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PAIN IN ELDERLY HAS BEEN OFTEN UNDERESTIMATED

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ABSTRACT:

The authors surveyed the clinical data and reviewed the literature on the pain management in elderly patients. The conclusion was made that chronic pain in older age is neglected and analgesia is often insufficient. Data for pharmacokinetic and pharmacodynamic characteristics of widely used analgesic drugs are summarized. The authors provide practical guidelines for pain management of elderly people in outpatients departments.

Key words: older age, pain management, analgesic drugs, pharmacokinetics, pharmacodynamics,

Aging is an inevitable component of life. However, there is no overall accepted definition about an elderly individual. One could be determined as old by physical characteristics, e.g. white or gray hair, changes in social activities, having grandchildren, by changes in occupational status (e.g. being retired) by biological characteristics - e.g. age, etc. An adequate definition should probably contain maximum characteristics of such kind. In this context, it could be assumed that the physiological age can have a more significant impact than the biological one. In the last decades, the age range of all societies has changed to a sustained increase towards older population. According to reliable demographic and sociological calculations, the segment of individuals over the age of 65 in industrial societies will increase from 17.5% in 2000 to 36.3% in 2050 [1]. Retrospective studies performed in the period between years 1983-2003, established that the US population over the age of 65 has increased from 11.7% to 12.4%, and the proportion of individuals over 80 increased from 2.4% to 3.5%. The prognosis is that in 2045 the proportion of these age groups will be 20%, and 7.2% respectively [2]. Within the global population, the proportion of the individuals over 65 increased from 6.9% in 2000 to 7.7% in 2009, and in 2050 will reach 16.7%. The proportion of population aged over 80 is dramatically increasing from 1.2% in 2000 to 1.5% in 2009, and in 2050 will increase more, up to 4.9%. These changes are mainly due to the increased life expectancy, which in 2020 for women will be 80.4 years and for men - 79.5 years [3]. There is a dissonance though between these facts and the data that the raised life expectancy does not actually correlate with wholesome living throughout these years [4]. There is an increased complex co-morbidity in the aging population, among which pain of different variety is a frequent symptom. Epidemiological studies indicate that 40-75% of adult individuals complain of chronic pain of various etiology and pathogenesis, with the largest group composed of elderly women [5]. The prolonged pain is most often a consequence of chronic musculoskeletal disorders, osteoporosis with fractures or fissures, metabolic and neuro-degenerative diseases with neuropathic symptoms, etc. The pharmacotherapy of pain syndromes in adults should be consistent with number of factors complicating the application of conventional analgesic approaches. Adult individuals have reduced nociceptive capabilities, i.e. feel less pain, but tolerate strong and continuous pain syndromes more difficult. They suffer with more than one disease, take many medications of different groups, and rarely report alarming symptoms. Their treatment is complicated by the diminished cognitive capacity in many of them or by the neuropathic pain caused by bone or vertebra fractures, diabetes or other chronic diseases. For the evaluation of pain intensity in elderly patients, different approaches should be used - preferably verbal scales with clear definitions, such as: no-pain, weak-, moderate-, middle-, or severe pain on visual, numerical, picture, mimic and other types of scales [1].

PHARMACOKINETICS

Advanced age is characterized by functional and structural changes in organs that are directly involved in drug metabolism. Changes in kidney, liver and gastrointestinal tract lining, reflect on the drug pharmacokinetics in elderly individuals.

1. Absorption

Typical changes taking place with aging are the decreased gastrointestinal motility and splanchnic area blood flow, the reduction in the absorbing epithelium and the decrease of protein's active transport. After the age of 60, decreased gastric secretion and reduced acidity are typical clinical findings in 25% of the patients [6]. When gastric evacuation is delayed and the transportation time is prolonged, the maximum plasma concentration of solid medicinal products received per os is reached later. The time for absorption of liquid medicines, however, remains unchanged. The transdermal absorption of drugs depends on the skin hydration and the condition of subcutaneous fatty tissue. In advancing age, undoubtedly, the hydration of corneal layer decreases, together with the elasticity and thickness of skin and the amount of subcutaneous fat. These structural skin changes enhance the properties of the corneal layer as a barrier for hydrophilic, but not for lipophilic drugs [7]. The absorption of medicines administered per rectum on other hand, depends on the coexisting colon diseases.

