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Cardiac Effects of Opioid Therapy

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Abstract

Objective. The use of opioids to treat chronic pain has come under increased scrutiny, as such use has been associated with significant risk of death, with limited data regarding the long-term effectiveness, especially when used to treat noncancer pain. The purpose of this manuscript is to discuss the cardiac effects associated with long-term opioid therapy.

Design. A literature search was performed using OVID.

Results. Most opioids have little direct negative effect on cardiac contractility. However, opioid administration can be associated with decreased cardiac function when administered in combination with other medications, including benzodiazepines. Opioids can lead to bradycardia and vasodilation, and as a result can rarely lead to edema, hypotension, orthostatic hypotension, and syncope when used at analgesic doses. While most opioids have no effect on cardiac conductivity, methadone, and buprenorphine can prolong QTc, especially when used in patients at increased risk for QTc prolongation. Electrocardiogram (ECG) monitoring of QTc at baseline and following dose increases is appropriate in patients receiving these medications.

Conclusions. There are limited data to suggest that chronic opioid administration may be associated with an increased risk for cardiac-related adverse effects. However, this observation has not yet been confirmed. Regardless, while opioids are an important medication for the treatment of a multitude of chronic pain conditions, careful patient selection, and diligent monitoring is likely to decrease the risk of harm and improve patient outcomes.

Key Words. Opioids; Chronic Pain; opioid cardiovascular effects

Introduction

The purpose of this manuscript is to review the impact of chronic opioid therapy on cardiac function. Unfortunately, even though opioids have been available for decades, their impact on cardiac function when used chronically has not been carefully studied. The richest information regarding the impact of opioids on cardiac function come from the anesthesia literature. It is important to note, however, that opioid effects may change based on the duration of exposure. Therefore, the cardiac effects of opioids observed with acute exposure may not be predictive of the effects of chronic opioid administration.

Opioids bind to opioid-specific receptors that are located in the central nervous system (CNS). Receptors have been located in many other organs, including cardiovascular tissue [1]. Opioid receptors are linked to G proteins, and activation of the opioid receptor leads to membrane hyperpolarization.

Opioids administered as part of an anesthetic are thought to have modest direct effects on the heart. When administered alone, opioids other than high-doses of meperidine do not depress cardiac

contractility. However, opioids are rarely the sole anesthetic agent used, and when combined with other medications there can be significant changes in cardiac function. In addition, while cardiac contractility may not be affected, the administration of opioids can impact other aspects of the cardiovascular system. Several opioids can cause vagus nerve-mediated bradycardia. In addition, acute administration of opioids can lead to vasodilation and decreased sympathetic tone. When administered with benzodiazepines, opioids can significantly decrease cardiac output. Likewise, significant cardiovascular effects can be observed when opioids are administered with inhaled anesthetics.

Morphine, hydromorphone, hydrocodone, and meperidine can lead to histamine release, and as a result can cause significant decreases in systemic vascular resistance and blood pressure. This effect can be treated with the administration of H_1 and H_2 antagonists, and may require the administration of vasopressors and intravenous fluids.

Opioids have been found to have minimal effect on coronary vessel vasomotor tone. Studies on the influence of opioids on perioperative ischemia have suggested that they can mimic ischemic preconditioning, reducing infarct size [2–4]. There may be multiple mechanisms involved, perhaps via a reduction in oxidant stress on cardio-myocytes or facilitated via the adenosine A1 receptor or protein kinase C [5,6]. However, opioid-based anesthetics have not been shown to reduce intraoperative ischemia, postoperative myocardial infarction or death [7].

Do Chronic Opioids Worsen Cardiac Outcomes?

Few studies have been published evaluating the effect of chronic opioids on cardiac outcomes. Carman et al. published a retrospective claims-based study that evaluated the incidence of myocardial infarction, or MI associated with coronary revascularization, among individuals taking chronic opioids at high doses vs low doses, and compared with cohort from general population with otherwise similar risk stratification [8]. This evaluation included 148,657 people in both the chronic opioid group and the control group. When the incidence rate ratios were adjusted for coronary heart disease risk factors, the risk for MI was 2.7 times higher and the risk for MI/CR (coronary revascularization) was 2.4 times higher in patients taking chronic opioids when compared with the matched controls. The study included a third group of 64,072 chronic users of celecoxib and 20,502 chronic users of valdecoxib. These COX-2 selective nonsteroidal anti-inflammatory drug users had 1.7–1.9 times the rate of MI and MI/CR when compared with the controls. Therefore, this study reported that the increased risk for myocardial infarction is higher in patients consuming chronic opioid than that observed in patients taking chronic COX-2 selective nonsteroidal anti-inflammatory drugs.

