CURRENT UNDERSTANDING OF FISH AND INVERTEBRATE ANESTHESIA AND ANALGESIA

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ABSTRACT

The objective of this presentation is to describe and highlight the current state of anesthesia, pain (nociception) and analgesia (antinociception) in fish and invertebrates. As a conservative estimate, there are more than 32,000 species of fish in the world.[23] Invertebrates comprise a vast range of terrestrial and aquatic organisms, with over 1.3 million species documented across greater than 30 Phyla making up more than 97% of the earth's animal species.[14]Thus, we have only made negligible progress toward understanding fish and invertebrate anesthesia and analgesia. Several key obstacles limit successful anesthetic and analgesic use, including: 1) subjectivity in pain assessment; 2) inadequate knowledge of anesthetic and analgesic efficacy, safety, dosages and dosing frequency across species; 3) inability to monitor anesthetic depth; 4) pharmacokinetics of anesthetic and analgesic drugs; and 5) the unknown relationship between risks and benefits for specific drugs.

Clinical Anesthesia

Terrestrial Invertebrates

Anesthesia of terrestrial invertebrates may be necessary for the following reasons: thorough physical examination, diagnostic sampling, or therapy (e.g., exoskeleton repair, manual removal of ectoparasites, limb amputation). Gas anesthetics are the method of choice for anesthetizing terrestrial invertebrates, including arachnids, insects, and scorpions.[4,11,16,17] Isoflurane and sevoflurane are both effective and commonly used anesthetic gases in a clinical setting. Carbon dioxide (CO_2) can also be used for anesthesia and euthanasia, although this remains controversial. The invertebrate can be placed under a large mammalian facemask, or in a chamber, and gas passed over the body. Most terrestrial invertebrates use a tracheal system for respiring, and can readily absorbed volatile anesthetic gases. Anesthetic gas, like air or oxygen, enters the tracheae through the spiracles and travels through the tracheoles to the fluid-filled tips, where the gas and O_2 diffuses directly from the tracheoles into the cells, and CO_2 diffuses from the cells into the tracheoles. An alternative to using a gas anesthesia system is to place the invertebrate in a closed container with a cotton ball saturated with isoflurane or sevoflurane liquid, being careful not to allow the invertebrate to come into direct contact with the saturated cotton ball.[16] The primary occupational concern with these methods is risk of environmental gas exposure. Monitoring anesthetic depth is

difficult other than lack of righting reflex, and reaction to a noxious stimulus, such as a hypodermic needle stick. Recovery may require exposing the invertebrate to O_2 in a mask or chamber.

Aquatic Invertebrates

Aquatic invertebrates may require anesthesia for the same reasons as terrestrial invertebrates: examination, diagnostics, and treatment. Bath anesthetics are most commonly used in aquatic invertebrates, and include ethanol (1.5-10% solutions depending on species), eugenol (active ingredient in clove oil), magnesium chloride, and MS-222 (tricaine methanesulfonate). Ketamine, xylazine, and lidocaine have also been administered intramuscularly (IM), primarily in crustacean species.[4,11,16,17] Anesthetic monitoring is difficult, but may include lack of righting reflex, lack of tentacle or arm withdrawal to stimulation, lack of shell closure after stimulating mantle, respiratory rate and pattern (cephalopods only), and Doppler flow probe (cephalopods only).[11,16,17]

Teleost Fish and Elasmobranchs

The use of efficient, predictable, and safely conducted anesthesia is imperative to the medical management of fishes. Diagnostic procedures can be facilitated by the effective use of anesthetic agents. The most efficient method for anesthetic delivery to most fish species is by an immersion bath. Larger species may require injectable agents such as ketamine, ketamine/xylazine, or ketamine/dexmedetomidine. The method of choice for most fish species is anesthesia by immersion bath. Tricaine methanesulfonate (MS-222) is an FDA-approved method for use in fish, and is the most commonly used bath method. Alternatives include eugenol[22,28], isoeugenol (AQUI-S 20E®, is now FDA-approved in the US)[8,22], and propofol[10,12,22,32], alfaxalone[20,22,32] and metomidate hydrochloride[3,12,22,32] as immersion agents. Injectable anesthetics tend to be used in larger teleost and/or elasmobranch species.[12,22,32] Common parenteral anesthetic agents include ketamine, alpha-2-agonists (xylazine, medetomidine or dexmedetomidine) usually in combination with ketamine, and propofol. Anesthetic maintenance for prolonged diagnostic or surgical procedures require recirculating bath anesthetics that are continuously passed over the gills. Rate of respiration can be determined by observing opercular movements. Heart rate can be evaluated by use of a Doppler flow probe placed on the skin overlying the heart, or an ultrasound probe, and heart rate/rhythm can be evaluated by using an ECG. Serial venous or mixed venous/arterial blood gases can be determined using a portable iSTAT clinical analyzer, but may only be useful if measured multiple times during the course of an anesthetic event.[28]