2. Distribution

Reduction of muscle mass, increased adipose tissue and decreased body fluid volume are characteristic for advanced age individuals, which inevitably lead to reduction of volume of distribution and an increase in plasma concentration of hydrophilic medicines, requiring decrease of their equi-effective dose. The opposite changes are valid for lipophilic drugs. Their volume of distribution increases, the plasma concentration decreases and the half-life time is prolonged. These changes are prerequisites for the observed accumulation of medications in elderly patients [7]. Malnutrition and decrease of the serum proteins are observed in many elderly individuals, determining the increase in the unbound fraction of medicines. All data above impose the need of careful dosage of medications with small volume of distribution and therapeutic index [8].

3. Metabolism

Convincing clinical research in elderly patients demonstrates a significant reduction in the hepatic parenchyma and blood flow. These structural changes decrease the hepatic clearance of the so called *flow limited* (high clearance) medicines by 60-80% and the one of the so called *capacity limited* (low clearance) medicines by 20-60% [9]. Drug metabolism in phase I (oxidation, reduction, and hydrolysis) is reduced, while the drug metabolism in phase II (acetylation, glucuronidation, and sulfonation) does not change significantly [10].

4. Renal excretion

It is well known that renal parenchyma and tubular excretion are severely reduced in elderly individuals. Glomerular filtration is reduced by 30-50% in patients over age of 80, which determines the accumulation of excreted medications in urine. In these patients, serum creatinine clearance is not informative, because of the combination of reduced glomerular filtration rate, and decreased muscle mass. It is recommended to apply a method taking into account age, body weight, gender, and serum creatinine in them [11]. The characteristic changes in main pharmacokinetic parameters associated with advanced age are summarized on Table 1.

Table 1. Main pharmacokinetic changes in elderly (modified, by Lussier D, Pickering G, 2010)

Parameter	Change	Clinical - laboratory parameters
Absorption	Increased gastric pH Reduced GI tract motility	Changes in weak acids ionization Delayed gastric evacuation: prolonged intestinal transportation of drugs
	Decreased plasma levels of active transporters	Reduced absorption of drugs with active transport (Ca^{2}+, Fe^{C}+, Vit. B)
Distribution	Increased fat tissue volume	Increased volume of distribution of lipophilic drugs (antidepressants, antipsychotics, benzodiazepines)
	Reduced volume of body fluids	Decreased volume of distribution of hydrophilic drugs (acetaminophen)
	Decreased levels of serum proteins	Increased free fraction of medicines (phenytoin, NSAID)
Metabolism	Decreased hepatic blood flow	Reduced hepatic clearance of drugs with high extraction coefficient
	Reduced liver parenchyma	Functional hepatocytes reduction
	Decreased enzyme activity	Delayed oxygenation reaction (Phase I)
Renal excretion	Decreased glomerular filtration	Decreased excretion of medications or metabolites with renal clearance
	Decreased tubular secretion	Accumulation of drugs requiring tubular secretion

PHARMACODYNAMICS

An increased sensitivity to drugs and incidence of adverse reactions are typical pharmacodynamics characteristics for the elderly individuals.

