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Updated Review of Fish Analgesia

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Analgesics are an integral part of routine pain management in mammals, yet their use in fish is still limited. Some recommendations on the use of analgesics in fish are currently in the literature; however, information on the properties of analgesic drugs in most fish species is still scarce and sometimes misleading. The present review of information on the use of analgesics in fish was thus compiled to help clinicians make an informed decision as to which drug and dose to use. The main agents that have been investigated are opioids, NSAID, and local anesthetics, primarily in rainbow trout and zebrafish. There is presently no overwhelming evidence of efficacy for most analgesics in fish, although beneficial effects on behavior and physiologic parameters have been reported in many instances, especially associated with morphine administration. Furthermore, most analgesics did not result in significant adverse side effects. Thus, analgesics could be administered whenever it is considered that an animal might experience pain, given that the drugs appear not to cause harm and may be beneficial. However, caution must be advised because 1) important interspecies variation has been reported and 2) unforeseen effects could affect experimental results. Further research is needed to investigate analgesic use in fish. This should be accompanied by research aimed at improving our knowledge of the various species of fish. The current lack of a validated approach to assessing pain in fish limits our ability to evaluate the efficacy of analgesics in fish.

Abbreviation: MAC, minimum anesthetic concentration

Fish are very commonly kept as pets[75] and have become increasingly popular animal models in research. According to the latest animal data report from the Canadian Council for Animal Care, fish are currently the largest group of all animals used in research,[10] closely followed by mice. As such, fish frequently undergo potentially painful surgical procedures.[31,32,60,62] Analgesics are used routinely in conjunction with such procedures in mammals, yet their use is still very limited in fish.[32] This situation is in part because the capacity of lower vertebrates such as fish to experience pain remains a matter of debate (see references 8 and 64 for both sides of the argument). However, all sides of the controversy accept the fact that these animals respond to noxious stimuli with a nocifensive response. Therefore minimizing such responses associated with surgical procedures by providing fish with appropriate analgesia is appropriate. Currently, fish are generally anesthetized without analgesics for such procedures,[13,50] yet it is generally best to adopt a multimodal approach combining anesthetic and analgesic drugs[6,41,47] to provide appropriate perioperative care.[47,58] Furthermore, the American College of Veterinary Anesthesiologists' position paper on the treatment of pain in animals strongly supports this approach, as it states that "regardless of the clinical signs demonstrated, if there is any doubt that an animal may be experiencing pain, then a trial treatment with analgesics is indicated."[1]

To date, only minimal research has been done in the field of fish analgesia; thus information is scarce regarding the treatment of fish with analgesics. A comprehensive review concerning analgesics in fish was published in 2012 to assist in this endeavor.[71] This previous review compiled the information available at the time, but fish medicine is a subject of ongoing investigation, and more research has since become available. The goal of our current review is to correct a few inconsistencies in the original review[71] and to update it with new information available in the literature.

Materials and Methods

We cross-referenced the information concerning analgesics presented in the article "Clinical Anesthesia and Analgesia in Fish"[71] with the information presented in its references. We also used the online databases PubMed, Science Direct, and One Search to search for new information by using the keywords 'fish analgesia,' 'fish analgesic,', 'fish <local anesthetic>,' 'fish morphine,' 'fish buprenorphine,' 'fish butorphanol,' 'fish ketoprofen,' 'fish carprofen,' 'fish lidocaine,' and 'fish tramadol.' Only the use of analgesics on live animals was included—that is, we excluded studies using isolated tissues. In addition, we included only articles that presented original information—that is, based on an experiment or case study. Only articles investigating the effects of analgesics and their pharmacologic properties in the clinical context were included as new sources of information. We did not count ecotoxicologic studies investigating the effects of analgesics on fish in natural environments as new sources of information; however, we do briefly mention these studies when they provided pertinent information. In cases where the source reported a volume of agent instead of a dose in mg/kg, we calculated the dose based on the average weight of the animals in the study and present it in the table. The literature search was completed in August 2017.

