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IN DENTISTRY

Opioids' Impact On Dental Anesthesia

This review presents data from the literature focusing on opioids' action on the central and peripheral nervous systems and subsequent influence on local anesthetics.

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EDUCATIONAL OBJECTIVES

After reading this course, the participant should be able to:

1. Describe the use and prevalence of opioid prescriptions in dentistry and the impact of these drugs on local anesthesia.
2. Explain indications for opioids in the dental setting, the principal opioid receptors, and impacts of "first-pass" metabolism on orally administered opioids.
3. Discuss considerations for local analgesics, especially when local drug concentrations increase, or the agents are combined with opioids.

According to Suda et al,[1] "Dentists write one in 10 opioid prescriptions in the United States" and "between one in four and one in two opioids prescribed to adult dental patients are overprescribed." This highlights the need for providers to understand nonopioid pain management strategies, as well as the interaction between medical or nonmedical opioid use and the administration of local anesthesia (LA). While adequate treatment of acute pain is an essential dimension of quality healthcare,[2] the inadequate treatment of acute pain is still common.[3,4] Furthermore, limitations of nonopioid analgesics' effectiveness for treating acute pain may necessitate the use of opioids for managing moderate to severe pain.[5]

When prescribing and administering opioids, clinicians should consider the potential for drug interactions, their durations, and the short and long-term effects of these interactions. In addition to interfering with other medications used in dental settings, the clinical factors associated with opioid prescribing underscore the impacts of opioids on the central and peripheral nervous systems.

A guarantee of continuous and adequate analgesia is vital for all dental patients. For opioid-tolerant individuals (e.g., patients in recovery or medically assisted addiction and maintenance treatment), avoiding perioperative pain is crucial. The optimization of perioperative pain therapy can only succeed when the dental practitioner understands the pharmacodynamics of the analgetic process and opioids' effects on analgesia.

Though local dental analgesia does not differ from those routinely used for patients without opioid tolerance, dentists have experienced difficulties obtaining complete analgesia in opiate-tolerant patients. This phenomenon can be partially explained by the low pain threshold caused by narcotic addiction originally described by Martin and Inglis[6] and further supported by the studies by Compton[7] and colleagues that provide clinical evidence of the negative impacts of addiction on pain tolerance in patients using opioids versus patients in remission.

Special conditions apply to dental patients who are in recovery (i.e., previously addicted to opioids) and those currently undergoing medically assisted treatment (either maintenance therapy or to manage withdrawal). According to Savage,[8] for such patients, a relapse to addiction will more likely be provoked by insufficiently successful dental analgesia than ineffective pain management.

This article examines opioid's impacts on the mechanism of action — as well as efficacy — of LA through the experimental data published in the scientific literature.

OPIOID OVERVIEW

According to the American Dental Association, "The term opioid is used to describe drugs that have pharmacologic activity similar to opium."[9] Opioid extracts derived from the exudate of the poppy plant naturally contain morphine and codeine. In addition to their beneficial analgetic qualities, such as sedation or cough suppression, opioids produce significant euphoria, respiratory depression, constipation, confusion and imbalance.

While opiates refer to natural substances derived from the poppy plant and include opium, codeine and morphine, opioids are synthetic derivatives of opiates that include drugs such as oxycodone hydrochloride, fentanyl and hydrocodone.

Opiates and opioids function similarly, with opioids being significantly more potent and having severe and even life-threatening side effects. As pharmaceutical agents, opioids stimulate opioid receptors and are primarily used to treat moderate to severe pain.

MECHANISM OF ACTION

Opioids act on the central nervous system (CNS), targeting opioid receptors located in the CNS and throughout the body. Since opioid compounds have a molecular structure similar to naturally occurring endorphins, they can effectively mimic the analgetic effects of endorphins within the peripheral nervous system (PNS). Endorphins are a group of peptide molecules that expressly bind with opiate receptors.

Clinically, opioids induce the CNS and produce multiple adverse effects that can be divided into three groups. The first group lowers the level of consciousness and promotes sedation, drowsiness and sleep disturbances. The second group affects the thinking process and ability to react, producing cognitive impairment, psychomotor impairment, delirium, hallucinations, dreams and nightmares. The third group involves opioids' direct toxicity on neurons and includes myoclonus, hyperalgesia and tolerance.

