

Undiscovered morphine. The effects of the long-term use of the opioids

Abstract

Morphine and other opioids are used much more often and for a longer time than before. This causes many relatively unknown adverse effects, which become apparent only after a while. One of them is opioid-induced hyperalgesia and abnormal magnesium metabolism. The adverse effect that negatively influences the quality of life is opioid-induced hypogonadism. Morphine can have a profound immunosuppressive and tumour-promoting effect. It is probably responsible for the increased rate of heart infarctions. Very interesting are suggestions that morphine and other opioids are changing the large bowel microbiome. All of these phenomena do not concern only few patients but are generalized in this population and the severity of the phenomenon depends only on the treatment period. Jet none of these adverse effects are mentioned in drug leaflets. All of these phenomena are treatable providing that the diagnose is made accurately and timely. It is very well possible that in the future we shall be able to prevent most of these adverse effects.

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Key words: morphine, fentanyl, opioids, buprenorphine, opioid-induced hyperalgesia, hypogonadism, magnesium, osteoporosis, myocardial infarction, immunosuppression, induction of cancer growth, gut microbiome

Introduction

Morphine as a component of opium is known in medicine for 6,000 years. For more than 200 years it is used as a pure drug. Since the time morphine became a part of modern medicine, it is well known that considerable adverse effects always accompany its analgesic effect. These adverse effects like constipation, nausea and vomiting and deterioration of cognitive functions are known to every medical student. However, some of the adverse effects are less well known, and they are never mentioned on the drug leaflets. These adverse effects are not known at all and never discussed with the patients before the beginning of therapy. We use more and more opioids,

not only for the control of pain in the course of the malignant disease [1].

Because patients with cancers live much longer than a couple of decades ago, probably they use opioids for a longer time than before. Formerly opioids were used for a couple of weeks to months only and this period invariably ended in the patients' death. Nowadays we have quite a large group of cancer survivors among whom opioids need to be used for a longer time, sometimes for years [2]. Above all, in the USA, and not only there, it also appears that there is a considerable group of patients treated with opioids for non-malignant conditions [1]. This all makes that we should think about the long-term effects of opioids.

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Tolerance and Hyperalgesia

Tolerance to opioids is known to clinicians for decades. Opioids are very successful at the beginning. However, their efficacy diminishes rapidly. To obtain the same analgesic effects clinicians must increase the dose of the drug [3]. This phenomenon is rare when the treatment is short, for example postoperatively, but becomes considerable when the drug is used for a long while, especially in genetically susceptible patients [4]. In the past, some influential authors suggested that the opioid tolerance could be prevented by using it “by the clock”, which means that the next dose should be administered before the effect of the first dose will wear [5].

Unfortunately, this way of administration was not entirely successful either. Continuous morphine and other opioids administration induce changes in glutamergic transmission [6] and excitation of the N-methyl-D-aspartate (NMDA) receptors [7]. These changes can be counteracted by the NMDA-inhibitor; ketamine [8, 9].

Tolerance to opioids has much in common with Opioid-Induced Hyperalgesia (OIH) which is defined as a nociceptive sensitisation caused by exposition to opioids [10]. The clinicians can easily mix up those two phenomena. In the case of OIH, the opioid given to the patient not only causes analgesia but is the cause of a “new pain” due to the spinal excitation. If this “new pain” is not explicitly recognised it would cause, similarly to opioid tolerance, the need for an opioid dose increase. The differences between tolerance and IOH are discrete. This “new pain” maybe, but not necessarily, be similar to the original pain. The original pain may be already efficaciously treated by the opioid. The patient shows increased sensitivity to pain impulses [11]. Investigations on the large patient populations showed that patients treated with opioids are more sensitive to pain impulses compared to the patients treated with non-opioid analgesics [12]. The reader interested in the problems around OIH is referred to specific publications [13, 14].

Management of OIH is usually based on making a specific diagnosis and decrease of the opioid dose [15]. If this is impossible, or for the patient and its family counter-intuitive, the opioid may be switched from for example morphine or fentanyl to the opioids with less potential of producing OIH — buprenorphine [16] or methadone [17]. In any case, the clinicians should refrain from using the mega opioid doses [18], which were so popular only two decades ago. Another strategy could be the addition of NSAIDs or paracetamol [19].

Hypogonadism induced by opioids

Already after the first dose opioids inhibit the secretion of the pituitary gonadotrophins [20]. Prolonged opioid administration may lead to hypogonadism, as well in man as women [21–23]. Deficiency of testosterone and other sex hormones manifests itself as fatigue, anaemia, increased sensitivity to pain stimuli, muscular atrophy, osteoporosis, erectile and menstrual cycle dysfunction. In total, hypogonadism translates into a lower quality of life of patients treated with opioids [24]. The management is straightforward and not very toxic. Terminally ill patients may be treated with testosterone [25]. However, it should be born in mind that testosterone deficiency may cause insensitivity to opioids [26]. Administration of testosterone rapidly changes this to increased sensitivity to opioids which may result in an unexpected respiratory depression [25]. It seems, for obvious reason, there is a consensus not to prescribe testosterone to patients with prostate and breast cancers.

