly patients.[124] Some NSAIDs with a long half-life may accumulate in the elderly. Agents with short half-lives like diclofenac, ketorolac, or ketoprofen are thus recommended in the postoperative pain management.

Renal failure after nonselective NSAIDs is of particular concern in the elderly, who are more likely to have renal impairment, cardiac failure, or drugs which are potentially nephrotoxic, such as aminoglycosides.[125-127] In the elderly, dosage reduction (25%-50%) and increased time between doses are recommended. An estimated creatinine clearance of less than 50 mL/min is a contraindication to the use of NSAIDs in the postoperative period.[54]

The Royal College of Anaesthetists has reviewed the literature concerning the use of NSAIDs and made recommendations regarding their use in the perioperative period.[128] NSAIDs should be avoided in patients with renal impairment and should be used with caution in the elderly after cardiac, hepatobiliary, renal, or major vascular surgery (grade C).

Selective NSAIDs: Cyclooxygenase-2 Inhibitors. The specific cyclooxygenase-2 (COX-2) inhibitors are the newest class of NSAIDs with reportedly equivalent analgesia compared with conventional NSAIDs,[129] but fewer hemostatic side effects (no modification of platelet function) and less gastric irritability.[130-132] However, COX-2 inhibitors appear to affect renal function in a similar fashion to nonselective NSAIDs, and particular care is required in patients with renal impairment, dehydration, and in frail elderly patients during or after hemorrhagic surgery or those taking aminoglycosides, vancomycin, diuretics, and angiotensin-converting enzyme inhibitors.[133,134] There are other unresolved questions regarding the utility of COX-2 inhibitors for postoperative pain. Does perioperative use of COX-2 inhibitors result in cardiovascular toxicity with hypertension, cerebrovascular accident, or myocardial infarction?[135-137] Do COX-2 inhibitors cause gastrointestinal toxicity in patients at risk?[133] It is known that nonselective NSAIDs can inhibit bone fusion and fracture healing, and COX-2 inhibitors appear also to affect bone formation.[138] Further studies are required to answer these questions, meaning that COX-2 inhibitors should be used with caution in the elderly patient.

Nefopam. Nefopam is a centrally acting nonnarcotic analgesic, probably through inhibition of serotonin and noradrenaline (norepinephrine) reuptake. Nefopam induces a sparing effect of morphine, and some authors report a decrease in the incidence of morphine-related adverse effects.[139-141] Nefopam does not affect platelet aggregation and has no central nervous system depressive effect. Its sympathomimetic action makes nefopam contraindicated for patients with limited coronary reserve, renal failure, prostatitis, and glaucoma. Nefopam causes minor side effects in 15% to 30% of treated patients (mainly nausea, vomiting, sweating, and sedation).[139]

Local Anesthetics. The plasma concentration of local anesthetics depends on the rate of absorption from the administration site, the volume of distribution, and the plasma clearance. Protein binding of lidocaine in the elderly is increased as is the elimination half-life, and there is a reduction in clearance of local anesthetic drugs.[10,11] The effect of age on the plasma concentration of local anesthetics after epidural anesthesia is controversial. Some studies showed that the peak plasma lidocaine and bupivacaine concentrations, the extent of sensory anesthesia, and the area under the plasma concentration-time curves were independent of age.[142] According to other authors, aging is associated with a marked decrease in the clearance and a moderate increase in the terminal half-life of bupivacaine after epidural analgesia suggesting that in older patients more extensive accumulation occurs during

continuous epidural infusion.[143-146] The dose of local anesthetic required to achieve a given sensory level during epidural anesthesia is often perceived to be less with aging, although not all reports describe a linear relationship between dose and age.[144,147] There are also anatomic changes in the epidural space and an increased surface area for absorption of local anesthetic solution and thus a higher plasma peak concentration of lidocaine in comparison with young patients.[144,148] However, longitudinal extradural spread of local anesthetics in the elderly may not be attributed to decreased leakage through the intervertebral foramina.[149]

After a plexus nerve block, the elderly patients have longer durations of complete sensory and motor blockade without local toxicity.[150,151] Duration of complete block is significantly correlated with age. These results possibly reflect the increased sensitivity to conduction failure from local anesthetic agents in peripheral nerves. An increased sensitivity to local anesthetics in older patients can be attributed to the reduced number of myelinated fibers in the dorsal and ventral roots and to increased permeability, which is caused by the deterioration of myelin sheaths.[152]

IV Pain Management in the Operating Room

Except for remifentanil, there is no study about IV morphine titration or loading doses of intravenous morphine in elderly patients receiving conventional analgesia (with sufentanil, fentanyl, or alfentanil) during surgery. These procedures are not recommended in older patients.

