PHARMACOLOGICAL MANAGEMENT OF PAIN IN THE ELDERLY

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Abstract. Pain was originally defined as "a perception of an unpleasant sensory and emotional experience associated with, or described in terms of, potentially actual tissue injury". Pain syndromes have an increased prevalence in elderly patients and they should not be considered a normal consequence of aging, therefore the etiopathogenesis of this syndrome is not easy to establish in the elderly and especially frail people. Care is needed in the selection and administration of analgesics to avoid drug–drug or drug–disease interactions at the elderly. Changes in pharmacodynamics, physiological aging with changes in the body's homeostasis are taken into account in the decision to select drugs for the elderly. The perception of pain differs in geriatric patients because clinical status is frequently complicated by other conditions such as depression, psychosocial factors and cultural differences. Comorbidities, contraindications, and possible drug-disease and drug-drug interactions are considered for choosing an analgesic at the elderly.
Key words: pain, elderly, drug interactions

Rezumat. Durerea a fost definită inițial ca „o percepție a unei experiențe senzoriale și emoționale neplăcute asociată cu sau descrisă în termeni de leziuni tisulare potențiale reale". Sindroamele dureroase au o prevalență crescută la pacienții vârstnici și nu trebuie considerate o consecință normală a îmbătrânirii, de aceea etiopatogenia acestui sindrom nu este ușor de stabilit la vârstnici și mai ales la persoanele fragile. Este nevoie de grijă în selectarea și administrarea analgezicelor pentru a evita interacțiunile medicament-medicament sau medicament-boală la vârstnici. Modificările de farmacodinamică, îmbătrânirea fiziologică cu modificări ale homeostaziei organismului sunt luate în considerare în decizia de selectare a medicamentelor pentru vârstnici. Percepția durerii diferă la pacienții geriatrici, deoarece starea clinică este frecvent complicată de alte afecțiuni precum depresia, factorii psihosociali și diferențele culturale. Comorbiditățile, contraindicațiile și posibilele interacțiuni medicament-boală și medicament-medicament sunt luate în considerare pentru alegerea unui analgezic la vârstnici.
Cuvinte cheie: durere, vârstnici, interacţiuni medicamentoase

INTRODUCTION

Pain was originally defined as "a perception of an unpleasant sensory and emotional experience associated with, or described in terms of, potentially actual tissue injury" [1]. Catananti and Gambassi [2] consider pain a complex, subjective and multidimensional experience without objective biological markers.

Pain syndromes have an increased prevalence in elderly patients and they should not be considered a normal consequence of aging, therefore the etiopathogenesis of this syndrome is not easy to establish in the elderly and especially frail people. Identifying the cause of pain is a challenge for the geriatric clinician who requires understanding the complex mechanisms from cellular, molecular to the semiology of its expression and its perception by patients associated with physical, psychological or environmental aggravating factors. The pain is classified as acute or chronic pain and depending on the nociceptors in skin, somatic, visceral pain. Pain control is achieved through various mechanisms to reduce the sensory capacity of the nerve, which can be done at the central or peripheral level.

The pharmacological treatment of pain is based on some drugs that have a specific pharmacodynamics through prevention on:

- Formation of nerve influx, in sensitive endings (local anesthetics, muscle

relaxants, vasodilators, anti-inflammatory);
- Transmission of nerve influx through sensitive fibers (local anesthetics);
- Pain perception, at the level of integration centers (general anesthetics, antipyretic analgesics, morphinomimetic analgesics).

A common classification of analgesics in substances is:

A. Non-opiod-analgesics
B. Opioid-analgesics
C. Other drugs (antidepressants, entiepileptic)

A. NON-OPIOID MEDICATION

1. Paracetamol (acetaminophen)

It is an effective analgesic for musculoskeletal pain, including osteoarthritis and back pain, and is recommended as the analgesic of first choice in several consensus guidelines [3].

Paracetamol taken in recommended doses is considered safe and is not associated with significant gastrointestinal, renal, cardiovascular or central nervous system adverse effects. It does not provide significant anti-inflammatory or antiplatelet effects as it does not inhibit thromboxane. Given the short withdrawal time, 500 mg every 4 hours is recommended for the desired analgesic effect. Although transient increases in liver transaminases have been reported, these do not translate into liver failure, provided maximum daily doses (4g/24h) are avoided. Several studies report an acute liver failure only in malnourished patients (weight <50 kg) and recommend dose reduction (maximum 2 g/24 h) if paracetamol supplementation is necessary for these patients [3]. Generally, elderly patients also have chronic kidney disease and in this case, doses should be adjusted with increased dosing intervals from 6 to 8 hours when eGFR <10 ml/min/1.73m2.

