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Use of Tapentadol in Frail Elderly Patients with Dementia: The Opinion of the Geriatrician

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BACKGROUND

The management of pain in the elderly and frail patient is complicated because of the risks posed by changes in pharmacokinetics and pharmacodynamics, polypharmacy, and drug-disease interactions. Literature suggests patients with dementia thought to have pain or a painful condition received opioid analgesics 67% less often, and 45% did not receive treatment at all in comparison with those without dementia. Age itself is one of the main risk factors for both potentially painful pathologies (osteoporosis, arthritis, cancer) both dementias. The treatment of pain in the elderly patient can be a problem that is made more complex if there is also the presence of a possible state of cognitive decline due to neurodegenerative diseases such as dementia. Given the difficulty in reporting pain and its extent, due to the state of dementia, in these subjects, this phenomenon risks being underestimated and under-treated [1]. Several drugs for the treatment of pain have even severe adverse events in the elderly patient, increasing the risk of bleeding, decreased filtration function by the kidney, increased pressure, and not least possible worsening of cognitive status. The most important side effects are nausea, constipation, urinary retention, central nervous system adverse effects (like sedation and mild cognitive impairment), pruritis, respiratory depression, cardiovascular events (related by QT prolongation), endocrine effects (about a hypothalamic-pituitary-adrenal axis, and also on the hypothalamic-pituitary-gonadal axis, resulting in a reduced serum luteinizing hormone and cortisol levels and increased prolactin levels). The recommendations from The European Association of Palliative Care (EAPC) Research Network for management of opioid side effects include dose reduction, symptomatic management of the adverse effects using drugs targeting the symptoms, opioid rotation, and switching the route of administration.

ROLE OF THE GERIATRICIAN IN PAIN THERAPY

Tapentadol is a powerful analgesic that has two mechanisms of action: it has an agonist activity on opioid receptors and inhibits the reuptake of noradrenaline. It exerts its analgesic effects directly without any pharmacologically active metabolites. It also has been shown to be effective in preclinical models of nociceptive, visceral, inflammatory, and neuropathic pain. For example, tapentadol prolonged-release (PR; 100–250 mg twice daily) has been efficacious and well-tolerated for managing moderate-to-severe, chronic osteoarthritis hip or knee pain in phase 3 studies with washout of previous analgesic treatment [2]. An even higher dose was tested on patients suffering from low back pain, a pathology that is often found in the elderly patient and which often coexists in the demented elderly patient, both for age and osteoarthritis and for the frequent assumption of positions of the incorrect spine and inadequate postures caused by psychic disorders [3]. An interesting finding was that, in the treatment of these painful conditions affecting the musculoskeletal system [4] or whit pregabalin [5], tapentadol still appeared effective but with fewer side effects than other opioids: in fact, of importance in the comparator trials was the finding that patients treated with tapentadol had a lower incidence of adverse gastrointestinal events, including nausea, vomiting, and constipation than those treated with oxycodone [6, 7]. But, because tapentadol has effects on norepinephrine reuptake, patients may experience a monoamine syndrome of poorly characterized irritability and agitation and this can be a problem in the patient