Prophylactic analgesia is the rule. Analgesia requirements must be anticipated from the pharmacokinetic properties of the analgesics. Moreover, balanced analgesia is a good way to reduce adverse effects and to increase efficacy. A combination of nonopioid analgesics usually allows reduction of morphine requirements in the postoperative period and improved analgesia by an additive or synergistic action.

Paracetamol increases the subjective and objective pain threshold for more than 4 hours with a maximal increase at 120 minutes.[153] It should therefore be administered during the surgical procedure for maximum efficacy in the PACU. In the same way, nonselective NSAIDs (ketorolac or ketoprofen) and nefopam require 1 to 2 hours to peak after an IV bolus. However, NSAIDs should not be used in patients with hypovolemia or uncontrolled hypotension.

Pain Management in the PACU: Morphine Titration

Postoperative intravenous morphine titration is used to obtain rapid and complete postoperative pain relief. Because of rapid onset of analgesia, small intravenous boluses of morphine permit titration of the dose needed to provide adequate analgesia.[44] In addition, intravenous morphine provides a long-lasting analgesic effect without any plateau, and its pharmacokinetics have been widely described.[154] Whether this titration can be safely administered in elderly patients remains a matter for debate.

On the assumption that titration is performed over a short period in which age-related changes in pharmacokinetics and pharmacodynamics might be less important, a prospective study has been performed assessing the same protocol of intravenous morphine titration in young and elderly patients.[45] When the patients were awake, they were questioned about the presence of pain in the PACU. When the pain rate intensity (VAS) increased to more than 30 mm, IV morphine was titrated every 5 minutes by 2- or 3-mg increments until pain was relieved as defined by a VAS score less than 30 mm. When the patients were asleep, no attempt was made to awaken them and the patients were considered as having pain relief. Morphine titration was stopped if the patients had a respiratory rate of less than 12 breaths/min, an oxygen saturation of less than 95%, or a serious adverse event. When the dose was normalized for body weight, there was no significant difference in the dose of morphine (0.14 mg/kg in the elderly vs 0.15 mg/kg in the young group).[45] The VAS scores were not significantly different in the 2 groups during and at the end of titration. In the same way, pain relief was not different between the 2 groups (Fig 1). The number of morphine-related side effects and the number of sedated patients were not significantly different between these 2 groups.[45] Another study has been conducted to compare postoperative morphine consumption after hip surgery in the PACU and during the first 24 hours postoperatively in young and elderly patients undergoing the same surgical procedure. The results of this study were similar, and there was no significant difference in the VAS, morphine consumption, and morphine-related side effects during initial IV morphine titration.[155] In contrast, in the wards, there was a significant reduction in the dose of subcutaneous morphine over the first 24 hours (−36%) and the dose of subcutaneous morphine was significantly correlated with age ($R = 0.15$, $P < .009$).[155]

The results of these studies are not in agreement

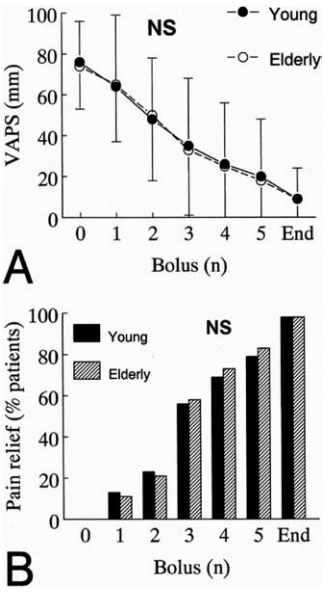

Fig 1. Comparison of (A) the score on the visual analog pain scale (VAPS, mean ± SD) and (B) the percentage of patients with pain relief in young (n = 875) and elderly (n = 175) patients. Pain relief is defined as a score on the VAPS of less than 30 mm. NS, not significant. The result of the initial 5 boluses and the result at the end of morphine titration (end) are shown, but the number of boluses was not limited. (Reprinted with permission.[45]).

with previous studies assessing factors that might influence the dose of opioids required in the elderly in the postoperative period. It should be noted that these studies assessed the variables influencing morphine requirements over a longer time period using PCA and not in the immediate postoperative period using titration.[156]

In conclusion, intravenous morphine titration can be safely administered to elderly patients using the same protocol as that used in young patients. Nevertheless, these results apply only to short-term control of pain in the PACU and not to long-term administration of morphine. However, these results may not apply to a frail elderly population or to patients with severe cognitive dysfunction.

