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PAIN IN OBESITY IS NOT OBESITY AND PAIN

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ABSTRACT:

The article clarifies that pain in obesity is not obesity and pain. The authors reviewed the literature and surveyed the clinical data about pain in people with abnormal body weight. The conclusion was made that pain in obese patients needs adequate management. Data for pharmacokinetic and pharmacodynamics characteristics of frequently used analgesic drugs are summarized. The authors include useful schemas of pharmacotherapy with non-opioid as well as opioid analgesics and practical guidelines for pain management in clinical ward or outpatient departments.

Key words: obesity, pain, analgesic drugs, pharmacokinetics, pharmacotherapy

Excess body weight is the most widespread non-physiological condition affecting people in modern industrial societies. In the United States, the relative share of overweight people is menacingly increasing. Meanwhile, more than 50% of individuals over 50 years of age demand medical care due to pain of different etiology. That's why the fact that the number of overweight individuals experiencing chronic pain is high, is not surprising [1].The degree of non-physiological increase in body weight is defined as overweight or obesity, and is determined by body-mass index (BMI) - a person's weight (in kilograms) divided by the square of height (in meters). BMI values 25-30 indicate overweight; values above 30 indicate severe (BMI 30-40), morbid (BMI 40-50) or super morbid (BMI> 50) obesity [2]. Overweight reflects the fat accumulation in the abdominal cavity - central obesity [1], causing in turn, body re-configuration and biomechanical alterations. Chronic pain is a consequence of the latter, and is the dominating clinical symptom in some of the most common musculoskeletal disorders among overweight individuals - low back pain and osteoarthrosis. Studies among adult patients have established that the central obesity significantly correlates with a twofold increase in the incidence of chronic pain [3]. Altered biomechanics is one of the main causes of low back pain syndrome among women with advanced pregnancy as well [4]. Obesity does not develop as an isolated disorder. Hormonal dysregulation and neurochemical disbalance manifest with increased leptin, corticosterone and β-endorfin, and reduced ghrelin levels in patients with substantial overweight [1]. In general biological context, nutrition takes priority over the responses to alogenic impacts.

However, the conclusions over a reliable relationship between overweight and chronic pain are hasty. Overweight imposes precise individualization of analgesic therapy, taking into account the subsequent changes in pharmacokinetic and pharmacodynamic characteristics of the medications.

Pharmacokinetics

Absorption: Overweight *per se* does not alter the intestinal absorption of analgesic medications [5].

Distribution: It has been established that plasma concentration of α1-acid glycoprotein in individuals with morbid or super morbid obesity is more than twice higher compared to individuals with normal body weight [6]. This could cause reduction of the active free fraction of slightly alkaline analgesic medications such as fentanyl and its analogues in plasma, thus reducing their analgesic effect. The main factor determining changes in the volume of distribution of analgesic medications is the increased fatty tissue mass. A well known fact is that the cardiac output, circulating blood volume and the size of liver and kidneys are increased in individuals with severe or morbid obesity, consequently leading to increased volume of distribution of the medicines. In order to achieve analogous plasma concentrations and specific clinical effects, higher analgesic doses should be applied in these individuals if compared to normal body weight patients.

Elimination: The excessive body weight does not result in substantial change of functional hepatic blood flow, regardless of the increased liver size, which in turn is most likely a result of its fatty infiltration [7]. Data from pharmacokinetic studies in patients with excessive overweight indicates, that the elimination of metabolized in hepatic phase 1 and of acetylated analgesic medications remains unchanged, irrespective of the increased activity of cytochrome P450. By contrast, the elimination of analgesic medications conjugated in extrahepatic biliary tract is enhanced [8]. The increased kidney size in individuals with morbid or super morbid overweight is combined with increased glomerular filtration and tubular excretion, resulting in enhanced kidney elimination of analgesic drugs [9]. The main pharmacokinetic parameters in overweight individuals are summarized on Table. 1.

