Fall 2019

Adverse Effects of Opioid Dependency on Central and Peripheral Aspects of the Neuromuscular System

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Abstract

Prevalence of chronic pain and health care costs have caused an escalation of opioid dependency. The current national crisis involving opioid dependency and drug overdose are growing problems that need to be addressed. Since 2000, there has been an increased awareness of pain relief; more people are looking at alternative ways to induce pain relief and stricter guidelines in prescription of addictive opioid medications (Manchikanti et al., 2012). Despite growing efforts, opioid use and dependency has risen dramatically in the past few years; since 1999, there has been an increase in the number of opioids sold and opioid-related deaths in the USA (Manchikanti et al., 2012). Opioid misuse is the leading cause of accidental overdose and death (Compton & Volkow, 2006). In 2015, more than 40% of the world's supply of thebaine, the main ingredient in hydrocodone and oxycodone, two forms of opioids, was consumed by the USA (Hedegaard et al., 2017). In 2008 there were 36,450 drug overdose deaths and 14,800 of those deaths were related to opioid pain relievers (CDC, 2011). By 2017 there were a total of 70,237 drug overdose deaths in the USA (Hedegaard et al., 2017). While short term use of opioids has benign effects, long-term usage has meaningful effects on rates of abuse or addiction (Compton & Volkow, 2006). It is estimated that over 4.3 million US adults are taking opioids regularly in any given week; opioids are one of the most widely prescribed class of drugs in the US based on a nationally-representative telephone survey (Parsells et al., 2008).

Keywords

Opioids, Neuromuscular system, chronic pain, opioid dependency, drug overdose

Disciplines

Medicinal and Pharmaceutical Chemistry | Mental and Social Health | Substance Abuse and Addiction

Comments

Written for HS 311: Neuromuscular Physiology.

Background & Opioid Prevalence

Prevalence of chronic pain and health care costs have caused an escalation of opioid dependency. The current national crisis involving opioid dependency and drug overdose are growing problems that need to be addressed. Since 2000, there has been an increased awareness of pain relief; more people are looking at alternative ways to induce pain relief and stricter guidelines in prescription of addictive opioid medications (Manchikanti et al., 2012). Despite growing efforts, opioid use and dependency has risen dramatically in the past few years; since 1999, there has been an increase in the number of opioids sold and opioid-related deaths in the USA (Manchikanti et al., 2012). Opioid misuse is the leading cause of accidental overdose and death (Compton & Volkow, 2006). In 2015, more than 40% of the world's supply of thebaine, the main ingredient in hydrocodone and oxycodone, two forms of opioids, was consumed by the USA (Hedegaard et al., 2017). In 2008 there were 36,450 drug overdose deaths and 14,800 of those deaths were related to opioid pain relievers (CDC, 2011). By 2017 there were a total of 70,237 drug overdose deaths in the USA (Hedegaard et al., 2017). While short term use of opioids has benign effects, long-term usage has meaningful effects on rates of abuse or addiction (Compton & Volkow, 2006). It is estimated that over 4.3 million US adults are taking opioids regularly in any given week; opioids are one of the most widely prescribed class of drugs in the US based on a nationally-representative telephone survey (Parsells et al., 2008).

Despite the recent research into opioid addiction, and other serious side effects that it may cause, opioid use has continued to increase in the USA; more than 3% of persons 70 years and older are regular users of opioids (Parsells et al., 2008). The reason for the continued prevalence is because opioids are commonly used as an analgesia in medical practice. Some patients that use opioids to relieve pain may require higher and higher doses and so these few

individuals exposed to opioids chronically will develop addiction over the course of pain management (Chia et al., 1999 & Eitan et al., 2017). In a randomized clinical trial involving the analgesic effect of fentanyl, one type of opioid, they found that acute fentanyl tolerance develops after administration of high doses during surgery and thus patients reported higher pain intensity and required greater fentanyl consumption (Chia et al., 1999). However, higher doses may not necessarily increase pain relief; there is no clear correlation between higher opioid dosage and clinical benefits (Chen et al., 2013; Gatti et al., 2013; Vondrackova et al., 2008). One study found that there was no true relationship between higher opioid doses and clinical pain scores (Chen et al., 2013). In fact, several studies done with oxycodone, another opioid, has found that lower doses of the opioid in combination with naloxone, an opioid antagonist, has better chronic pain treatment outcomes (Gatti et al., 2013; Vondrackova et al., 2008). There has been increasing research in replacing opioids with other drugs or other treatments that are more effective in providing pain management and can reduce the various complications that come with opioid usage (Forouzan et al., 2019; Law et al., 2017 Radhakrishnan & Sluka, 2005;Vance et al., 2014; Walley et al., 2013; Weiss & Rao, 2017).