It can be used for moderate to severe pain in combination with codeine-type opioid, which potentiates the analgesic effect but also has side effects like constipation.

2. Non-steroidal anti-inflammatory drugs (NSAIDs) (Ibuprofen, Ketoprofen, Meloxicam, etc.)

These drugs are the most commonly used in the population but prescribing them should be indicated only for a short period in moderate or acute pain and if there is inadequate pain relief with paracetamol or topical NSAIDs [4]. The lowest dose should be used for the shortest period and therapy should be reviewed regularly.

NSAIDs should be used with great caution in the elderly because of potentially serious side effects. Many NSAIDs are drugs that can be obtained from pharmacies without a prescription, leading to several complications in the elderly and frail. NSAIDs have been involved in up to a quarter (23.5%) of hospital admissions due to adverse reactions in the elderly [5].

Given the different pharmacodynamics of NSAIDs, prescribing should be based on their safety profiles and individual patient risk profiles. According to the Beers criteria made by the American Geriatrics Society, they are part of the class of drugs to be used with caution in the elderly [6].

Among the most common side effects of NSAIDs are gastrointestinal bleeding, peptic ulcer, especially in patients on anticoagulant/antiplatelet therapy. For that reason, it is associated with proton pump inhibitors, which can reduce but not eliminate the risk. Upper gastrointestinal ulcers, severe bleeding or perforation caused by NSAIDs occur in about 1% of patients treated for 3-6 months and in about 2%-4% of patients treated for 1 year [5].

In patients with chronic kidney disease, NSAIDs should not be administered at eGFR <30 ml/min/1.73m2. In patients with heart failure or poorly controlled hypertension, the administration of NSAIDs will cause decompensation of these conditions and should be avoided.

3. Selective COX-2 inhibitors (Celecoxib, Naproxen, etc.)

The European Medicine Agency has made the recommendation that COX-2 selective inhibitors should be contraindicated in patients with ischemic heart disease and/or stroke, should be avoided in patients with risk factors for coronary heart disease and that all patients should be given the lowest effective dose for the shortest time necessary to control symptoms. Although selective Cox-2 inhibitors were initially used enthusiastically because fewer bleeding complications were reported, recent studies have demonstrated renal impairment to the same extent as NSAIDs, with caution when used in patients on chronic diuretics or angiotensin converting inhibitors [7].

4. Steroidal anti-inflammatory drugs (Cortisone, Prednisone, etc.)

This class includes short-acting systemic glucocorticoids with low potency (cortisone, hydrocortisone), intermediate-acting glucocorticoids with medium potency (prednisone, prednisolone, methylprednisolone) and long-acting glucocorticoids with high potency (dexamethasone, betamethasone). They have an anti-inflammatory, anti-allergic and "anti-shock" effect but with a negative effect on carbohydrate metabolism (diabetes mellitus decompensation), protein metabolism, hydroelectrolytic (hydrosaline retention), endocrine (osteoporosis), neurocognitive system (psychosis, depression) and ophthalmic sensory (glaucoma, cataracts). They are usually not used in elderly patients in long-term treatment [6].

B. OPIOID MEDICATION

Opioids are generally safe and provide effective pain relief as part of a comprehensive pain management strategy. The "start low and go slow" approach is essential when administering opioids.

Strong opioids are commonly used in the management of chronic, severe, non-cancer pain in the elderly. A US cohort study from a long-term institution found that the use of extended-release opioids improved functional status and social engagement compared with short-acting opioids [8]. Studies have demonstrated short-term efficacy in persistent musculoskeletal pain, including osteoarthritis and low back pain, and various neuropathic pain, such as post-herpetic neuralgia and diabetic peripheral neuropathy. However, long-term efficacy and safety data are sparse [9].

In the elderly, opioids should be started at 25-50% of the recommended adult dose. Common side effects such as sedation, nausea and vomiting tend to be more severe around opioid initiation or dose increase and usually disappear after 2 or 3 days. On the other hand, constipation does not improve and should be managed with laxative therapy. In the elderly, drowsiness and dizziness occur and are associated with an increased incidence of falls and fractures. Cognitive function is relatively unaffected in patients taking stable doses of opioids, but may be impaired up to 7 days after a dose increase [10].