It is important to point out that this was a retrospective claims-based study, and other confounders that were not identified may ultimately account for the differences observed between these study groups. However, if confirmed, it will be important to identify the underlying cause(s) of the excess death rate associated with the administration of chronic opioids to allow for the development and implementation of efforts to improve patient screening to identify patients at high risk for harm, as well as monitoring strategies during treatment to avoid potentially serious adverse events. It is likely that the effect of chronic opioids on the cardiovascular system is multifactorial. For example, as is seen when opioids are used in the operating room, it is very likely that risk of harm associated with opioid administration is increased when opioids are used in combination with some other medications and in patients with significant underlying disease. Indeed, underlying cardiac disease may be present in up to 50% of patients receiving opioids through a pain center [9]. Care will need to be taken to avoid the risk of harm while also effectively treating pain in those patients in whom opioids are effective.

Cardiovascular Effects of Specific Opioids

This section explores the potential cardiovascular adverse side effects associated with specific opioids.

Buprenorphine

Buprenorphine is a partial mu agonist, a kappa receptor antagonist, a delta receptor agonist, and an ORL-1 (nociception) receptor partial agonist. Given its partial mu agonist properties, it has a ceiling effect on analgesia. However, buprenorphine binds tightly to the mu opioid receptor, and as a result can have a prolonged duration of effect [10].

Buprenorphine is not thought to have any direct negative effects on cardiac function. However, buprenorphine administration can lead to hypotension, and orthostatic hypotension and syncope [11].

Buprenorphine may have a dose related effect on QTc. Transdermal buprenorphine at low doses of 10 mcg/h have been reported to have no clinically meaningful effect on mean QTc. However, transdermal buprenorphine at a dose of 40 mcg/h have been reported to prolong QTc by 9.2 (90% confidence interval 5.2–13.3) ms [11]. Patients with hypokalemia, unstable atrial fibrillation, bradycardia, unstable congestive heart failure, or active myocardial ischemia may be at increased risk for prolonged QTc. In addition, patients taking quinidine, procainamide, disopyramide, sotalol, amiodarone, and dofetilide may also be at increased risk of prolongation of QTc.

Fentanyl

Fentanyl is a synthetic mu opioid receptor agonist. It is not associated with histamine release. Fentanyl has

been evaluated for use as an anesthetic agent during cardiac surgery. When used in this setting, intravenous fentanyl leads to minimal changes to cardiovascular function other than (usually) modest changes in heart rate and blood pressure [12]. However, it is important to note that the use of fentanyl with benzodiazepines can lead to profound cardiovascular changes, including decreased stroke volume and cardiac output, as well as profound decreases in blood pressure.

As with all opioids, fentanyl administration in analgesic doses can cause hypotension, including orthostatic hypotension and syncope, but is generally well tolerated, even in patients with coexisting cardiac disease. Bradycardia has been reported following chronic use at analgesic doses, but is also rare. Fentanyl is not associated with QTc prolongation.

Hydrocodone

Hydrocodone is a semisynthetic mu opioid receptor agonist. Hydrocodone is not thought to have any direct negative effects on the heart. Although, it can lead to histamine release. Administration of hydrocodone can cause hypotension, and orthostatic hypotension and syncope. Risk of hypotension is increased when hydrocodone is used in combination with other medications such as phenothiazines that can decrease vasomotor tone.

A single case report documented vagally-mediated AV block leading to prolonged ventricular asystole as a serious side effect to low dose hydrocodone administration in an otherwise healthy woman [13]. However, this appears to be a potentially rare adverse effect of all opioids, and does not appear to be an adverse side effect specific to hydrocodone.

Hydromorphone

Hydromorphone is a semisynthetic mu opioid receptor agonist that is a derivative of morphine. As with all opioids, hydromorphone can cause hypotension, including orthostatic hypotension and syncope. Hydromorphone has been reported to be associated with histamine release and the adverse side effects associated with histamine release. However, hydromorphone appears to be much less likely to lead to histamine release when compared with morphine [14]. As described earlier with hydrocodone, hydromorphone has been associated with vagially-mediated sinus pauses leading to significant decreased in heart rate in a patient with no known cardiac conduction disease [15].

Meperidine

Meperidine is a mu opioid receptor agonist. It use has waned due to meperidine's increased risk for adverse effects compared with other potent opioids. Indeed, chronic oral use is relatively contraindicated due to the significant risk of metabolite accumulation leading the CNS toxicity. Meperidine administration is associated with decreased myocardial contractility and can cause significant decreases in blood pressure and cardiac output following intravenous administration [16]. The cardiovascular effects of meperidine appears to be due to a combination of a direct effect on myocardial contractility and peripheral vasodilation [17].

Methadone

Methadone is a potent mu opioid receptor agonist that is used for the treatment of pain as well as for the treatment of opioid substance use disorder. Methadone is a synthetic opioid analgesic that has been associated with an increasing number of deaths, most commonly when the drug is used for the treatment of chronic pain [18]. The causes for these deaths is likely multifactorial, but methadone's effect on cardiac conductivity may certainly be a contributing factor.