Opioid analgesics

Morphine: The main products generated in morphine hepatic metabolism phase II are derivatives glucuronated at position 3 (M3G) or 6 (M6G). In elderly patients with renal insufficiency, M6G accumulates and passes easily via blood-brain barrier (BBB). This is the reason why morphine should not be administered to adult patients with impaired renal function or dehydration. Morphine is contraindicated in adult patients, high risk of cognitive and / or psychotic adverse drug reactions. Elevated plasma levels and prolonged elimination of morphine after *oral* or *parenteral* treatment in elderly patients are established, as a consequence of delayed hepatic metabolism and renal insufficiency. Clinical data indicates that application of morphine in the postoperative period of surgical interventions for gastrointestinal tract malignant tumors at a dose of 10 mg, s. c., has a strong and long-lasting analgesic effect in adult patients [12]. *Hydromorphone*: Possess a lower affinity to μ-opioid receptors, suggesting that in elderly patients the induced side effects would be weaker and less common. Hydromorphone has pronounced lipophilic properties and hardly passes through the BBB, thus the induced adverse cognitive episodes should be significantly lower [4]. *Oxycodone*: In patients over 70 the half-life of oxycodone and the elimination of noroxycodone are longer, and plasma levels of oxycodone remain high 12 hours after treatment. Clinical data indicates high bioavailability of

oxycodone in such patients after a single administration at a dose of 10 mg, p.o. for the purpose of post-operative analgesia [13]. Currently it is accepted that oxycodone is an opioid analgesic with good tolerability and high efficiency and could be recommended as the first choice for analgesia in elderly patients with moderate to severe pain [14]. *Codeine*: Its analgesic effect is due to the active metabolites of morphine and norcodein. It was found that 15-20% of caucasians have genetic deficiency of CYP2D6. In them, as well as in patients accepting medications like CYP2D6 inhibitors (selective inhibitors of 5-HT uptake) codeine has no effect. Due to the significant adverse effects of codeine it is not recommended for treatment of pain in elderly patients. *Long-acting opioid analgesics (transdermal medicinal products)*: Currently, patient-controlled analgesia (PCA) with opioids is the preferred approach for treatment of prolonged or severe pain. Senile cognitive impairments that are frequently observed in elderly patients complicate the implementation of PCA. In elderly patients with cognitive insufficiency, it is recommended to apply alternative transdermal approaches for initial administration of opioid analgesics, in which an adequate dosage of short-acting opioids have already been implemented. *Fentanyl*: the reduction of muscle mass and subcutaneous adipose tissue decreases the efficiency and impedes the precise dosage of the drug. It is now assumed that transdermal fentanyl formulations are indicated in patients with limited capabilities for treatment with opioids *per os* but with good tolerance to short-acting opioids, and the initial dose in opioid-naive patients should be lower than 12 μg / h. *Buprenorphine*: constitutes a partial ì-opioid agonist and ê-opioid antagonist with high lipophilicity. It is eliminated through the kidneys (30%) and the gastrointestinal tract (70%). Data from a large post-marketing study indicates that the incidence of adverse reactions post-treatment with buprenorphine are equal in young and elderly patients [15]. The medication product should be administered with caution in elderly patients, although it does not violate basic cognitive functions [4]. *Oxycodone*: Results from clinical studies indicate that following transdermal administration of oxycodone, its plasma concentrations are 15% higher in patients older than 65 years than in patients younger than 50. *Methadone*: It possesses high lipophilicity and protein binding capacity, which determines its larger volume of distribution and half-life, ranging from 8.5 to 120 hours. It is recommended to be applied only with great care in clinical settings. *Morphine, hydrophone*: Rare and fragmented pharmacokinetic and clinical studies over the effects of opioid medication products with prolonged release in elderly patients are available. The opinion that these products are not suitable for analgesia in elderly patients, are dominating.