Table 1. Pharmacokinetic parameters of fat- and non-lipid soluble analgesic medications in individuals with morbid or super morbid overweight (modified, [2])

Pharmacokineticparameters	**Fat soluble**	**Non-lipid soluble**
Albumin-bound free fraction	Unchanged	Unchanged
APG- bound free fraction	Reduced	Reduced
Central volume of distribution	Increased	Increased
Total volume of distribution	Considerably increased	Increased
Hepatic elimination	Phase I: Unchanged Phase II: Increased	Phase I: Unchanged Phase II: Increased
Renal elimination	Increased	Increased

Pharmacodynamics

Data regarding the pharmacodynamics of analgesic medicines in overweight individuals is insufficient and multidirectional, and results vary from moderate decrease to considerable increase of nociceptive thresholds in overweight patients [2]. Below, data over pharmacodynamics of some commonly used opioid and non-opioid analgesic medicines is presented.

Morphine: So far no specifically designed studies on its pharmacodynamics in overweight patients have been conducted. In plasma, morphine is conjugated and could be theoretically assumed that in such patients its metabolism is increased and it is eliminated via kidney, without accumulation of active metabolites. This assumes, that in patients with morbid or super morbid obesity, the dose of morphine should be higher. Careful attention to these patients should be encouraged, because the risk of morphine-induced respiratory depression among them is significantly higher if compared to normal body weight patients [10]. In such cases, the risk is smaller in combined analgesic therapy, where the dose of morphine could be reduced.

Fentanyl, Alfentanil, Sufentanyl, Remifentanil: The dosages of these opioid analgesics should be calculated based on the so called pharmakinetic mass and the rate of elimination. An universal recommendation is that they should not be applied repeatedly or in high doses, because of the risk of accumulation. Transdermal forms of these analgesics are not recommended for morbid or super morbid overweight patients. Alfentanil has small volume of distribution and does not accumulate. Sufentanil has high lipid solubility, high volume of distribution and delayed elimination (due to its high lipid solubility) [11]. Remifentanil has a small volume of distribution and rapid elimination, which makes it the medicine of choice for anesthesia of overweight patients.

Codeine, Oxycodone, Hidromorphone, Tramadol: So far, no specifically designed pharmacodynamic studies for overweight patients have been performed. Codeine is a prodrug, which is transformed to morphine by the enzyme debrisoquine hydgoxylase (CYP2D6), so its action is manifested with a certain delay. It was established that 10% of the European population lacks CYP2D6 so they do not convert codeine to morphine [12]. Oxycodone is a semi-synthetic opioid for oral application, a structural analogue of codeine. The action is similar to morphine and a serious side effect is the respiratory depression. It should not be used as a therapy of choice for opioid analgesia in overweight patient. *Hydromorphone* is a powerful fast-acting opioid analgesic, widely used in many European countries. *Tramadol* is an opioid analgesic, a racemic mixture of two enantiomers with good lipid solubility and similar pharmacokinetics. Its volume of distribution is 3.51/kg, and the elimination rate is 500 ml / min [13]. Tramadol undergoes hepatic phase I CYP2D6 transformation, after which five metabolites occur. O-desmethytgamadol is active and cumulates after repeated administration [14]. It is recommended to start the therapy with tramadol of morbid or super morbid overweight patients with high initial doses and subsequently to increase the intervals between two consecutive doses.

Carbamazepin, Clonazepam, Gabapentin, Pregabalin: These medicines are commonly used for treatment of neuropathic pain. Untill now, pharmacodynamic studies specifically designed for overweight patients have been performed only with carbamazepine. Its increased volume of distribution and normal elimination may cause accumulation when applied in multiple doses, low plasma concentration and longer half-life [15]. For treatment of patients with morbid or super morbid obesity, it is recommended to apply higher initial doses and longer intervals between two consecutive doses. *Clonazepam* has high lipid solubility and volume of distribution. It is not recommended as first line treatment in overweight patients. *Gabapentin* has high volume of distribution and the treatment should start with dose titration. *Pregabalin* is poorly soluble in lipids, with small volume of distribution and is appropriate for treatment of neuropathic pain in overweight patients.

Nonsteroidal anti-inflammatory drugs (NSAID): This class of medicines exhibits low lipid solubility and small volume of distribution. Besides the typical NSAID side effects, they are not contraindicated in morbid or super morbid overweight patients. Their administration as adjuvants in perioperative analgesia (aiming to reduce the opioid analgesics dose) is recommended [2].

Acetaminophen (Paracetamol): Its average volume of distribution imposes to be used in higher doses in overweight individuals, to achieve adequate analgesia.

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