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Pharmacological properties of natural opioids, their toxicity and dangers of use

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ABSTRACT

Despite their effectiveness as analgesics, antitussives, antispasmodics and constipation drugs, opioids possess many side effects. Moreover, their easy availability contributes to the problem of addiction. In the following review, we focused on the toxicity and side effects of the four most common opioids – morphine, Codeine, Noscapine and Papaverine – to provide reliable information for students, doctors and pharmacists. Their pharmacological effects, as well as side effects have been described.

INTRODUCTION

The term "opioids" includes all substances acting on opioid receptors, such as natural opioids, synthetic and semi-synthetic alkaloids, and endogenous peptides. The pharmacodynamics of opioids relies on its effect upon specific G-coupled receptors (GPCR) which leads to the closure of presynaptic Ca^{2+} ion channels inhibiting neurotransmitters release (e.g., glutamate) and inhibiting postsynaptic neurons by opening K^+ ion channels. Interestingly enough, opioids have both stimulating and inhibitory activity on various physiological functions, for example, acute toxicity due to opioid overdose generates respiratory depression and cardiac arrest.

Gastrointestinal motility and respiratory depression are primarily mediated by the μ opioid receptor, thus, recent studies show that these issues can result from β-arrestn-2 pathway activation. Importantly, respiratory depression can develop minutes after injection or inhalation. However, due to the systemic circulation and the problem to get through the brain-blood barrier, the opioid effects take longer to come about *via* oral administration. As to chronic toxicity and long-term action, most of the opioids have little positive influence on cardiac activity due to their sympatholytic effects that can cause bradycardia, hypotension and vasodilation.

Long term therapy involving opioid intake can be associated with symptoms such as decreased libido, erectile dysfunction, infertility, amenorrhea, night sweats, decreased muscle mass and strength, depression and anxiety, tiredness, fatigue, osteoporosis and fractures. Importantly, the development of tolerance during the use of opioids can cause overdose due to a need of taking a higher amount to obtain the same impact.

Opioids induce persisting neuroadaptation at the cellular and molecular levels which causes neuroplasticity changes and remodeling of reward neuronal circuits. As established, activation of μ opioid receptor at the ventral tegmental area (VTA) induces indirectly dopamine secretion in the nucleus accumbens (NAC). However, direct activation of opioid receptors in the ventral striatum is sufficient to induce the rewarding impact of opioids. In the case of opioid dependence, relapse to substance abuse occurs in 90% of all patients [1].

All of these aspects indicate that opioid intake, despite its effectiveness, comes with dangerous side developments, including addiction. In this review, we have collected literature data on 4 common opioids, morphine, codeine, papaverine and noscapine.

Morphine

Morphine is an organic chemical compound and the main psychoactive substance found in opium. Morphine is a pure opioid agonist with the affinity mostly to μ (with greater affinity to μ 1 than μ 2) receptors and, to a lesser degree, to κ and σ receptors. Morphine undergoes metabolic processes in the liver, intestinal walls, kidneys and the central nervous system (CNS) – mostly through the pathway of linking to glucuronic acid with the use of glucuronyltransferase.

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It is main metabolites are morphine-3-glucuronate (M3G) and morphine-6-glucuronate (M6G). A minor amount of morphine (<5%) is metabolized with the use of CYP450 to normorphine.

M6G is an active metabolite of morphine with affinity to the opioid μ receptors, and the potency exceeding many times the analgesic potency of morphine. Another metabolite, M3G, does not manifest analgesic action, but it has neurotoxic properties confirmed in numerous animal-model tests. Its accumulation may lead to cognitive disturbances, delirium, agitation and myoclonia. After oral administration, due to the first pass effect, the concentrations of M3G to M6G and morphine are significantly higher than in patients receiving morphine parenterally.

Because of the fact that in normal conditions up to 30% of morphine is metabolized extrahepatically, moderate degree damage to the liver does not significantly disturb its processes of metabolism. Increased bioavailability of morphine is observed in patients with liver cirrhosis, probably due to decreased hepatic flow of blood. In patients with kidney dysfunction, renal elimination of morphine metabolites is impaired and the half-life of M6G is extended three times. Thus, patients with abnormal renal function are more susceptible to undesirable effects of morphine and require close monitoring, reduction in applied doses, extension of time between consecutive doses, and a change in the route of administration from oral to subcutaneous. Ideally, a change of morphine to a different opioid whose metabolites are excreted through the alimentary canal (e.g., to buprenorphine, methadone, fentanyl) is advised [2].