Pain Management in the Wards: PCA

Pain assessment is sometimes difficult in elderly patients particularly because this age group is reluctant to request analgesia. In this situation, PCA provides a finely tuned continuous titration of morphine in analgesic doses.[157] Age-related increases in the analgesic efficacy of morphine have been consistently reported in the postoperative period.[92-158] In comparison with young patients, the elderly obtain greater pain relief in response to a fixed dose of morphine.[56,92] Using PCA, they self-administer less opioid than young patients but report comparable pain relief[156,159] and high satisfaction.[4] Morphine is the preferred drug for PCA because it is a well-known, efficient, and inexpensive agent. Nevertheless, in patients with renal failure, an opioid with no active metabolites, such as fentanyl, might be preferred.[157,160]

Gagliese et al.[159] performed a study to identify factors that facilitate and hinder effective use of PCA. Older patients expected less intense pain and preferred less information about and involvement in their medical management than young patients. There were no age differences with regards to pain at rest or with movement. The older group self-administered less opioid than the younger group. The groups did not differ in concerns about pain relief and adverse effects. Satisfaction with PCA was high and did not differ between age groups.[159] There were several limitations to this study, and the results may not apply to very old patients. Because acutely and chronically confused elderly patients were excluded, these results are only applicable to elderly elective surgery patients with sufficient cognitive ability to understand the use of PCA. Moreover, some patients are unwilling or unable to use PCA effectively.[161]

PCA allows a reduction in the incidence of confusion and pulmonary complications.[4] Egbert et al.[4] compared patient-controlled analgesia and as-needed intramuscular narcotics in frail elderly patients undergoing major elective surgery. This study focused on subjects with multiple systemic illnesses at high risk for elective surgery. PCA resulted in significantly fewer major confusional episodes (2% vs. 18%), fewer major pulmonary complications (0% vs. 10%), and improved analgesia without increased sedation. This observation was also related to earlier mobilization afforded by PCA. Patients who had previously received IM injections described PCA as a better method of analgesia. Narcotic overdose did not occur, and serum morphine levels were significantly less variable in comparison with IM group patients. The same authors showed that the use of PCA was not associated with increased postoperative anxiety or alterations of psychological parameters.[162] According to several authors,[156,163] low incremental doses of morphine (1 mg per bolus) are recommended after morphine titration in the PACU. A lockout interval of 5 or 7 minutes and a maximum permissible hourly or 4 hourly dose seem appropriate. The use of a continuous background infusion of morphine is strictly contraindicated.[157,163,164] The maximum dose per 24 hours and hence the PCA settings may be determined using the formula devised by Macintyre and Jarvis,[156] who showed that age was the most sig-

nificant predictor of postoperative PCA morphine requirement and the average first 24-hour morphine requirements for patients over 20 years of age was 100 − age.[156]

However, PCA does not always provide effective analgesia, and flexibility of the analgesic regimen may be more important than the route of administration. PCA has been compared with subcutaneous morphine administration after total hip surgery.[165] Even if the VAS at rest and with movement was significantly lower in elderly patients using PCA, the clinical significance regarding pain scores was weak and the Mini Mental Status, the morphine consumption, the length of hospital stay, and the incidence of adverse effects were similar in both groups.[165]

In conclusion, PCA is definitely not contraindicated in the elderly and allows great pain relief and high satisfaction. PCA allows also a reduction in the incidence of postoperative confusion but is not recommended in patients such as the frail elderly who have pre- or postoperative cognitive dysfunction or those who are unwilling or unable to use this self-administered analgesic method.

Regional Analgesia

After spinal anesthesia, there is a prolongation in the duration of the blockade in the elderly because of decreased blood flow in the vessels surrounding the subarachnoid space (in patients with arteriosclerosis) and then a decreased vascular absorption of local anesthetic. Intrathecal morphine provides effective analgesia after hip or knee arthroplasty[166] after gynecologic surgery or prostate transurethral resection.[167] However, intrathecal morphine may be associated with dose-related adverse effects like nausea and vomiting, drowsiness, urinary retention, or delayed respiratory depression. A smaller dose of intrathecal morphine may provide effective analgesia and reduce postoperative analgesic requirements while minimizing the incidence of adverse effects in the elderly.[166,168] According to Murphy et al.,[169] 100 μg intrathecal morphine provides the best balance between analgesic efficacy and adverse effects profile in older patients after hip surgery.