These drugs act on neurons via their interaction with neuronal cell membrane receptors, similar to beta-endorphins that produce analgesia by binding to opioid receptors at both pre- and postsynaptic nerve terminals, with particular affinity to presynaptic neuro-binding. The three primary opioid receptors include the mu, delta and kappa. These receptors contain seven transmembrane-spanning domains of amino acids that couple with guanosine triphosphate (GTP) or G-proteins, which are guanine nucleotide-binding proteins. G-proteins are composed of three subunits: alpha (α), beta (β) and gamma (γ). When an agonist binds a G-protein-coupled opioid receptor, the α subunit replaces guanosine diphosphate with GTP. This transition causes the α-GTP complex to detach from the βγ subunit, creating two separate complexes. These complexes interface with several ion channels, inhibiting calcium release while stimulating potassium release. In addition, binding causes a decrease in intracellular cyclic adenosine monophosphate (cAMP). The culmination of these actions results in lower cAMP levels, decreased release of neurotransmitters, and cell hyperpolarization.[10]

The pharmacologic impacts of opioids will vary depending on the type of receptor. For example, when occupied, the mu opioid receptor produces analgesia, bradycardia, respiratory depression and sedation. It can also cause gastrointestinal effects, such as nausea, vomiting, and reduced gastric motility. Similarly, stimulating the delta opioid receptor produces spinal and supraspinal analgesia while decreasing gastric motility. Finally, activation of the kappa opioid receptor causes spinal analgesia, dysphoria and diuresis.[11]

CLINICAL APPLICATION

Known mainly for their strong analgesic properties, opioids are centrally acting analgesics that have earned an important place in medical and dental practice due to their longstanding record of successful pain management. While injectable opioids are generally administered in hospital settings, dentists prescribe oral formulations for patient convenience.

Even though orally administered opioids are quickly metabolized, the "first-pass effect" results in only a minimal amount of the drug effectively reaching circulation. The effects of first-pass metabolism of orally administered medications significantly limit the analgesic impact of compounds such as codeine, hydrocodone and oxycodone. This stands in contrast to agents such as morphine and fentanyl, which are traditionally and exclusively clinically delivered parenterally to control acute pain.

SIDE EFFECTS OF OPIOIDS

Opioids are depressant drugs that gradually slow down processes in the body, leading to a gradual shutdown of some physiological functions. Longer-term and larger-amount opioid use and misuse lead to increased tolerance and addiction. Importantly, using opioid drugs — even for a short period — can be a stepping stone toward a significant addiction and substance use disorder.

DENTAL ANESTHETICS

In clinical use, LA blocks the transmission of impulses in nerve fibers, leading to the reduction or elimination of pain stimuli, while preserving some other sensory functions. In dental practice, topical anesthesia, peripheral nerve blocks, and tissue infiltration are the most common ways to administer LA.

The action of LA inhibits nerve transmission by reversibly binding to voltage-gated sodium channels within the nerve plasma membrane. In addition, LA attachment to the sodium channel makes it impermeable to sodium, subsequently inhibiting the initiation of action potential and reversibly inhibiting the propagation of the signal and nerve transmission.12 This action occurs in a concentration-dependent manner. As LA concentrations increase, the action potential peak decreases, the firing threshold increases, the refractory period is prolonged, and the impulse conduction is attenuated. Higher concentrations can inhibit nerve conduction altogether, leading to profound anesthesia.

EXPERIMENTAL FINDINGS

According to Cohen and Mao,[13] when used together, LA and opioids produce "synergistic analgesia." While the mechanism of this interaction remains unclear since the cellular effects of opioids differ from those of LA, the potential of opioids to decrease the effectiveness of LA can lead to unpredictable perioperative outcomes and complex postoperative patient management.

Regardless of these differences, the natural connection between opioids and LA lies within the target action of both groups that affect the PNS.

The academic literature does not present specific research data focusing on the topic or mechanism of opioid and LA interferences; however, the data collected through animal studies present conclusive evidence that opioid use impacts the effects of local drugs on peripheral nerves.

An experimental study by Liu and Gold[14] demonstrated a significant decrease in the potency of lidocaine-induced block in the sciatic nerves of rats receiving three or seven daily injections of morphine compared to saline-treated and non-injected rats. The authors note, "The magnitude of the decrease in potency was injection-number dependent, where the decrease was greatest after seven daily injections and smallest after only three daily injections."

The experiment demonstrated that repetitive morphine administration induces opioid tolerance in rats, subsequently producing resistance to lidocaine-induced nerve blockade.[14] The study was completed on live animals and reflected ex vivo findings, effectively demonstrating the potency of lidocaine is reduced in opioid-dependent subjects following exposure of the CNS to opiate (in this case, morphine). The data presented in this study suggest that morphine-induced loss of LA potency is duration dependent.

The LA potency in rats was negatively affected by the duration of opiate injections, with "a significant ($P = 0.025$) loss of analgesic efficacy in each [experimental] group by Day 7" leading to "analgesic tolerance in vivo and a reduction in potency of nerves in vitro of lidocaine to block the compound action potential."[14]

Morphine-induced loss of LA potency is dose dependent. The association between the percentages of change appears to be linear and highly significant, "wherein a 50% decrease in analgesic efficacy is associated with more than a 100% decrease in lidocaine potency."[14] An additional consideration is that morphine-induced loss of LA potency is reversible given adequate time. Due to increasing tolerance to opiates, LA efficacy is reduced; however, efficacy recovers after morphine injections are discontinued. The loss of lidocaine potency associated with morphine injections remained 35 days after the last morphine injection.