The use of morphine in the treatment of severe pain, mostly the pain occurring in the course of neoplastic disease, should be mentioned among its main medical applications. Morphine is the strongest natural analgesic which is prescribed for cancer patients. According to the analgesic ladder, it belongs to group III of substances used in the treatment of chronic cancer pain. Morphine is also used in patients after operations, after myocardial infarction, in ischemic heart disease, after injuries and accidents. Morphine is prescribed both orally and parenterally, however, absorption of the drug from the gastrointestinal tract is significantly weaker. Therefore, in order to obtain the equivalent analgesic effect, doses administered orally should be 2-3 times higher than parental doses. In the form of solution for injections, morphine is administered so to combat severe neoplastic pain, post-traumatic pain, pain after myocardial infarction and in general anesthesia. In the form of tablets, morphine is prescribed in the treatment of chronic pain [3].

Apart from an analgesic effect, morphine also shows intense sedative and hypnotic action. It causes intoxication, relaxation, the feeling of bliss and euphoria and sharpens the senses of hearing and touch. Moreover, it suppresses negative thoughts and emotions, decreases the feeling of anxiety and induces the state of tranquility. In its physical aspect, morphine also acts depressively on the respiratory center – it decreases the respiratory rate (possibly leading to apnea, but usually only in higher doses or when the renal excretory function is deteriorated), and causes depression of the cough center and stimulates parasympathetic nuclei of the oculomotor nerve, which brings about narrowing of the pupils (pinpoint pupils). Additionally, it also stimulates the chemoreceptor zone of the brain stem, which results in nausea and vomiting – an effect, especially frequently observed at the beginning of the therapy with morphine [4].

It should be also emphasized that morphine has a very high addictive potential. Just 1-2 applications are enough for the patient to develop mental dependence, which results in a very strong need for another dose. After several or a dozen uses, morphine causes physical dependence (the body demands constant and greater amounts of the substance). In the case of missing the dose, a craving for the drug develops, i.e., a number of withdrawal symptoms occur, among others: muscle tremor, watering of the eyes, nausea, vomiting, diarrhea, sneezing, profuse perspiration, restlessness, anxiety and depressive conditions. In extreme cases, high doses of morphine, circulatory disturbances or even death due to heart infarct may occur. Usually, morphine withdrawal symptoms last for 2-3 days and then disappears. After 8-10 days, the organism is completely detoxified, and, as a result, it again becomes sensitive even to small amounts of the drug. However, due to the mental dependence, addicts usually return to their addiction sooner [5].

Morphine increases formation of free radicals, acting as lipid peroxidation agent. Lipid peroxidation is increased after blocking the antioxidant enzyme. The process leads to formation of free radicals or reactive oxygen species (ROS). Free radicals or ROS cause damage to the cellular membrane and DNA fragmentation. Morphine is quickly metabolized in the liver, which induces a series of adverse physiological effects: direct or indirect toxic action, immunological action and oncogenic action. Research on rats demonstrates that morphine causes damage to hepatic cells and exerts genotoxic action on the liver of the studied animals. Other data indicates that morphine brings about oxidative stress through the induction of formation of ROS that are, in turn, able to initiate and promote oxidative damage in the form of lipid peroxidation. It is known that lipid peroxidation causes damage to cells through inactivation of membranous enzymes and receptors. The main pathway of morphine metabolism is co-oxidation to cotinine which is catalyzed by CYP2A6 in the liver [6].

Codeine

Codeine is a morphine derivative with a methyl constituent in position 3 (3-methyl-morphine). This alkaloid was originally extracted from the dried latex of the seed capsules of the opium poppy *Papaver somniferum*. Codeine, despite its effectiveness as an analgesic, antidiarrheal and antitussive agent can lead to abuse and dependence development. Interestingly enough, codeine is the most widely available and most commonly used opioid worldwide. Indeed, codeine is listed in controlled substances acts schedule II and in schedules III-V in the United States. Scheduling is based on the dose, indication, as well as coformulation of codeine with nonsteroidal anti-inflammatory drugs (NSAID) or acetaminophen.

Codeine is considered as a "weak" opioid which binds with the G-coupled μ opioid receptor. It is commonly believed that its stronger effects rely on its conversion to

further morphine and its appropriate derivatives by the biotransformation with the use of CYP2D6 cytochrome isoenzyme. Additionally, codeine is metabolized by an unknown mechanism to hydrocodone which possesses antinociceptive, as well as euphoric properties. Due to the bioactivation of codeine to morphine by the hepatic cytochrome P450 2D6 isoenzyme (CYP2D6), it can be assumed that the safety and the effectiveness of codeine are governed by the polymorphism of CYP2D6.

