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The combination of long-acting opioids has not been sufficiently documented in the literature.
Patient J.L., aged 67, with disseminated malignant process. Complaints of pelvic and visceral pain. Treatment: sustained release morphine 60 mg/daily. There occurred a need to increase the dose of the drug up to 120 mg/daily; the patient was referred to the Pain Management Outpatient Department. Nociceptive pain was diagnosed at the intensity of 7.5 on the VAS scale. Ketoprofen was included in the treatment at a dose of 200 mg/daily. After three days the morphine dose was increased to 180 mg/daily. Due to the lack of adequate pain control sustained release oxycodone was started, initially at a dose of 20 mg/daily, and after three days 40 mg/daily. After two weeks, the dose of morphine was decreased to 140 mg/daily. Adequate pain control was obtained.

Key words: opioid, morphine, oxycodone, opioid combination, pain management.

Opioid combination. Case report

Krzysztof Brzeziński

Institute of Rural Health, Lublin

Efficient management of pain in the course of cancer diseases often encounters serious difficulties [1, 2]. A very frequent problem is, e.g. concomitant occurrence of many types of pain in the same patient. The course of the disease is often complicated by persistent post-surgical pain, pain related to bone metastases, neurogenic pain, or various types of neuropathic pain due to the infiltration of nerves, post-herpetic neuralgia, or chemotherapy-induced peripheral neuropathy. Unfortunately, very frequently there also occurs a lack of effectiveness of opioids, or a rapid increase in tolerance to the therapy applied.

The principles of pain management, coded in the form of the WHO analgesic ladder, on assumption, introduce the principle of combining various drugs in order to increase their effectiveness, due to the use of combining and synergistic mechanisms [3]. Multimodal therapy in the form of opioids, non-steroid anti-inflammatory drugs (NSAIDs) and co-analgesics, in the majority of cases allows efficient analgesia to be achieved, without the necessity for increasing the dosage of drugs, and often allows reduction of the amount of drugs applied.

Simultaneous application of NSAIDs, opioids and co-analgesics, therefore, is the rule [4]; however, the administration of several drugs of the opioids group still evokes controversy. To date, few reports are available concerning the implementation of such a method of treatment [5]; therefore, it cannot be considered that there is scientific evidence which would justify such models of therapy [6]. At present, one can only rely on the opinion of experts that considering the variation in opioid receptors and varied susceptibility to exogenous ligands used, it is permissible to combine opioid drugs [5, 6].

Case report

Patient J.L., aged 67, with endometrial cancer detected at the terminal stage. The patient was in a relatively good condition, in full possession of her faculties, running a household together with her daughter, totally independent. The complaints had started three months earlier, with intensifying pain in the pelvic bone radiating to the left buttock region. Pain was approached as osteoarticular and treated with diclofenac administered promptly. After a month there occurred visceral pain, interrupting sleep, which was not associated with the consumption of meals.

The patient was referred to the Oncological Outpatient Department, where, after the performance of auxiliary examinations, a disseminated cancerous process was diagnosed, with multiple metastases to the pelvic bones, liver and mesentery. The patient refused any other oncological treatment. Due to the intensification of complaints, long-acting morphine was started at a dose of 60 mg/daily, as the only medication. After a week, the patient still experienced strong pain complaints; therefore, within the following two weeks, the morphine dose was successively increased to 90, and then to 120 mg in two separate doses. Due to the rapidly increasing pain not responding to the medication, the patient was referred to the Outpatient Department for Pain Management.

The intensity of pain as measured according to the visual analogue scale (VAS; 0-10 cm) was 7.5 cm. The complaints were located in the left pelvic region and within the entire abdomen, and pain was not associated with bowel function. The abdomen was painful at palpation, especially in the right sub-

costal region. Pressure-evoked pain in the left ala of the ilium and sacroiliac joint, on the same side, was consistent with the scintigraphic image, documenting a disseminated malignant process within the skeletal system. Pain was of nociceptive character, without the neuropathic component, and occurred permanently, with periodic aggravation up to 9 cm on the VAS scale, several times daily.

Considering the mixed pain syndrome (skeletal and visceral), at the first stage of the treatment ketoprofen was included at a dose of 200 mg twice daily.

At the subsequent visit (after three days), the patient reported a slight decrease in complaints within the pelvic region, without changes in visceral pain, the intensity of pain evaluated as 5-6 cm on the VAS scale; however, sudden pain episodes decreased. Morphine applied at a dose of 180 mg per day caused a further decrease in acute pain episodes; however, it remained without an effect on the complaints of a permanent character (VAS 5 cm). In this situation, the decision was made to introduce another opioid drug in the form of long-acting oxycodone at a dose of 10 mg in two separate doses. This brought relief to the patient in the form of decreased intensity of pain down to 4-5 cm on the VAS.

