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Review Article

Pharmacological therapeutics and implications of opioid administration in veterinary practices: A current perspective

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Abstract

Through the years, many synthetic or partially synthetic opioid agonists have also been developed that are being employed in medicinal therapeutics. Mu, kappa and delta which have been named after Greek alphabets are some of the most prolific opioid receptors targeted for their analgesic and sedative effect. However, serious cardiovascular implications and extremely addictive nature of these drugs have limited their widespread application. Patients who have been prescribed opioids, need to be systematically weaned-off, as abrupt cessation of use may lead to debilitating withdrawal effects. Cognizance regarding the physiology of pain stimulus and neural pathways associated with sensation of pain would be essential to develop anti-nociceptive therapeutic regimens. Both ascending and descending nociceptive pathways which include Primary Afferent fibers, Dorsal Horn Neurons, Ascending Spinal Tracts, Thalamocortical structures, Periaqueductal gray matter (PAG) and Rostroventral medulla (RVM), all have receptors for opioids and alpha 2-agonists. It has already been established that the anesthetic efficacy and pain management could be significantly improved by engaging both of these receptor agonists in multimodal pain management protocols. Yet, the fear of misuse has often limited implementation of opioid therapy

in veterinary settings. In this review, authors have intended to summarize the pharmacological action of opioids and their possible application for therapeutic purposes. Scientists would find this review quite insightful for devising innovative multimodal approaches and stipulating future research endeavors for development of opioids derivative devoid of their pernicious addictive tendencies.

Keywords: Multimodal pain management; Neuropathic pain; Nociceptive Pathways; Opioid withdrawal

Introduction

Opioids such as morphine are natural derivatives of opium poppy [1]. They have been used for thousands of years and are technically referred to as opiates [2]. These days many synthetic or partially synthetic compounds that can act as opioid agonists have also been developed [3]. The poppy plant was cultivated even during the ancient Persian, Egyptian, and Mesopotamian civilizations whereas first known written reference to the poppy appeared in a Sumerian text which dated around 4000 BC [4]. Opioids are valuable tools in a veterinarian's armamentarium of drugs. Although most of the drugs in this group are considered controlled substances because of their potential for abuse by humans, yet they could bear profound consequences in veterinary therapeutics [5]. These drugs affect receptors in the brain to create a number of effects including pain relief. Opioid analgesics have been referred to as the most reliable and effective analgesia for quite a considerable time [6]. They possess high viability, are extremely potent, and their effect could be reversed in case of overdose. The three different opiate receptors namely, Mu, kappa and delta play different physiological roles in the nervous system [7]. There are several subtypes of these three receptors and their expressions differ according to their respective location inside the body [8]. The receptor named mu has been divided into mu-1, mu-2, and mu-3, yet ongoing molecular studies suggest that there might be somewhere around seven subtypes of this particular opioid receptor [9]. These receptors are present throughout the body therefore opioid agonists are probably going to have different effect based on their systemic location [10]. Medicines such as meperidine, morphine, hydromorphone, oxymorphone and fentanyl are opioids agonists [11]. These drugs mainly act at the mu receptor due to a have high affinity [12]. The opioids receptors located in the peripheral and central nervous system are occupied by these drugs and cause a conformational change. This phenomenon raises the affinity for Guanine Nucleotide Binding Proteins (G-coupled) to take effect [13]. Before most operative procedures requiring general anesthesia, opioids are administrated as a premedication drug to bring about analgesia and sedation [14]. Infusion or epidural administration of opioids, namely morphine has been used to provide perioperative analgesia. Such protocols have proven to limit anesthetic dosage and prolong it's sedative effects [15]. There isn't any doubt about the unintended consequences of opioid administration, but under controlled conditions benefits could possibly outweigh the cost. This may especially be true for circumstances where pain relief is a priority. Adverse effects attributed to long-term opioid usage undercut their immense potential for management of chronic pain. Most veterinary practitioners are comfortable in employing opioid agents for controlling acute post operative pain in controlled settings of an operation theater. But their concerns are mostly directed towards opioid usage in case of chronic pains. Most opioid derivatives are addictive in nature so terminating their administration is often associated with a debilitating

withdrawal syndrome. In this regard, opioid withdrawal is a huge challenge in patients where underlying cause for pain has been resolved but the patient continues to depend heavily on medicinal assistance. This scenario is also true for patients that have been consuming dangerously high doses and a reduction in dose is prudent [16]. Now a days, several reports suggest that veterinarians have not been prescribing enough opioids for companion animals [17]. The limited utilization of opioids may be attributed to a number of reasons, for example manufacturing shortage, changes in compounding regulations or fear of misuse by owners [18]. However, the opioid epidemic stands out as a significant contributing factor. This review aims to provide an overview of the current profile of opioid analgesics and their impact in veterinary practice [19]. In the present review article, authors have endeavored to highlight pharmacological basis of opioid usage, withdrawal mechanism and strategies to manage the adverse outcomes in veterinary practices.