As it was established, the activity of CYP2D6 is under genetic control. Thus, it can be assumed that individuals can be categorized as poor, intermediate, extensive or ultrarapid metbolizers. Patients with ultrarapid metabolism with multiple functional CYP2D6 alleles are at risk of adverse effects. including respiratory depression. It has been established that patients who are CYP2D6 poor metabolizer will encounter no analgesic effect with regard to codeine intake, but may experience the adverse effects of codeine uptake. In contrast, ultra-rapid metabolizers patients are capable of metabolizing higher fractions of codeine to morphine. Thus, it is possible that patients may experience morphine overdose symptoms such as sleepiness, shallow breathing and confusion while undergoing normal codeine dosage treatment [7].

Due to the fact that codeine causes euphoria, apathy and blissful drowsiness, and shows antidepressive properties, codeine abuse is common. Worth mentioning is that over-the-counter sales (OTCs) in pharmacies ensures that availability of codeine is extremely high. The accessibility to this medication is correlated with poor awareness of the toxicity and abuse potential among society. As it was established by Wright *et al*. during research conducted in Scotland, codeine-containing medicinal products were most frequently perceived to be misused. According to the Roxburgh *et al*., who conducted comparative studies on an Australian population, the overall rate of codeine-related deaths had increased from 3.5% per million (data from 2000) to 8.7% in 2009 [8].

All these aspects can contribute to the toxic effects of codeine. Codeine intake comes with the typical side effects for opioids. However, it has been acknowledged that codeine rarely results in immediate adverse effects. Codeine, however, increases the release of histamine, which explains reports of contact dermatitis. It has also been reported that intravenous administration of codeine in children results in thurticarial and maculopapular rashes recurrent pseudo-scarlet fever and tachycardia. Additionally, severe hypotension apnea and cutaneous vasodilation have been seen. Indeed, Parke *et al.* (1995) noted that intravenous administration of codeine phosphate in adults can result in life-threatening hypotension. This conclusion resulted in issuance of a statement by the American Medical Association that codeine phosphate should not be administered intravenously in children and adults. Worth mentioning, children ultra-rapidly metabolize codeine. This leads to fatal amounts of morphine in the liver [3]. Thus, the data indicates that codeine is a highly abused dangerous substance. Due to the low awareness of the society and the easy availability of OTC preparations, the use of codeine may result in serious short- and long-term health effects.

Noscapine

Noscapine is a phthalideisoquinoline alkaloid, a plant specialized metabolite that belongs to the large and structurally diverse group of benzylisoquinoline alkaloids. The only commercial source of noscapine is cultivated opium poppy plants. Despite being isolated from opium more than two centuries ago, the nearly complete biosynthesis of noscapine was only established in recent years, thanks to an impressive combination of molecular genetics, functional genomics and metabolic biochemistry. Noscapine's antitussive properties were discovered in 1930, and the alkaloid has been widely used as a cough suppressant since the 1960's due to its low toxicity and non-narcotic nature.

Although the antitussive mechanism is unknown, noscapine was shown to have high affinity and stereo-specific binding to guinea pig brain, implying that noscapine acts on the CNS. Another study found that noscapine has an antagonistic effect on the β2 receptor, which could contribute to its inhibition of bradykinin-induced cough. Noscapine, long known for its mild mitotic poisoning effect, was recently shown to have antitumor properties when several natural compounds with similar structural features to commonly known antimitotic drugs (such as colchicine and podophyllotoxin) were tested as potential anticancer drugs. Noscapine significantly slows the progression of cancers such as lymphoma, melanoma, breast, ovarian and bladder cancer [9].

Noscapine has low toxicity because it does not overpolymerize microtubules, and the resulting subtle change in microtubule dynamics is enough to cause mitotic arrest. Noscapine has been tested for the treatment of multiple myeloma in Phase I and II trials. However, noscapine has some pharmacokinetic limitations, such as low bioavailability and a high ED_{50} (median effective dose), which make commercial formulations difficult to develop. Several synthetic analogs of noscapine (collectively known as 'noscapinoids') have recently been shown to have more potent anticancer properties than the parent molecule [10].

Noscapine is a noncompetitive antagonist of bradykinin receptors that has been shown to protect certain organs from ischemia-reperfusion injury. As a result, a bradykinin antagonist such as noscapine may reduce stroke sequelae and mortality. A rat model of brain edema was used to investigate noscapine›s potential in this regard. Accordingly, noscapine was found to be effective in reducing cerebral injury in neonatal rats suffering from hypoxic ischemia. Furthermore, a small clinical study found that oral noscapine reduced mortality from 80 to 20% in patients with signs and symptoms of ischemic stroke for less than 12 hours. Hemorrhage did not occur, and surviving noscapine-treated patients recovered faster than controls [11].