After the following three days, due to the persistence of complaints (VAS still 4-5 cm), the oxycodone dose was increased to 20 mg twice daily. At the subsequent stage of observation, the intensity of pain noted was 2-3 cm VAS, and the pain complaints were considered as managed. The patient was continually treated with ketoprofen at a dose of 200 mg/daily, extended release morphine at 180 mg/daily, and extended release oxycodone at a dose of 40 mg/daily. Two weeks after the therapy described above, the dosage of morphine was decreased to 140 mg/daily, the remaining drugs being administered without changes.

Discussion

The case of the patient described, with a simultaneous visceral and bone pain syndrome and developing tolerance to opioids, illustrates the dilemmas of medical practitioners who, on an everyday basis, deal with the necessity to solve similar problems.

It cannot be excluded that the course of treatment would be somehow different if, at the beginning, the NSAIDs had not been stopped. This is one of the methods, apart from bisphosphonates and radiotherapy, of managing pain complaints associated with a disseminated cancer process within the skeletal system [4,7-9].

A further aspect of treatment at the initial phase was the administration of strong opioids, directly after the drugs of the first level of the WHO analgesic ladder. This is a practice which is aimed at the protection of a patient against onerousness associated with slowly progressing through the subsequent stages of the WHO analgesic ladder. The experiences to date indicate that such a procedure may bring about the desired effects in a large number of patients, and is relatively frequently applied in clinical practice and guidelines [9-14]. Unfortunately, in the presented case, it did not bring about the desired effect.

Periodic pain intensity increase up to 9 cm on the VAS scale suggested the occurrence of breakthrough pain; nevertheless this diagnosis was not confirmed, because after increase of the morphine dose the complaints were managed, without the necessity to apply rescue medication.

The treatment of chronic pain based on the scheme of the WHO analgesic ladder should be effective in 70-90% of patients [7, 8]; nevertheless, the first reports concerning the possibility of ineffective therapy appeared soon after its publication [15]. The reasons for such a state of affairs were sought for in the low percentage of adequately diagnosed and treated neuropathic pain, too rare use of any scales of pain intensity, delayed referral of patients to pain management outpatient departments, or insufficient accessibility to invasive techniques. Obviously, not all possible causes of unsuccessful pain therapy have been mentioned, but undoubtedly we still deal with the situation when a patient is suffering.

The studies by Brevik *et al*. of 2006 and 2009 describe the present state of pain management in the course of a cancer disease in Europe [1, 2]. The conclusions drawn based on the material presented do not evoke optimism, because some patients still experience such strong pain complaints that they would prefer to die. The seriousness of the situation is enhanced by the fact that within the three-year period that had elapsed between the two publications, no significant changes occurred. This justifies the search for new drugs and therapeutic methods which may possibly prove more effective.

At present, the problem is discussed whether the simultaneous administration of various strong opioids has at least a theoretical scientific basis. Opioid receptors are a relatively varied family of membrane receptors related to the G protein [16], while the mechanism of the effect of opioid drugs consists in the activation of these receptors, and, therefore, inhibition of nerve conductivity in the fibres transmitting 'pain information'.

Three classes of opioid receptors are distinguished, μ, δ, κ, and also so-called 'orphan receptors', with the occurrence of subclasses of μ and δ observed. At present, there is not yet reliable evidence for the existence of various subclasses of κ receptors, because the presence of specific ligands has not been noted, nor have they been cloned [17].

Until recently it has been considered that mainly μ receptors are responsible for analgesia, whereas at present it has been confirmed that this process is regulated by all the described classes of opioid receptors [18]. Therefore, the conclusion is drawn that the process of antinociception, related to the activity of opioid receptors, is far more complex, and should rather be approached as a dynamic balance. In this way one may explain the various analgesic effects of the drugs from the group discussed, and justify the frequent use of the opioid rotation manoeuvre, consisting in the substitution of one drug for another after observing the lack of effectiveness of the original drug [19].

Studies have been undertaken the results of which allow the conclusion that simultaneous activity on receptors from various classes may induce a better analgesic effect [20].

Many reports describe both the differences and similarities in the activities of drugs against μ and κ receptors [21-24], as well as the combined use of morphine and oxycodone [25].

Morphine is a pure μ receptor agonist. Although due to its high hydrophilicity it reaches slightly lower concentrations in the central nervous system (CNS), compared to lipophilic

substances, such as fentanyl, it shows considerably higher activity with respect to the peripheral nervous system [17].

Oxycodone shows a greater affinity to κ receptors, which explains its greater effectiveness in visceral pain [24, 25], while the better penetration into the central nervous system probably depends on active transport through the blood-brain barrier [26, 27]. These two drugs have different pharmacokinetic properties and activity against membrane receptors, whereas the differences allow the conclusion that their simultaneous application is permissible, despite the fact that they belong to the same pharmacological group [6, 17, 28, 29].

At present, there is limited scientific evidence to justify the combination of strong opioids; however, studies on experimental models, as well as pilot studies on small groups of patients, indicate that within a short time the acceptance of such a procedure may be expected in everyday practice.

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Address for correspondence

Krzysztof Brzeziński
Outpatient Department for Pain Management
Institute of Rural Health, Lublin
Jaczewskiego 2
20-090 Lublin
e-mail: k.brzezinski@op.pl
tel. 605 228 412