Clinical Analgesia

The primary question is whether fish and invertebrates "experience" pain or are they merely capable of demonstrating a "reflexive" response to a noxious stimulus (nociception)? More importantly, can we recognize pain in fish and invertebrates and is the perception of pain by a fish or an invertebrate equivalent to that of a mammal? Many would argue that fish and invertebrates do not have the same anatomic and/or physiologic capabilities to "process" pain. However, recent research in fish, amphibians, reptiles, and birds has demonstrated that the transmission of peripheral sensory signals, via the spinal cord, to midbrain and forebrain regions that are homologous to mammalian cortical and limbic structures.[2,7,9,18,29,30,31,33] Additionally, the

endogenous opioid system, which is activated in response to nociception and contributes to analgesia, is also well conserved throughout vertebrate phylogeny.[30] Thus, the physiologic and anatomic requirements for pain and analgesia appear to be remarkably similar among all vertebrate species. While much less is known about invertebrates, many species (especially the cephalopods) have well-developed nervous systems, and some species respond to exogenous opioids in a similar manner as mammals.[4,7,15,16,18,19,21]

There is substantive and compelling evidence from the neuroanatomic, neurophysiologic and behavioral literature to suggest that, at some level, a variety of fish species experience pain under certain contexts. Opioid drugs have been used to alleviate behavior associated with exposure to noxious stimuli in fish, and several pharmacokinetic studies have been conducted after opioids were administered to a variety of fish species.[1,5,13,24-27,31,33] In my clinical experience, mu-opioid agonists appear to be most effective in providing pain relief, particularly post-surgically. In my research with koi, morphine sulfate (5 mg/kg, IM) is the most effective analgesic drug with fewest side effects compared to butorphanol tartrate (10 mg/kg, IM), and I tend to use morphine or hydromorphone in clinical practice.[1] The evidence in support of invertebrates experiencing pain under a variety of conditions remains inconclusive, but is compelling, nonetheless. Subjectively, in our research using tarantulas, there is little question that they react to noxious thermal stimuli similarly to mammals, birds, and reptiles.[15] In addition, hypodermic needle insertion into the exoskeleton incites an immediate withdrawal reaction, followed by limb rubbing at the site of needle insertion. Opioid administration will attenuate responses to noxious stimuli in tarantulas, but the dosages required are relatively high (morphine sulfate administered at 50-100 mg/kg intracoelomically; butorphanol tartrate administered at 20 mg/kg, intracoelomically).

Conclusion

While substantial information exists with respect to fish anesthesia, particularly the application of immersion bath and use of recirculating anesthetics, very little is known about invertebrate anesthesia. The general veterinary approach is that all terrestrial invertebrates can be anesthetized using one or two methods, and the same thinking is applied to aquatic invertebrates. Much is yet to be learned about invertebrate anesthetic efficacy and safety, species differences, dosing and duration of effects. Our understanding of analgesia in fish and invertebrates is only just beginning to be evaluated. However, veterinarians have an ethical obligation to treat painful conditions in all animals, including fish and invertebrates, as effective pain management reduces stress-induced disruption to homeostatic mechanisms, and also decreases morbidity and mortality associated with trauma or surgery. It is my hope that future research will help us to determine if, and at what phylogenetic level, fish and invertebrates feel pain. Until then, we must use all available evidence, especially in those species most closely related to the species being studied, to err on the side of the animal in subjectively assessing that a procedure considered painful in a mammal, should also be considered potentially painful in an invertebrate or fish species.

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