Noscapine treatment of PC12 rat adrenal pheochromocytoma cells resulted in a significant reduction in dopamine content without being cytotoxic in one study of its effect on dopamine biosynthesis. Noscapine research has also expanded into other clinical areas, such as a potential treatment for PCOS due to its antiangiogenic properties. Because of its disruption of cytoskeletal components, it has also

been proposed that noscapine could be used as an antiviral, although studies have shown that there is no such effect [12].

Papaverine

Papaverine (PPV), a benzylisoquinoline alkaloid extracted from the *Papaver somniferum* plant, is currently used as a vasodilator. It has a nonspecific relaxant effect on all types of smooth muscle and is used in clinical settings as a vasodilator and spasmolytic agent. According to research, PPV inhibits phosphodiesterase 10A (PDE10A), resulting in the accumulation of cyclic adenosine 3,5-monophosphate (cAMP), which affects multiple downstream pathways, including PI3K/Akt, a mammalian target of rapamycin (mTOR), and vascular endothelial growth factor (VEGF). The activation of protein kinase A (PKA), which, in turn, activates the mitochondrial complex I, can further affect mitochondrial metabolism.

PPV has been shown in the literature to have anti-proliferative effects in several tumorigenic cell lines, including adenocarcinoma alveolar cancer (A549) and human hepatoma (HepG-2). Cell cycle studies have yielded varying results, with the effects depending on concentration and cell type, with data indicating an increase in cells in the sub-G1 phase, which is indicative of cell death. PPV may be hypothesized to be a promising compound for use in anticancer research [13].

Papaverine can be oxidized to papaverinol, papaveraldine, and 2,3,9,10-tetramethoxy-12-oxo-12H-indolo[2,1-a]. Due to the presence of a methylene group, -isoquinolinium chloride is a chemical compound. Spasmolytic activity is lower in papaverinol and papaveraldine.

The pharmacokinetics of papaverine has also been assessed. The compound has a half-life of 60-120 min. Papaverine is approximately 90% bounded to plasma proteins. Metabolism takes place in the liver; it is excreted in the faeces and by the kidneys in the form of glucuronides [14].

In a publication from 2016, the authors report that papaverine toxicity occurs in the setting of its antimuscarinic action and blood-cerebrospinal fluid and blood-brain barrier compromise owing to acute subarachnoid hemorrhage and the direct effect of papaverine. In a case report included in the study, a 55-year old patient also experienced severe vasospasm and a minor stroke, both contributing to further blood-brain barrier disruption, and relatively acidic pH of the subarachnoid hemorrhage milieu [10].

Smith *et al.* (2004) assessed the neurotoxicity of papaverine in study from 2004. Five consecutive patients with cerebral vasospasm were treated with intra-arterial papaverine preserved with chlorobutanol and imaged with MRI fluid-attenuated inversion recovery and diffusion-weighted imaging after treatment. At autopsy, one patient's brain was histologically examined. All five patients experienced significant neurological decline immediately following treatment, which lasted until they were discharged from the hospital. MRI images in all cases revealed selective gray matter-only signal changes within the papaverine-treated vascular territory. Histological examination of one autopsy case also revealed selective neuronal injury with relative white matter preservation. Other research has concluded that Intra-arterial administration of papaverine preserved with chlorobutanol into vasospastic anterior cerebral arteries may result in significant neurological deterioration with selective gray matter changes on MRI imaging. This effect is consistent with a long-term toxic effect on the human brain. It is unclear whether this toxicity is caused by papaverine or chlorobutanol, and its use in the treatment of cerebral vasospasm should be limited to cases where no other options are available [15].

CONCLUSIONS

Opioids have long been the subject of research. The fact that they act on many physiological functions makes them effective drugs for pain, cough and symptomatic treatment of diarrhea. Unfortunately, their operation is not limited only to the desired effects, but they also have many side effects. Their addictive potential makes opioids abused for euphoria. The easy availability of drugs containing, for example, codeine, makes society struggle with the problem of abuse. In addition to side effects such as bradycardia, respiratory depression and histamine release, the effect on the nervous system is important, induce persisting neuroadaptation at the cellular and molecular level which brings about neuroplasticity changes and remodeling of reward neuronal circuits. In conclusion, opioids, although effective, carry many side effects about which society seems to be less and less aware.

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