1. Codeine has no noticeable effect if taken alone and has adverse effects of constipation which requires administration with laxatives.

2. Tramadol is a centrally acting analgesic with two mechanisms of action: weak mu-opioid agonist activity and inhibition of serotonin and norepinephrine reuptake. It should be used with caution in patients taking other serotonergic drugs. May have less effect on respiratory and gastrointestinal function than other opioids, but may cause confusion in the elderly. Tramadol is contraindicated in patients with a history of seizures because it may lower the seizure threshold, especially at doses greater than 300 mg/day.

A prospective, age-controlled study suggests that older people require 20% less Tramadol than younger adults, although

pharmacokinetics remained unaffected by age [11]. Initiation in elderly patients is 25 mg once or twice daily and increased in increments of 25 mg every 2-3 days, up to a maximum of 100 mg/day [6].

3. Morphine-When starting treatment, a low and extended release dose is recommended. In renal dysfunction, a reduced dose should be used or, in case of severe impairment, avoid the use of active metabolites which may accumulate and cause toxicity. Fentanyl patch is frequently used in the elderly [10].

C. OTHER DRUGS

1. Antidepressants (Duloxetine)

Serotonin and norepinephrine reuptake inhibitors (SNRIs), such as duloxetine**,** have demonstrated efficacy in some neuropathic pain conditions and may have better tolerability than tricyclic antidepressants. RCTs have established the analgesic efficacy of duloxetine in four chronic pain conditions, i.e. diabetic peripheral neuropathy, fibromyalgia, chronic back pain and osteoarthritis, knee pain [12].

Duloxetine is usually started at 30 mg/day and can be increased to 60 mg/day after 2 weeks, if necessary. The most commonly reported side effects include dry mouth, nausea, constipation, diarrhea, fatigue, dizziness, drowsiness and insomnia. The use of duloxetine should be avoided in patients with hepatic impairment or heavy alcohol consumption, as hepatitis and liver failure have been reported [13].

2. Antiepileptic drugs (Gabapentin, Pregabalin)

Antiepileptic drugs, such as gabapentin and pregabalin, have become widely used in neuropathic pain conditions because several studies have demonstrated analgesic efficacy and fewer side effects than older antiepileptic drugs. Efficacy has been demonstrated in diabetic peripheral neuropathy and central pain syndromes [9]. Although the potential for drug-drug interactions is lower, clearance of gabapentin and pregabalin depends on renal function and dose adjustment is necessary for renal impairment.

Dose titration is required during the initiation of treatment with gabapentin or pregabalin, initiation of therapy with gabapentin 200 mg administered three times daily having similar efficacy and side effects to the lower doses studied. When indicated, treatment should be started at the lowest possible dose and increased very slowly based on response and side effects [5].

General principles for the administration of analgesics to elderly patients

Care is needed in the selection and administration of analgesics to avoid drug–drug or drug–disease interactions at the elderly.

The timing of medication administration is important. Severe, episodic pain requires treatment with fast-acting, short-acting drugs. However, if a patient is experiencing ongoing pain, regular administration of analgesics is most effective, possibly using extended-release preparations [14]. Changes in pharmacodynamics, physiological aging with changes in the body's homeostasis are taken into account in the decision to select drugs for the elderly.

Analgesics administration at the elderly should consider the following aspects:

- Only one drug should be started at a time, using a low dose, and this should be followed by gradual dose titration;
- Allowing sufficiently long intervals between the introduction of medicines to allow assessment of the effect;
- Combination therapy using drugs with different mechanisms of action may have synergistic effects to provide greater pain relief with fewer side effects than higher doses of a single drug;
- Consider using non-pharmacological strategies, such as physiotherapy,

cognitive-behavioral approaches and acupuncture, in combination with medication;

- Treatment should be monitored regularly and adjusted if necessary to improve efficacy and limit adverse events.

CONCLUSIONS

Assessment of pain in elderly patients should be a routine part of medical care by all health professionals, and especially in geriatrics. Pain is highly prevalent in frail elderly with multiple co-morbidities and multiple drugs. The perception of pain differs in geriatric patients because clinical status is frequently complicated by other conditions such as depression, psycho-social factors and cultural differences. Comorbidities, contraindications, and possible drug-disease and drug-drug interactions are considered for choosing an analgesic at the elderly.

Disclosures and conflict of interest statements

There are no potential financial or personal conflicts of interests.

Authors' contributions

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