Physiologic basis of opioid analgesic therapies

In recent studies it has been demonstrated that nociception is a lot more complex in its mechanism than simple somato-sensation [20]. However, admittedly there are certain fundamental similarities between pathways responsible for feeling of sensations and perception of searing pain in human and animal subjects [21]. This disparity is quite evident when investigating the underlying processes involved in production of chronic or neuropathic pain. Some researchers have proposed a ‘‘body-self neuromatrix’’ phenomenon [22]. Whereby, multiple nerve impulses of varying intensities, received by different neuronal groups, may extrapolate a multidimensional experience with regards to sensation of pain. These unique nerve impulses are recognized in central nervous system by their unique neuro-signatures. Therefore, several factors, namely sensory impulses, genetic predispositions, stresses, and cognition must be considered while modulating pain [23]. As it has been explained in the aforementioned text that it would be counterintuitive to describe pain in terms of linear pathways. However, cognizance of neural pathways associated with perception of acute pain is paramount for effective analgesia in veterinary patients (Fig. 1).

Ascending antinociceptive pathways

As a stimulus is received by specialized nerve ending termed as nociceptors, the force of this tactile pressure is converted into electrical signals [24]. These nociceptors are present all over the peripheral regions of the body. Their mechanism of depolarization involves intracytoplasmic translocation of Ca^{+2} and Na^{+1} ions governed by external instigators such traumatic forces, temperature or chemical action [25]. Some fibers are capable of carrying different types of noxious signals while others can only transmit signals for a specific type of stimulus. Researchers have observed that there are several types of ion channels [26]. Amongst them, the most common is a group of ion channels frequently located on the cell membrane termed as “Transient receptor potential channel (TRP)” [27]. These transducers are mostly associated with conjuring pain attributed to chemical and thermal stimuli. There are several types of TRP transducers. Within the TRP family are several subfamilies, including TRPM (melastatin), TRPV (vanilloid), TRPC (canonical), TRPML (mucolipin), TRPN (NOMPC-like), TRPP (polycystic) and TRPA (ankyrin). Additionally, a member of the 2P-domain K1 channel family namely TREK-1 (polymodal K+ channel) is also quite important [28]. Other ion channels, e.g., acid-sensing ion channels (ASICs), have also been associated with nociception.

Pharmacological interaction of drugs, nociceptors and primary Afferent fibers

Currently there aren't many drug formulations that can directly interact with a non-sensitized nociceptor and influence the process of transduction. However, pharmaceutical industries are investigating possible drugs capable of desensitizing TRPV1 receptors [29]. A noxious stimuli generated at the receptor induces a depolarization across the entire axon. This action potential is generated by subsequent opening of Na ion channels of primary afferent nociceptive fibers [30]. Specifically, Na channels involved in nociception have been classified as $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$ channels [31]. These channels have usually been identified as tetrodotoxin (TTX)-sensitive [32]. The higher the stimulus the more resistive, the potentiation of the aforementioned Na channels becomes. Two main types of afferent nerve fibers have been identified as Aδ and C fibers [33]. The various sensory features of quick and slow pain are due to their differential activity. The ability of local anesthetic agents namely lignocaine and bupivacaine are quite remarkable in blocking Na channels, thereby negating the possibility of action protentional generation [34]. Another class of drugs, α2 agonists may also exhibit impairment of impulse conduction when administered as para-neural nerve blocks [35]. But these regiments are nonspecific in function and when used appropriately would completely desensitize the area in question. Therefore, a specific voltage gated Na channel i.e., $Na_v1.8$ has been identified to be responsible for carrying pain stimulus [36]. A drug capable of antagonizing this particular channel specifically would only invite an anodyne effect at the circumscribed region while maintaining motor activity.