Opioid Effects on Various Organ Systems

Despite increased use of opioids for long term pain management, there are large gaps in understanding the efficiency and side effects of opioids. There is now more research being done on these adverse side effects and studies are finding that patients that take opioids chronically as a form of therapy face adverse effects on various organ systems, including respiratory, gastrointestinal, musculoskeletal, cardiovascular, endocrine, and central nervous system (Carman et al., 2011; Longstreth et al., 2006; Mogri et al., 2009; Rajagopal et al., 2004; Stewart & Owen, 2013; Walker et al., 2007). Many patients on opiate therapy experience constipation,

functional bowel disorders, and nausea (Longstreth et al., 2006). Chronic opioid use can also be associated with sleep apnea and ataxic breathing (Mogri et al., 2009; Walker et al., 2007). A large study found that there were increased risks of myocardial infarction and cardiovascular revascularization among patients using opioids chronically relative to the general population (Carman et al., 2011). Chronic opioid usage has an impact on the male and female endocrine system as well; in one study males, who survived cancer and are chronically dependent on consuming opioids, experienced hypogonadism (Rajagopal et al., 2004). The focus of this paper will be on the negative effects of opioids on the musculoskeletal system and the mechanisms behind these effects.

Opioids & Musculoskeletal System: Understanding the Increased Rates of Fractures

Chronic opioid use can be damaging to the musculoskeletal system, for instance, chronic opioid dependence is associated with increased fracture risk according to multiple cohort studies (Guo et al., 1998; Li et al., 2013; Saunders et al., 2010; Shorr et al., 1992; Spector et al., 2007; Stewart & Owen, 2013; Vestergaard, Rejnmark, & Mosekilde, 2006). Studies focused on older adult populations, find that opioid prescriptions like codeine or propoxyphene tend to lead to increased rates of hip fractures (Guo et al., 1998; Kamal, Stuart & Beers, 2006; Li et al., 2013; Shorr et al., 1992). In a study done on 4,500 residents of Saskatchewan, Canada, who were 65 years or older, the risk of a fracture was 1.6 times greater for current users of codeine or propoxyphene compared to nonusers (Shorr et al., 1992). Concurrent users of both prescriptions and other psychotropic drugs were 2.6 times more likely to sustain a fracture injury than nonusers of either drug class (Shorr et al., 1992). Similar results were found in another study on just propoxyphene that correlated increased fracture rates and opioid usage among older adults (Kamal, Stuart & Beers, 2006). Similar studies done on morphine, fentanyl, methadone,

oxycodone, nicomorphine, ketobemidone, tramadol, and codeine found that all were associated with increased fracture rates attributed to central nervous system effects (Vestergaard, Rejnmark, & Mosekilde, 2006).

Clinical trials have suggested that the opioids have acute effects on the central nervous system including cognitive impairment, sedation, and dizziness all of which causes elevated risk of falls and fractures (Guo et al., 1998; Li et al., 2013; Vestergaard, Rejnmark, & Mosekilde, 2006). The importance of opioid prescription in managing pain requires a better understanding of opioid drugs and the side effects these drugs have on overall health so clinicians can weigh out the benefits and harms of prescribing this class of drugs. It is also important to consider the type of opioid prescribed because codeine and propoxyphene were correlated with increased fracture risks higher than other opioids like morphine (Li et al., 2013). The dosage is also important to consider because higher opioid doses that were greater than or equal to 50 mg a day were associated with a 2.00 increase in risk of fractures whereas lower doses did not have as high of a risk (Saunders et al., 2010). The mechanism in which opioids affect the central nervous system is through the specific binding receptors.

Cognitive effects of Opioids and the Specific Binding Receptors

Opioids, drugs that stimulate opioid receptors, induce adverse effects on the central nervous system, that can be divided into three groups. The first group includes effects that lower the level of consciousness-sedation, drowsiness and sleep disturbance. The second group affects the thinking process and includes psychomotor impairment, delirium, hallucinations, dreams and nightmares. The third group is of the direct toxic effects of opioids on neurons (Jane, 2007). Patients that receive long term chronic opioid therapy often discontinue due to adverse cognitive effects including memory deficits, sleep disturbance, and fatigue (Dhingra et al., 2015). Observing the adverse side effects of opioids on patients that take pain medication and the

various effects of different opioids and the receptors that they bind to, became an area under intense research. Gene coding and brain mapping revealed the three opioid peptide systems that were responsible for the effects and addictiveness of various opiate drugs, these three receptors were (μ) MOR, (κ) KOR, and (δ) DOR (Valentino & Volkow, 2018).