Potentially harmful side effects: The limited physiological reserves and adaptive capabilities in eldely patients are prerequisite for more frequent manifestations of adverse reactions after application of opioid analgesics. An immediate life threatening danger is the opioid-induced *respiratory depression*. In order to avoid such complication a precise titration and dosage of opioids is required. *Impaired body balance* during treatment with opioids is the reason for increase frequency of bone fractures in elderly individuals. Common symptoms during treatment with opioids are *constipation* and *urine retention*, as a result of the increased smooth muscle tone. In such cases conventional symptomatic therapy and rehydration should be applied. In elderly patients, opioids have enhanced *sedative effect*, which in many individuals paradoxically manifests as *delirium*. Upon the risk of developing such adverse drug reactions, the use of oxycodone or hydromorphone, which pass the BBB difficultly, is recommended. Opioid analgesics that should not be applied in elderly patients are: *Meperidine*: metabolizes to normeperidine, an active metabolite with long half-life, accumulating in cases of renal insufficiency, acting as a central stimulant and increasing the risk of seizures. In patients with muscle atrophy can cause an inflammatory reaction after intramuscular injection. *Propoxyphene*: forms active metabolites accumulating in renal insufficiency and causing deterioration of cognitive functions. In many countries its use was banned after reports of suicidal incidents. *Peptazocine*: has a long half-life and easy accumulation. According to the official regulations for treatment of elderly patients, this opioid analgesic is not permitted [16].

Non-opioid analgesics

Nonsteroidal antiinflammatory drugs (NSAID): Conventional and COX2 selective inhibitors are commonly prescribed for musculoskeletal system disorders in elderly patients due to their effectiveness and well clarified toxicity. The most frequent adverse reactions are not attributed to age-related changes, but to the combination of diverse co-morbid pathology with inevitable polypragmasy. Large-scale retrospective studies indicate that NSAID are administered unreasonably often in elderly patients [17]. Treatment with a COX inhibitors and a NSAID can result in ulcerations and gastrointestinal tract bleeding, renal and cardiovascular injuries significantly more frequently in elderly than in younger patients. Due to the increased risk of adverse reactions, the administration of NSAID in elderly patients should be very careful [16]. In topical administration of NSAIDs, no restrictions are imposed.

Acetaminophen (paracetamol): It is recommended as a first line per os analgesia in elderly patients. Administered at a dose of 500-1000 mg, p.o., every 4-6 hours to a maximum daily dose of 4.0 g, paracetamol can extremely rarely cause potentially dangerous adverse drug reactions. The most dangerous paracetamol therapy complication in elderly patients is the liver damage. The potential risk of hepatotoxic effects is higher in elderly patients with depleted hepatic reserves of glutathione - a common finding in elderly individuals with malnutrition, starvation, cachexia, alcoholism [18]. The risk of hepatotoxicity generally increases in elderly patients with hepatic, renal or cardiovascular decompensation, or severe dehydration. The elderly patients are often object of drug polypragmasy. The therapy in such cases may include cytochrome P450 inducers, which enhance the risk of paracetamol induced hepatotoxicity. It is recommended not to combine a Warfarin anticoagulant therapy with paracetamol in high doses, because of the risk of profuse bleeding [4]. *Tramadol*: a synthetic analgesic with central action, with characteristics of both opioid and non-opioid agonist. Doesn't induce potentially dangerous

side effects. Tramadol is appropriate for treatment of elderly patients with moderate to severe pain. Results from clinical trials over the effectiveness of tramadol in post-operative period indicate that the analgesic effect of Tratadol - Acetaminophen combination is identical to the combination between Hydrocodone/ Acetaminophen, but with less adverse reactions [19].

Anticonvulsants and antidepressants

Anticonvulsants: They possess a potent analgesic effect and good tolerance in treatment of elderly patients with neuropathic pain of different etiology and pathogenesis. In such cases, *Gabapentin* and *Pregabalin* are the drugs of choice. They are eliminated primarily by renal excretion, which is reduced in many elderly patients. This requires the therapeutic dose for elderly patients to be lower than the usual ones. In many elderly patients somnolence, impaired body balance, cognitive disorders and peripheral edema have been described [4]. If these symptoms do not resolve spontaneously, dosage reduction is required. *Phenytoin* or *Carbamazepine* should not be used for treatment of neuropathic pain in elderly patients [4].