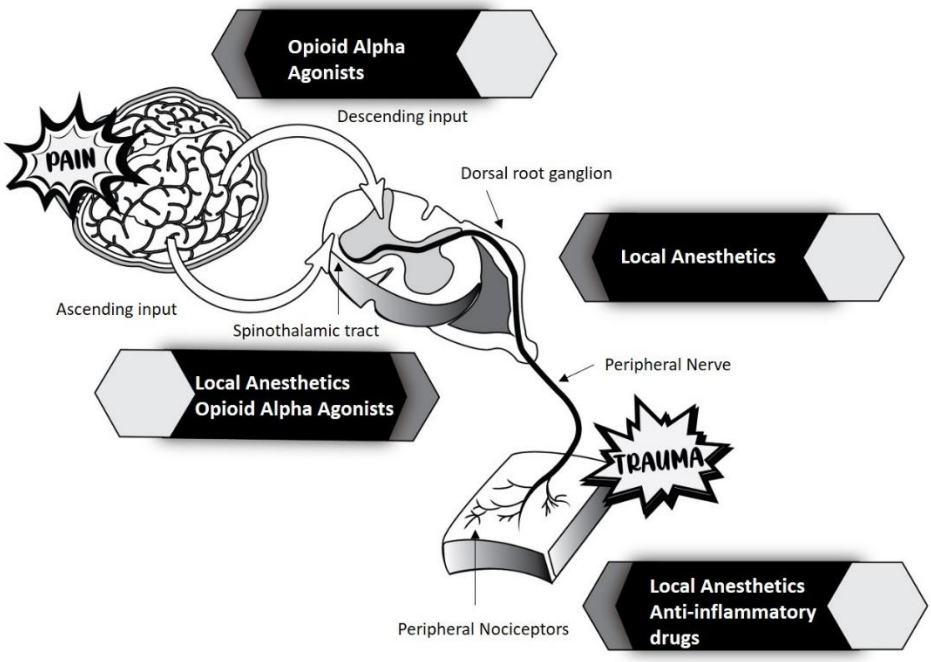

Figure 1. Pharmacological interaction of drugs along the ascending and descending nociceptive pathways

Pharmacological interaction of drugs, dorsal horn neurons and ascending spinal tracts

The dorsal horn of spinal column receives both Aδ and C afferent nerve fibers. There are α- amino-3-hydroxyl-5-methyl-4-isoxazole propionic acid (AMPA) receptors present between the terminals of dorsal horn neurons and afferent fibers **[37]**. Nociceptive-specific (NS) neurons and wide dynamic range (WDR) neurons are responsible for projecting pain to the brain [38]. In veterinary practices, alpha 2 (α2) agonists and opioids are extensively used to manage pain because dorsal horn of spinal cord has a large number of both receptors. Administering opioids reduces influx of Ca^{2+} at presynaptic level thereby inhibiting nociception, as release of substance P ("Preparation" or "Powder") is impaired **[39]**. Additionally, non-steroidal anti-inflammatory drugs (NSAIDs) are quite effective as well. These drugs possess anti-prostaglandin effect and inhibit cyclooxygenase enzyme (COX) within the dorsal horn of spinal cord.

Pharmacological interaction of drugs and thalamocortical structures

Drugs such as opioids are unique in regards to their effects on thalamocortical structures. These drugs may be able to influence certain aspects of pain perception **[40]**. Opioids, similar to anesthetics can alter state of consciousness. However, processes of pain stimulation continue even in a subconscious patient. Consequently, multimodal palliative approaches to pain management must be implemented in surgical patients.

Descending antinociceptive pathways

Similar to ascending pathways to pain, the periaqueductal gray matter (PAG) and rostroventral medulla (RVM) are involved in up as well as down regulation of pain response **[41]**. A specific group of cells found in RVM can either reduce nociceptive transmission or get excited and engage thalamocortical structures. In case of PAG, opioids can suppress serotonergic activity by inhibiting GABA dependent ion channels from functioning **[42]**.