suffering from mental disorders related to dementia. So, the prolonged-release formulation can be used for elderly patients, frail patients, for liver diseases who, for example, cannot take paracetamol. It can be used as an alternative to combinations that are already on the market (such as paracetamol associated with codeine, in cases where for one year there has been the note of codeine restricted to three days, especially due to the risk of toxicity in those people who have some genetic polymorphisms of cytochrome 2D6 which allow a metabolism not of 10% but of 40-50% of codeine into morphine) [8]. The new tapentadol at a dosage of 25 mg is particularly useful for adjusting the dosages in the most complex therapeutic pathways, but also in the management of the early developmental stages of the disease, thus representing a concrete completion of the therapeutic options available today. It is also indicated for frail patients, such as the over-eighty-year-olds - which in Italy are about 3.7 million - and hepatopathy patients (patients with chronic viral hepatitis and cirrhosis) - 2.5 million and 1 million respectively [9,10]. The indication is also an alternative to the inappropriate use of non-steroidal anti-inflammatory drugs (NSAIDs) in people who have a contraindication to use NSAIDs. Tapentadol 25 mg can therefore prove to be a new and valuable aid to the advantage of therapeutic appropriateness also for the general practitioner. For recurrent or shorter forms of musculoskeletal pain, for which drugs indicated for acute pain are still heavily prescribed today, and certainly, inappropriately, a lower dose of tapentadol can certainly represent the therapy of choice. The forms of chronic pain in which this new formulation can prove to be a valid therapeutic remedy are joint pain, muscle, and peri-articular, all painful forms that can also be the result of minor trauma, but also the pain in the brachial plexus at the level of the cervical spine and postural lumbago. Finally, there is the therapeutic indication that goes in the direction of those pains that are not yet severe chronic but not even acute but are moving towards a chronic form even if it is not yet, for periods of time that can be 2-3 weeks. This period of time corresponds to the maximum period of time of use of non-steroidal anti-inflammatory drugs, in order not to incur severe adverse effects. In cases of chronic pain in which this molecule is already being used but an adequate dosage, such as 50 mg or 100 mg or even greater, the dosage adjustment which is very selective (on the specific person) allows to proceed with increases of 25 mg and not 50 mg as before. This aspect of the different use of the drug in the different subjective conditions of the patient and according to his specific treatment path if for a young patient with chronic lower back pain, or for a polytraumatized sportsman in physiotherapy, we will recommend higher doses of tapentadol, to allow him to reduce the time of functional recovery and thus return to work and sports activities, a dosage of 25 mg is certainly indicated for frail patients. In all cases, in the final phase of the physiotherapy process, tapentadol 25 mg is a precious ally to allow optimal patient management. The fundamental concept is that this dosage should never be taken as the first step in chronic pain. For tapentadol the first dosage is 50 mg, you should never start with 25 mg. This new dosage, therefore, covers that market segment in which the pain is no longer acute but is not yet chronic severe, it can be moderate but it can also be recurrent and therefore it can have a certain intensity [11-13]. This molecule is an opiate that would be identified as a strong opiate, however, precisely because of the characteristics of tapentadol to have a noradrenergic component, which is actually the mechanism main, it also covers the neuropathic component of certain forms of pain that are transitioning to a chronic form and that have the neuropathic component that cannot be treated with other drugs mentioned above [14].

USE OF TAPENTADOL IN THE PATIENT WITH DEMENTIA

Unfortunately, there are not many data and therefore strong evidence regarding the use of tapentadol in patients specifically with dementia. Due to this possible connection, some authors examined the role of opioid use as a risk factor for developing dementia. Overall, they analyzed more than 2,500 adults over the age of 65 without a diagnosis of dementia. They continued to study this population over 10 years to assess the effects of opioid use in older adults. The results of the study indicate that prolonged use of these prescription drugs could lead to the development of Alzheimer's disease and dementia [15]. There are observational experiences in Italy and patients with dementia are not mentioned [16]. In a recent study by Freo et al. however, no effects of the drug on mini-mental state examination were detected and in the patients studied, even older than 84 years, treatment with tapentadol did not show that the performance of cognitive function and prolonged attention tests remained stable but even improvement was observed [17]. The same author investigated the possibility of using the given molecule even at moderate and high doses in a small cohort of patients with pain and with Parkinson's disease (but not Parkinson's related dementia) [18-22].

CONCLUSION

Chronic pain is something we see very often in frail elderly patients. Again, it is frequent in the demented patient, although it is more difficult to assess and is also complex to treat. In addition, the presence of chronic pain is clearly associated with decreased cognitive performance over time and an increased risk of dementia. Tapentadol with its synergistic analgesic action and dual mechanism of action (reduction of ascending pain signals and improvement of descending inhibition), broad-spectrum in chronic nociceptive, neuropathic and mixed pain, not requiring dose adjustments in elderly patients. It shows a beneficial action on the quality of life, thus contributing not only to the reduction of pain but to an improvement in daily activities and in the emotional sphere. Furthermore, despite the still low number of evidences present regarding patients with dementia, data from the recent TaPE study have highlighted positive effects with regard not only to mental pathology (anxiety, depression) but also to the cognitive sphere. The geriatrician is the reference figure to better understand the most appropriate indication and with favorable cost-benefit in elderly patients, with chronic pain, even demented, also to collect further data that allow an optimal algological therapy with a well-considered safety, in compliance of the commandment "do no harm" but also of the mission to guarantee a life without pain to all patients, including the most mentally disadvantaged.

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