Antidepressants: The medicines from this group act as highly effective analgesics for mechanism-targeted treatment of neuropathic pain of different etiology (herpes zoster neuropathy, peripheral neuropathy, diabetes, stroke, peripheral nerve trauma neuropathy, HIV infection, etc.) in patients resistant to the trivial analgesic therapy. It should be taken into consideration that in elderly patients the indications for treatment of pain with antidepressants from different subgroups can range from ban on application because of harmful side effects to use as first choice, due to high efficiency and negligible side effects. The Tricyclic antidepressants are of limited use as effective analgesic medicines in elderly patients with neuropathic pain, due to the great number of adverse drug reactions. The analgesic action of this group (Amitriptyline, Clomipramine, Maprotiline, Reboxetine) is combined with adverse vagolytic effects (dry mouth, constipation, urinary retention), cognitive changes (delirium, memory deformation), cardiovascular disorders (orthostatic hypotension, tachycardia).

As we age, hepatic metabolism slows down as the period of half-life of various tricyclic antidepressants may increase 3-4 folds. This group of medicines have a high affinity binding (90-98%) to plasma proteins. In elderly individuals the development of dysproteinaemia is characteristic, with hypoproteinaemia as the most commonly observed feature. As a result, there is a significant increase of the free drug factions' plasma levels. Currently, the view that tricyclic antidepressants are not effective as analgesic drugs in elderly patients dominates. At imperative indications, secondary and tertiary amines might have limited value in treatment of elderly patients with tricyclic antidepressants for neuropathic pain [4]. The selective inhibitors of 5-HT reuptake (Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Vortioxetine) are an acceptable alternative for treating of elderly patients with neuropathic pain. This group of medicines slightly suppress the CYP206, and exert a satisfactory analgesic effect, which the elderly tolerate well. Fluoxetine is the only medication product from this group that shouldn't be administered to elderly patients with neuropathic pain, because of the long half-life that may induce substantial side effects [20]. Some of the most commonly used analgesic medications in elderly patients are presented in Table. 2.

Table 2. Guidelines for pain pharmacotherapy in elderly patients (modified, by Lussier D, Pickering G, 2010)

Group I medicinal product	**Recommended initial dose**
Opioid analgesics	
Morphine	
Parenteral	1.0 - 5.0 mg, (4+, x-x)
Oral	0.5 - 1.0 mg, (4+, x-x)
Oxycodone	2.5 - 5.0 mg, (4+, x-x)
Hydromorphone	
Oral	0.5 - 1.0 mg, (4+, x-x)
Parenteral	0.25 - 0.5 mg, (4+, x-x)
Codein	
Oral	15.0 - 30.0 mg, (4+, x-x)
Parenteral	5.0 - 10.0 mg, (4+, x-x)
Fentanyl	
Transdermal	Not applied in opioid-naive patients
Buprenorphine	
Transdermal	35 μg / h, (o-o)
Non-opioid analgesics	
Acetaminophen (Paracetamol)	325 - 650 mg, (4+, x-x)
NSAID	Individual dosing
COX-2 inhibitors	100 mg, *(2x)*
Anticonvulsants	
Gabapentin	100 - 300 mg, *(1x – 3x)*
Pregabalin	25 mg, *(1 x before sleep – 3x)*

Antidepressants	
Bupropion	75 mg, *(1x)*
Duloxetine	30 mg, *(1x)*
Tricyclic antidepressants	10 mg, *(1 x before sleep)*
Venlafaxine	37.5 mg, *(1x)*

(1 x) once daily, *(2x)* twice daily, *(3x)* three times daily, *(4+)* every 4 hours, (o-o) every 3 days, (x-x) if needed.

In elderly patients with contraindications for systemic administration of analgesic drugs, the neuraxial analgesia should be applied, with analgesics introduced epidurally or intrathecally. This approach minimizes the likelihood of adverse drug reactions development and enables the analgesia to be controlled by the patients themselves.

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