DISCUSSION

According to current scientific knowledge, opiates (such as morphine) are CNS-acting medications. Therefore, they are not acting directly on the periphery, and their effects on the PNS (axons) should not be significant enough to connect their action to the reduction of LA potency. However, the experimental data presented in the study indicate the onset of morphine-induced loss of LA potency correlates to the opiate's actions on the nervous system — perhaps on the peripheral levels, as well as on the central levels of the nervous system.[14] Additionally, it was directly proportionate to the concentration of the drug and frequency of injections, suggesting that opiate-induced analgetic effects negatively impact the analgesia produced by LA compounds, regardless of their different areas of action.[14]

Furthermore, ancillary linking between opioid-induced and LA-induced analgesia was established when morphine injections caused a significant reduction of LA analgetic potential. The study also showed that recovery, regardless of expectations, was not immediate. The reduced LA potency sustained for more than 30 days after morphine discontinuation, suggesting that opiates have long-term effects on the PNS, regardless of their main impacts on the CNS.[14]

The data proves that opiates produce a significant number of bodily changes, including suppression of nociceptive signals. While the evidence suggests it is unlikely that any synaptic mechanisms are involved in the development of analgesic tolerance, the morphine-induced decrease in LA potency indicates that additional mechanisms affect the decline in LA potency observed in animal studies.[14] Finally, the data presented in the study indicate this apparent loss of LA potency may be attributed to an intrinsic change in the peripheral nerve caused by systemic morphine administration. This theory was not presented in this article, but certainly warrants additional inquiry.

A peripheral nerve block with LA in dentistry is integral to perioperative pain management. While it is generally appreciated that perioperative pain management in opioid-tolerant patients can be challenging, experimental clinical data suggest this phenomenon may be attributed to a decrease in the potency of LA on the PNS, regardless of the fact opioid analgesics primarily affect the CNS.

The rat-model data from Liu and Gold[14] further suggest the morphine-induced decrease in LA potency is perhaps due to the intrinsic changes in the peripheral nerve caused by opiate side effects or physiological changes induced by the opiates on the nervous system at large. While it is clear that such anesthetics as lidocaine, bupivacaine, tetracaine, procaine and prilocaine interact with mu and kappa opioid receptors, there is no evidence of their interaction with the delta opioid receptor, leading to the conclusion the "blanket effects" of opioids on the nervous system are relatively limited. Additionally, the reversible nature of these influences suggests the effects of opioids on the nervous system are not of a permanent nature.

Considering that opioids reduce the efficacy of LA, these effects can dramatically increase the need for higher perioperative doses of LA and potentially promote toxicity in opioid-tolerant patients — pushing dental practitioners into dangerous territory during routine dental procedures.[15,16]

Furthermore, poor perioperative pain control can cause dental practitioners to utilize opioids preoperatively, resulting in CNS depression through pharmacodynamics synergism, as reported by Cohen and Mao.13 Poor perioperative pain management predominantly affects patients most vulnerable to pain-induced anxiety — the opiate-tolerant dental patient.[15,16] Those caring for abstinent patients understand that an inadequate dosage of analgesics administered perioperatively or poor postoperative pain management can potentially reactivate addiction. A successful recovery and withdrawal from opioids, as well as prolonged abstinence, may be interrupted by a routine postoperative opioid therapy that results in an exaggerated response.[13] These patients are most likely to relapse. In short, an unfortunate development in recovery may stem from unsuccessful perioperative or uncertain postoperative dental pain management.[8]

CONCLUSION

Given the limited clinical data and scientific evidence, the dental profession needs more research to determine why opioid-tolerant patients are resistant to LA peripheral nerve blocks. Admittedly, this is a difficult patient population to study due to a variety of drug-use histories, history of drug combinations in polypharmacy users, and patients in recovery who are prescribed drugs (such as methadone and buprenorphine) as part of their medication-assisted therapy.

Dentistry is an invasive discipline requiring practitioners to manage acute pain. When opioids are judged to be clinically appropriate for a patient in recovery, the prescribing clinician should consider multiple approaches to mitigate the patient's relapse potential. Such efforts to avoid unnecessary use may include:

- Preoperative intake of non-steroidal anti-inflammatory drugs
- Utilization of long-acting anesthetics (e.g., bupivacaine liposome; tetracaine/lidocaine/epinephrine; or bupivacaine and meloxicam)
- Limited supply of opioids (24 hours maximum)
- Discussion of prescribed opioid use with family, caregivers or 12-step sponsors to control the intake and prevent possible abuse
- Coordination of relapse preventive efforts with the patient's addiction professional to prevent misunderstandings of positive urinalysis results

While non-opioid pain management alternatives are increasingly popular, dentists still write millions of opioid prescriptions annually. This scenario, combined with the observation that interactions between opioids and certain medications can lead to severe or possibly life-threatening events, indicates that additional studies on the nonlethal and potentially lethal use of opioids are warranted and essential.

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