Opioids interactions with the Mu, Delta, and Kappa Receptors

Opioids act on the opioid system consisting of the three most researched opioid receptors: mu, kappa and delta, also known as (μ) MOR, (κ) KOR, and (δ) DOR respectively, whose receptors are activated by opiates like morphine (Grechko et al., 2017; Guarraci et al., 2017;Ozaki et al., 1994 ; Shahbazian et al., 2002; Valentino & Volkow, 2018). Opiates have interesting effects on contraction in various parts of the body, for instance, they may inhibit gastrointestinal propulsion (Shahbazian et al., 2002). Opioids like morphine seem to induce inhibition of peristalsis depending on the dosage, with a dose-dependent maximum effect observed in the dose of 10 mg/kg in one study (Grechko et al., 2017). Other findings support that opiates can cause presynaptic inhibition of excitatory neurotransmission at two sites within the wall of the gallbladder: these findings support the concept that opiates can contribute to gallbladder stasis by inhibiting ganglion activity and neurogenic contractions (Guarraci et al., 2017).

Mu-opioid receptor agonists, kappa-opioid receptor agonists and a delta-opioid receptor agonist were studied in one study through guinea pigs. Experiments with the delta-opioid receptor antagonists, the kappa-opioid receptor antagonist and the mu-opioid receptor antagonist revealed that the inhibitory effects of opiates on involuntary contractions were mediated by kappa-opioid receptors and that of morphine through mu-opioid receptors. The results show that the neural pathways controlling peristalsis in the guinea-pig small intestine were inhibited by

opioids acting via mu- and kappa-, but not delta-, opioid receptors (Shahbazian et al., 2002). Similar results were found in another study in isolated guinea-pig ileal longitudinal muscle, using selective mu, kappa and delta opioid receptor antagonists where the mu antagonist produced a concentration-dependent twitch inhibition (Ozaki et al., 1994). These studies explain why KORs have been found to localize to axon terminals and inhibit neurotransmitter release and MOR has been found to inhibit norepinephrine, substances important in the ends of nerve fibers that increase the force of muscle contraction (Valentino & Volkow, 2018).

Opioids Inhibit Neurotransmitter Release

Opioids affect various parts of the body, and can inhibit neurotransmitter release from different parts of the body inhibiting muscle contractions. Release of norepinephrine, also known as noradrenaline, was inhibited in the mouse vas deferens via opiate receptors (Knoll et al., 1981). Interestingly, other consecutive studies done on animal species, have found that morphine, pethidine, naloxone, N-methylnaloxone, naltrexone and levallorphan seem to inhibit muscle contraction mediated via the peripheral opiate binding site (Berggren, Rubenson, & Sillen 1992; Ramabadran et al, 1983; Sim & Chua 1986; Sim & Ramabadran 1983). One study found that morphine depresses twitch and tetanus of guinea-pig ileum by reducing acetylcholine output from nerve endings (Paton, 1997).

Different opioids are grouped into different categories suggesting sub-types of binding sites in the contraction of skeletal muscle; the classification of the four classes are as follows, morphine and naltrexone each formed their own class, naloxone, N-methylnaloxone and pethidine formed another class; levallorphan and dextrallorphan formed the fourth class (Ramabadran et al, 1983). The significance of each of the sub-types, their binding sites, and how they may affect skeletal muscle contraction is still an area under research but based on different

animal studies, one way opioids seem to inhibit contraction is through acetylcholine (Ramabadran et al, 1983; Sim & Chua, 1986; Sim & Ramabadran, 1983). An interesting study done on the toad rectus, found that certain opioids, except morphine, nalorphine and levorphanol, inhibit the ACh-induced contraction through multiple modes of action; the opioids inhibit competitively indicating that they are able to compete with ACh for cholinergic receptors at the nicotinic site (Sim & Ramabadran, 1983). Further research, found that the opioids which are poor or non-inhibitors of AChEase, the enzyme that breaks down acetylcholine, are strong inhibitors of the ACh-induced contraction of the toad rectus, whereas the reverse is true for inhibitors of AChEase (Sim & Chua, 1986). Another study, however, done on fetal vessels of human placentae find that only high concentrations of synthetic opioids or opioid antagonists reduced ACh output; thus, therapeutic concentrations of morphine and pethidine would not affect placental ACh output (Gude et al., 1989). Thus, while we know that opioids affect neurotransmitter release in the brain and central nervous system there is still more research to be done on whether the inhibition affects contraction of skeletal muscles in humans and the type of opioids that may induce these effects.

Clinical Interventions: Opioids and Naloxone Interactions

Naloxone, an opioid antagonist, counteracts some of the effects of morphine and causes a significant facilitation of the electrical field stimulation-induced contraction, in both rat and human detrusor. This suggests that naloxone may be able to counteract some of the inhibitory effects of morphine (Berggren, Rubenson, & Sillen 1992). The interactions between these two drugs may explain why buprenorphine/naloxone, methadone and lofexidine are medications that are often used in the treatment of opiate withdrawal; methadone/lofexidine and buprenorphine/naloxone have comparable outcomes and efficiency when treating detoxification

in low dose opiate users (Law et al., 2017; Walley et al., 2013; Weiss & Rao, 2017). Naloxone and other medications are not the only treatments for opioid dependency under study.