Sensitization of nervous system

Several different types of sensory disturbances may occur due to changes in nervous system processing. Cellular damage subsequently followed by inflammatory cells causes production of materials capable of agonizing tyrosine kinase (TrK) receptors which are sensory receptors for nociception **[27,43]**. Consequently, it has been reported that inflammatory mediators could act directly or indirectly to cause pain. Direct acting ones often act on sensory receptors responsible for the perception of pain while the indirect ones only sensitize those terminals making them hyperresponsive to the action of ensuing stimuli. Prostaglandins are effectively nociceptor sensitizers, causing phosphorylation of TRPV1 receptors thereby decreasing its thermal threshold **[44]**. Bradykinin is a direct acting inflammatory mediator capable of activating TRPV1 receptors **[45]**. Several neurotrophic factors have also been indicated responsible for causing chronic pain. These factors can either directly bind with receptors or sensitize them by activating mast cells. Traditionally NSAIDs have been associated with controlling peripheral sensitization while opioids have been considered centrally acting analgesics. However, their efficacy in controlling transmission of pain in peripheral route has also been reported **[46]**. Nociceptor neurons of dorsal horn may also be sensitized in a similar manner to peripheral sensory terminals. In addition to normal sources of inflammatory mediators, glial cells have been reported as key instigators of pain subsequent to neuronal injury.

Opioids withdrawal in veterinary patients

It is difficult to terminate or withdraw the Opioids therapy as it can lead to debilitating syndrome in long time users. The abrupt cessation of Opioids may cause the

development of some unwanted signs and symptoms including gastrointestinal distress, tension, sleeping disorder, muscle issues and hyperhidrosis [47]. Addicts become dependent on opioids, to avoid these side effects. Hence it is not prudent to withdraw the Opioid use at once, rather it should be planned and tapered.

Practices in use to mitigate the effects of opioids withdrawal

Current practices support the usage of long acting and less euphoric opioids in place of short acting ones as an alternative treatment. This method minimizes the required daily dosage while maintaining a bare minimum blood serum opioid level to avoid any withdrawal symptoms [48]. Methadone is are being currently employed for this purpose. However, a deficiency of authorized doctors and its overall inaccessibility has seriously limited the application of this strategy.

Forthcoming drug development

With the understanding of Opioids Pharmacology and reviewing different biochemical cycles, some methods for withdrawal of Opioids have been proposed. One methodology is to control the course of Opioid receptor-initiation [49]. Stimulus of Opioids receptors involves the inhibitory G-proteins linked to the β-arrestin flagging pathway, which are primarily associated with undesired results of Opioid usage [50]. A ligand known as PMZ21 has been discovered by utilizing computational screening and designing which behaves similar to opioid analogues but is believed to be non-addictive [51]. Other methodologies in this regard have included modifying the sites of opioid activity to counter the activation of aforementioned pathways. It has been well-established that, tissue injury and neurotic agony are caused due to tissue acidosis [52]. This phenomenon has prompted researchers to investigate pH-delicate narcotic ligands, known as NFEPP (N-(3-fluoro-1-phenethylpiperidin-4-yl)-N-phenylpropionamide), which specifically bind with Mu receptors (μ-receptors) [53]. Both of these ligands have exhibited extraordinary efficacy in experimental rats, creating pain relieving outcomes without showing habit-forming attributes. In any case, these new discoveries would require thorough investigation in both preclinical and clinical settings (Fig. 2).

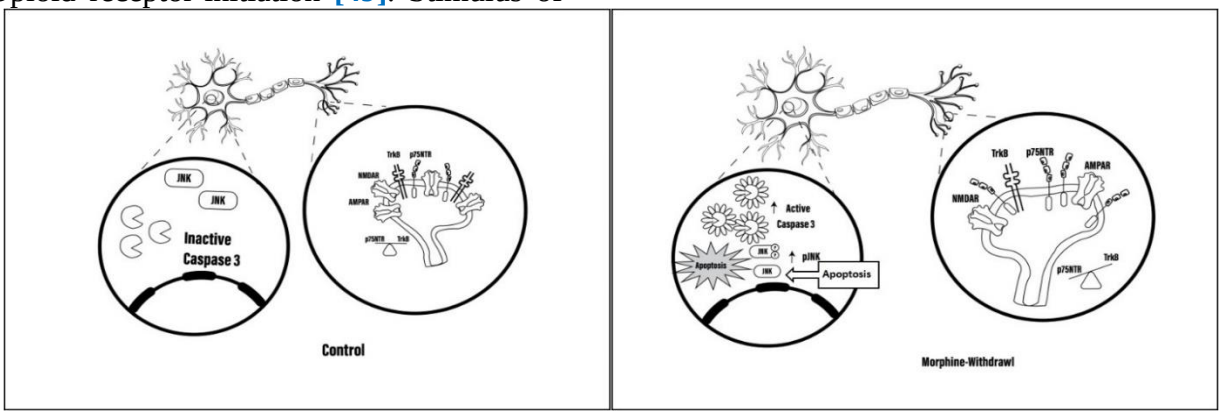

Figure 2. Physiological processes involved in the withdrawal of an opioid analogue i.e., morphine