Osteoporosis

Long term administration of opioids, probably induces bone decalcification and osteoporosis and decalcification translates in an increased risk of bone fractures [27, 28]. However, in falls, other factors as weakness and disturbances of consciousness may play a role too.

Disorders of magnesium metabolism

Magnesium is one of the most critical ions involved in pain origination and transmission [29]. It plays a vital role in muscle and bone metabolism as well as in the metabolism of carbohydrates. Deficiency of this ion causes among others opening of the NMDA ion channels and promotes their activation [30] which translates in pro-nociceptive activity. Long term treatment with morphine causes increased renal magnesium excretion and hypomagnesaemia [31]. On the other hand, the administration of magnesium sulfate together with morphine considerably increases morphine analgesic effect [32]. In the meta-analysis of multiple trials with magnesium sulfate and morphine, this effect was confirmed beyond any doubt [32, 33].

Effects of opioids on the tumour growth

Morphine has an immunosuppressive effect and increases proliferation and migration of the tumour

cells as well as it promotes tumour angiogenesis [34]. In this respect, morphine is the most immunosuppressive of all opioids [35] and least immunosuppressive is buprenorphine [36]. That in case of terminally ill the immunosuppressive effects of opioids is the least of concerns, but in many thousands of cancer survivors that need to be treated with analgesics for a long time, it may be of paramount importance.

Nocturnal breathing disorders

Patients treated with opioids for chronic pain have a high probability of nocturnal apnea and hypoxemia [37]. Resting hypoxemia can be observed in these patients also in the day time, especially after the awakening [37].

Cardiovascular diseases

Not much is known about the influence of opioids on cardiovascular diseases. In one large cohort covering 297 314 patients [38], and receiving opioids for at least 180 days in 3.5 years the Adjusted Incidence Rate Ratio (AIRR) of myocardial infarction was moderately increased and equal to 2.66 (CI, 2.30 to 3.08). Patients prescribed opioids at the cumulated MEDD (Morphine Equivalent Daily Dose) of 1350 mg during 90 days the AIRR was 1.21 (CI, 1.02 to 1.45) while the AIRR in patients treated with a MEDD between 1350-2700 mg in 90 days was calculated as 1.42 up to 1.89. These risk values are higher than the risk of myocardial infarction after treatment with ibuprofen or diclofenac [39].

Gastrointestinal disorders

Opioids are known to affect the delay in gastric emptying and slow the intestinal movements which result in increased nausea and vomiting as well as constipation. Opioids are also known to change the bacterial content of the large bowel [40]. In patients addicted to opioids, there is a remarkable deficit of *Bifidus* and *Prevotella sp.* bacteria. This phenomenon may influence the development of psychological depression [41] and cancer cachexia [42] as well as many other symptoms accompanying neoplastic diseases.

Conclusions

The consumption of opioids, including morphine, increases year by year. These data include not only the treatment of pain in the course of cancer but also the treatment of non-cancer pain. Some patients use morphine and other opioids for a more extended

period. In this situation, it is essential to consider the long-term effects of treatment with morphine and other opioids. Besides well-known more or less acute adverse effects of morphine and other opioids, there are some less well-known long-term effects which are a problem only after more extended use.

The most important is the development of OIH and disturbance of magnesium metabolism and excretion. Here morphine is the cause of new pain and suffering, which without a specific diagnosis usually ends up in the increase of opioid dose and treatment failure. If the diagnosis of OIH is correctly made the first-choice treatment is decreasing and not increasing the dose. Another strategy is to swap one opioid of the higher IOH potential to buprenorphine or methadone.

After OIH, the often occurring and rarely recognised hypogonadism is very important for the quality of life of patients. Here, we should probably sooner substitute with testosterone. In women, this can lead to unpleasant virilisation. It is essential, however, to realise that these adverse effects do not occur only in some but in virtually all patients. The extent of the phenomenon probably depends on genetics, dose and the duration of opioid treatment. It looks like buprenorphine has the most interesting profile in this aspect and is suitable as no one other opioid for the long term treatment [43]. Exciting is the change in microbiome in large bowel under the influence of opioids. Perhaps this is the key to the understanding of many ailments related to long-term use of opioids.

Does this all mean that we should use fewer opioids instead of more? Yes and No. For sure, where opioids can be replaced by other drugs or non-drugs methods of treatment, this should be done at once. On the other hand, physical rehabilitation in palliative medicine has great potential and should be further developed [44, 45]. Intensive rehabilitation is associated with the reduction of opioid doses and decrease of intensity of pain [46]. On the other hand, we should not overreact, because still numerous patients remain undertreated with opioids.

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