After epidural anesthesia, the cephalad spread is often more extensive, which implies that small volumes will be needed to cover the same number of dermatomes in comparison with younger patients.[143,170] There is a progressive occlusion of intervertebral foramina with connective tissue; thus, less local anesthetic escapes through the intervertebral foramina and there is increased spread in the epidural space. Epidural analgesia with a local anesthetic combined with an opioid provides better pain relief and improved postoperative outcome compared with systemic opioids. Continuous epidural analgesia improves early rehabilitation after major knee surgery with lower pain scores at rest and during continuous passive motion and allows greater amplitude of maximum knee flexion compared with the patient-controlled analgesia group.[171] Epidural analgesia after elective colon surgery using combination of bupivacaine and morphine accelerates postoperative recovery of gastrointestinal function, feeding, and time to fulfillment of discharge criteria within a context of a multimodal recovery program.[172] Mann et al.[157] performed a prospective, randomized study to compare the effectiveness on postoperative pain and safety of PCEA and PCA after major abdominal surgery in elderly (>70 years old) patients. Pain relief was better at rest and after coughing in the PCEA group during the first 5 postoperative days. Satisfaction scores were also better in the PCEA group. The PCEA group recovered bowel function more quickly than did the PCA group. Cardiorespiratory complications and the incidence of delirium were similar in the 2 groups.[157]

Epidural analgesia or PCEA using an opioid either alone or in combination with a local anesthetic are major advances in the management of pain after major surgery. However, the risk:benefit ratio of regional analgesia has been shown to be poor in elderly patients. Mann et al.[173] showed that the incidence of episodes of postoperative hypotension after major abdominal surgery was significantly higher in the PCEA group in comparison with the PCA group. The limitations of epidural analgesia concern side effects and, more precisely, respiratory depression, hypotension, or motor blockade that may induce severe postoperative complications.[171-173] The only case of paraplegia observed in a prospective survey of serious complications related to regional anesthesia occurred in an elderly patient. The most probable cause was spinal cord ischemia as a result of prolonged hypotension after epidural and general anesthesia.[174] Nevertheless, in comparison with continuous epidural analgesia, self-adjustment provided by PCEA allows a reduction in analgesic consumption and then a decrease in adverse effects. Moreover, local anesthetic concentrations inducing an optimal balance between pain relief and hypotension or motor blockade are 0.05% to 0.15% bupivacaine and 0.15% to 0.20% ropivacaine.[157] In comparison with PCA, the PCEA technique is only partly patient-controlled and offers a possibility of setting a background infusion. However, the efficacy of PCEA requires patient education and participation.

Upper limb trauma occurs frequently in elderly

patients for whom peripheral nerve blocks are often preferred to general anesthesia. A plexus block allows a longer duration of postoperative analgesia and allows improved rehabilitation and comfort of the patient.[151-175] The limitations of this procedure should be noted. Previous neuropathy is a risk, and vascularization of peripheral nerves is fragile in the elderly. Moreover, consequences of paresis and perioperative compressions are deleterious. The question of whether perioperative cognitive dysfunction is a limitation to nerve blockade remains, as yet, unanswered.

Conclusion

The proportion of the population in the elderly and very old age groups is increasing. These individuals have more illness than younger people and consume a disproportionate share of drugs. Changes in physiology and pharmacology in the elderly are an indication for the wide use of the titration concept in postoperative pain management. Sophisticated analgesic methods, like PCA, regional analgesia, and PCEA, are not contraindicated in the elderly, but pain assessment, evaluation of treatment efficacy, and analgesic side effects should be monitored. Research programs addressing the management of acute and chronic pain should be developed in the elderly population. As in the youngest, protocols in the older population are recommended to avoid undermedication and empirical pain management. The American Geriatrics Society has for several years been developing guidelines for the exchange of information between physicians of many specialties such as general surgery, orthopedic surgery, physical medicine, rehabilitation, and anesthesiology.[102] Research and education about pain management in the elderly patients should be one of the main priorities in medicine worldwide.

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