Opioid epidemic and its impact on veterinary practices

An overwhelming surge in the abuse of opioids has been dubbed as a worldwide epidemic. Concerns associated with misuse have seriously impacted their application in veterinary sector [54]. The controlled dispensation of opioids as a consequence of

this epidemic has created serious implications for veterinary patients. Most anesthetic protocols in small animals, advocate using opioids as perioperative analgesics or pre-anesthetic medicines. A survey conducted in USA indicated that out of 697 respondents, 99.7% practitioners used and recommend opioids in their veterinary patients **[19]**. Such a high recommendation rate despite justifiable clinical concerns could only be rationalized by the extra-ordinary results attributed to opioids. Some of the most widely prescribed opioids for peri-operative pain management include butorphanol, buprenorphine and tramadol **[55]**. An electronic survey conducted in the USA among the members of the Veterinary Information Network (VIN) showed that veterinarians prescribed tramadol in more than 50% of the recent surgical cases **[56]**. Other frequently prescribed opioids included hydrocodone (29%) and buprenorphine (26%). Buprenorphine was frequently employed in companion animals to prevent postoperative pain as it possessed a relatively longer analgesic period (~8 h) **[55]**. Hydrocodone was supposedly used to cure respiratory distress especially in case of serious coughing **[57]**. Popularity of tramadol amongst veterinarians might be explained by the inaccessibility of other more potent alternatives. Recently most western countries have relaxed regulations governing opioid dispensation for veterinary patients considering their importance as therapeutic **[23]**. This has allowed veterinary practitioners to feel relatively comfortable while prescribing opioids. Instead of making all opioid medications completely in-accessible for veterinarians, sale and purchase of specific ones like morphine, hydromorphone, oxymorphone and fentanyl should be strictly controlled which are more prone to abuse by addicts. The shortage or inconsistent availability of the required opioids has caused serious problems for veterinarians in management of pain. It has also created a significant hindrance in proper anesthetic administration of veterinary patients. Nevertheless, the operative procedures are rarely postponed due to unavailability of the desired opioids. Instead, other alternative regimens including combinations of ketamine, butorphanol, dexmedetomidine are used along with local anesthetic blocks. A multimodal approach has facilitated veterinarians to modify their peri-operative analgesic approaches in the absence of opioids. However, none of these techniques have been able to completely replace opioids as an efficacious anesthetic component. Moreover, the risk of drug abuse by owners continue to loom over a practitioner while having to prescribe these opioids. This factor just amplifies a veterinarian's responsibility as they now have to take note of both the patient and the owner **[23]**. Further surveys that target larger populations are imperative to gain a clear picture regarding the difficulties faced by veterinary practitioners.

Conclusion

In recent years, researchers have been focusing on specific inflammatory profiles of instances involving pain, and prescribing medication accordingly. For such practice to become a norm, in-depth investigations into processes involving pain are imperative. Once inflammatory profile has been established, mitigation requires suppression of the particular inflammatory mediator that has been deemed responsible allowing for inhibition of neuronal impulses. The prospect of utilizing unique pharmacological capabilities of opioids is an extremely encouraging prospect, yet practical application in veterinary settings has been seriously limited due to several sociological and clinical implications. Primary reason could be attributed to serious side-effects observed subsequent to the withdrawal of opioid agents. Investigations into

understanding physiological processes responsible for such dire consequences could be very helpful in alleviating some clinical concerns and develop withdrawal strategies unique to veterinary patients. Secondary cause for hesitant opioid prescribing in veterinary patients may be associated with concerns that dispensed drugs may be abused by owners. Several studies have been undertaken in USA, especially after coinage of the so-called term "opioid crisis". However, the clinical application is too important for these drugs to be completely cast out of regular clinical practices. Therefore, substance control strategies and clinical procedures must be ratified to assist in safer application of pain management regimens involving opioid drugs.

Author Contribution

Conceived the idea: Q Ullah, O Naseer & M Shahid. Wrote the Paper: AH Rabbani, M Safwan, A Waheed & S Ali. Proofread the data: ML Sohail, K Hussain, Ahmad Ali & YR Khan. Final revisions: AS Ahmad.

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