Clinical Interventions: Transcutaneous Electrical Nerve Stimulation (TENS): therapeutic treatment in Replacement of Opioids

Transcutaneous Electrical Nerve Stimulation (TENS), is clinically used as a therapeutic mechanism to reduce pain by activating large diameter afferent fibers in order to reduce pain (Levin & Hui-Chan, 1993; Radhakrishnan & Sluka, 2005; Vance et al., 2014). TENS produced an anti-hyperalgesia effect on induced hyperalgesia in the knee joints of rats, this anti-hyperalgesia is beneficial in reducing use of other forms of pain relievers like opioids (Radhakrishnan & Sluka, 2005). A human study found similar results, and found that TENS activated similar peripheral afferent fibers in humans in order to provide an acupuncture-like relief from pain (Levin & Hui-Chan, 1993). The reduction of pain through TENS will replace other forms of analgesics like opioid drugs that have serious side effects including contraction inhibition and addiction.

Clinical Interventions: Education to Reduce Opioid Dependency

Opioid overdose and addiction is a serious concern for the nation, in order to combat this growing problem not only will we need to rely on alternative forms of pain management like TENS and other medications like naloxone but the nation must actively provide overdose education. In Massachusetts, overdose education and nasal naloxone distribution known as OEND programs are utilized and opioid overdose rates were reduced in communities where OEND programs were implemented (Walley et al., 2013).

Conclusion

It is clear that the country is facing a national opioid crisis with rising rates of opioid dependency and rising rates of drug overdose deaths (Compton & Volkow, 2006; Manchikanti et al., 2012). Opioids have taken over the country with an estimated of over 4.3 million US adults taking opioids regularly in any given week; Americans have become dependent on opioid drugs for pain relief and these drugs continue to be prescribed daily to more and more people (Parsells et al., 2008). Opioids should not be used for long term pain management because of the various side effects these class of drugs can induce. There has been increasing research that shows a negative impact on overall health and these adverse effects can target various organ systems including respiratory, gastrointestinal, musculoskeletal, cardiovascular, immune, endocrine, and central nervous system (Carman et al., 2011; Longstreth et al., 2006; Mogri et al., 2009; Rajagopal et al., 2004; Stewart & Owen, 2013; Walker et al., 2007).

Chronic opioid usage has been associated with increased fracture risks according to multiple studies and many studies have suggested that opioids cause acute effects on the central nervous system including cognitive impairment, sedation, and dizziness which leads to elevated risks of falls that lead to increased rates of fractures in patients taking opioids (Guo et al., 1998; Li et al., 2013; Vestergaard, Rejnmark, & Mosekilde, 2006). Opioids act on specific opioid receptors in the central nervous system that may cause these different effects. The three opioid receptors that are commonly discussed in the literature include (μ) MOR, (κ) KOR, and (δ) DOR (Valentino& Volkow, 2018).

Opioids like morphine bind to mu receptor and can induce effects in various parts of the body and some of these effects include inhibition of contraction. Other findings support that opiates cause inhibition of excitatory neurotransmitters or inhibit twitches (Guarraci et al., 2017; Ozaki et al., 1994 ; Shahbazian et al., 2002). Morphine and other opioids seem to inhibit muscle

contraction through inhibition of acetylcholine according to a few studies (Berggren, Rubenson, & Sillen 1992; Ramabadran et al, 1983; Sim & Chua 1986; Sim & Ramabadran 1983). However, these results are not conclusive and there has been no human clinical trials but the research into opioids and their binding sites is still ongoing because there is still a lot the scientific community doesn't know about opioids.

While we may not know everything about opioids, the country is still facing an opioid epidemic. There is no single solution to the opioid crisis, but action needs to be taken now because as the death toll rises and opioids claim more lives patients are still being prescribed opioid medications. Some of these patients may take these drugs without fully understanding the adverse effects opioids have on overall health. Naloxone, may be one solution because this drug can counteract some of the effects of morphine and can be used in the treatment of opioid withdrawal or detoxification (Law et al., 2017; Walley et al., 2013; Weiss & Rao, 2017). Other solutions may be to prevent opioid dependency in the first place through educational reform that has proven to be effective for Massachusetts (Walley et al., 2013). Replacing opioid medication with other forms of analgesics may also be an option, TENS, for instance is one such clinical practice being used to relieve pain (Levin & Hui-Chan, 1993; Radhakrishnan & Sluka, 2005). As further research continues on opioids, their adverse effects on health, and the receptors that they bind to causing inhibition of normal function, action needs to be taken to reverse the growing number of opioid overdose deaths and addicts.

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