Similar to what is seen with other opioid compounds, methadone can cause edema, as well as syncope, flushing and hypotension. Methadone is not thought to have any direct negative effect on cardiac contractility.

The major concern regarding methadone's impact on the cardiovascular system is the potential for methadone to prolong QTc, which can lead to Torsades de points. Recent guidelines regarding the use of methadone that include specific guidelines regarding ECG monitoring have recently been published [18]. These guidelines suggest careful patient selection and monitoring, especially in patients who are at increased risk for QTC prolongation.

Increased risk for life threatening arrhythmia exists for patients with a QTc greater than 450 ms, and continues to increasing with increased QTc Patients with a QTc equal to or greater than 500 ms have substantially increased risk for Torsades de points when compared with individuals with QTc less than 450 ms. Existing guidelines urge clinicians to obtain a baseline ECG before starting methadone therapy, to carefully consider the advisability of methadone therapy in patients with QTc above 450 ms, and to not initiate methadone therapy in patients with QTc above 500 ms. ECG should be repeated 2–4 weeks after methadone therapy has been started, and after dose increases.

Risk for QTc prolongation appears to increase with increased methadone dose, although concern has been raised regarding the potential impact of methadone on QTc at the lower doses commonly used for the treatment of pain [19]. Care should be used when methadone is administered at any dose.

Morphine

Morphine is a mu opioid receptor agonist, and is used for the treatment of acute, cancer-related, and chronic

noncancer pain. Morphine was isolated in the 17th century by Friedrich Serturner. Morphine has been evaluated for use as the primary anesthetic for cardiac surgery [20]. However, its use in this setting was associated with numerous adverse effects. As discussed earlier, morphine can cause histamine release and consequent vasodilation and hypotension. It is important to note, however, that long-term open-label safety trials of long-acting morphine preparations have reported few cardiovascular-related adverse events [21].

Oxycodone

Oxycodone is a potent opioid agonist that is relatively selective for the mu receptor at analgesic doses. Oxycodone is not thought to have significant adverse effects on cardiac function. However, as seen with other opioids oxycodone can cause bradycardia and hypotension, including orthostatic hypotension. Oxycodone has been associated with histamine release, but this adverse side effect is rare.

Oxycodone has been reported to lead to a modest dose-related increase in QTc. Fanoe and associates reported that doses greater than 100 mg/day can lead to a 10 ms (95% confidence interval 2–19 ms) prolongation of QTc [22]. However, this finding needs to be confirmed by other researchers.

Oxymorphone

Oxymorphone is a semisynthetic mu agonist opioid analgesic. It can have an effect other opioid receptors at higher doses. Cardiovascular adverse effects associated with analgesic doses of chronic oxymorphone appear to be rare. Bradycardia, palpitation, syncope, tachycardia, and postural hypotension have all been reported, but the reported incidence is less than 1% [23]. The risk of harm may be higher in patients aged 65 years and higher, as these patients have a higher burden of both underlying cardiac disease as well as concomitant medications that may, in combination with oxymorphone, lead to adverse effects. In addition, patients 65 years or older appear to demonstrate different pharmacokinetics compared with younger adults, as they have a 1.4-fold increased in oxymorphone AUC and a 1.5-fold increase in C_{MAX}.

Tapentadol

Tapentadol is a centrally acting analgesic that works at least in part as a mu opioid receptor agonist. While tapentadol has several potential adverse side effects, it appears to have a low risk of cardiovascular adverse events at doses used for chronic analgesia. Afilalo et al. reported that no cardiovascular adverse events were observed in over 300 patients who received tapentadol as part of a 3-arm Phase 3 efficacy and safety trial [24]. However, hypotension (probably via peripheral vasodilation) has been reported. The risk for hypotension caused by tapentadol is increased when tapentadol is used in combination with other CNS depressants, or in patients with significant compromise of cardiac function. Tapentadol does not impact the QT interval. However, tapentadol administration can lead to serotonin syndrome, which can certainly lead to serious cardiac arrhythmia.

Tramadol

Tramadol is an opioid and also acts as both a serotonin and norepinephrine reuptake inhibitor. Tramadol at analgesic doses has a low risk for cardiovascular adverse effects. However, tramadol administration can lead to serotonin syndrome, [25] which can lead to cardiac arrhythmia. Cardiac side effects may range from agitation and palpitations to rhythm abnormalities, conduction defects, and cardiac arrest [26].

Conclusion

While opioids are an important tool that can be effective for the treatment of chronic pain, it is important for the clinician to be aware of the risks associated with this class of medication. Careful patient selection, patient education regarding the proper use of the medication, careful monitoring of coexisting health conditions that may increase the risk of harm, as well as careful ongoing monitoring of other medications the patient is taking are vital to safe opioid administration. Special care must be taken in patients with pre-existing cardiac disease, the elderly, and in patients receiving methadone.

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