Results and Discussion

In Table 1, we summarize doses with reported analgesic effects and side effects of analgesic drugs tested in fishes. Since the 2012 review, 14 studies investigating the properties of analgesics in fish have been published. To date, opioids are the most studied analgesics in fish, followed by NSAID. Other drugs such as amitriptyline, clonidine, gabapentin, lidocaine, and

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Table 1. Analgesic effects and side effects of analgesic drugs tested in fish

Agent (schedule)	Dose	Species (route)	Side Effects	Beneficial effects	References
Opioids					
Buprenorphine (III)	5µM, 0.005–0.2 µg/mL	Zebrafish (W)	Hyperactivity	Reversed thermal aversion Ameliorated behavioural changes	22, 74
	0.01–0.1 mg/kg	Rainbow trout (IM, SC)	Depressed activity at 1 mg/kg	Ameliorated ventilation and heart rates	29, 49
Butorphanol (IV)	0.4 and 10 mg/kg	Carp (IM)	Decreased ventilation rate and buoyancy problems	Mild behavior-sparing effect Improved food consumption	4, 33
	0.25-5 mg/kg	Chain dogfish (IM)	—	—	23
	0.1-0.4 mg/kg	Goldfish (IM)	—	—	76
	0.2 and 0.5 mg/L	Zebrafish(W)	—	—	65
Morphine (II)	10–50 mg/kg and 0.12–48 mg/L	Goldfish (IM, W)	Hyperactivity	MAC reduction Ameliorated pain related behaviors	35, 55, 57, 76
	40 and 300 mg/kg	Rainbow trout (IM, IP)	—	ED_{50} = 6.7 Ameliorated pain related behaviors and ventilation	52, 70, 72
	17 mg/kg IV and 40 mg/kg IP	Winter flounder (IP, IV)	Bradycardia followed by a prolonged increase in cardiac output and heart rate	Blocked cardiovascular response to a noxious stimulus	51
	3 and 6 mg/kg and 1, 2, and 48 mg/L	Zebrafish (IM, W)	Hyperactivity	Possible anxiolytic effect Ameliorated activity	20, 45, 46, 80
	300 mg/kg	Atlantic salmon (IM, IP)	—	Possible anxiolytic effect	56
	5 and 20 mg/kg	Carp (IM, IP)	Hyperactivity	Ameliorated ventilation and food consumption Antiinflammatory effects	4, 12
Tramadol (IV)	10–100 nmol/g	Carp (IM)	—	Increased nociceptive threshold	16
	10 µg/fish	Zebrafish (IM)	Hyperactivity and surface respiration	—	82
NSAID					
Aspirin (OTC)	1 and 2.5 mg/L	Zebrafish (W)	—	Ameliorated activity and ventilation	45, 46, 65
Carprofen (Vet)	1–5 mg/kg	Rainbow trout (IM)	Depressed activity at 5 mg/kg	—	49
Flunixin (Vet)	0.5 mg/kg	Rainbow trout (IM)	—	—	63
	8 and 20 mg/L	Zebrafish (W)	—	—	45, 46
Ibuprofen (OTC)	5–470 mg/L	Fathead minnows (W)	—	Antiinflammatory effects	59
	400 µM	Zebrafish (W)	—	—	22
Ketoprofen (Rx)	2 mg/kg	Carp (IM)	—	Reduced postsurgical muscle damage	33
	1–4 mg/kg	Chain dogfish (IM)	—	—	23
	0.5–2 mg/kg	Goldfish (IM)	—	MAC reduction	76
	2 mg/kg	Rainbow trout (IM)	—	—	60
Ketorolac (Rx)	0.5 mg/kg	Rainbow trout (IM)	—	—	63

Table 1. Continued

Agent (schedule)	Dose	Species (route)	Side Effects	Beneficial effects	References
Local anesthetics					
Lidocaine (Rx)	4.5–18 mg/kg	Rainbow trout (SC)	—	—	49
	1–5 mg/L	Zebrafish (W)	—	Ameliorated activity and ventilation	45, 46, 65
Others					
Medetomidine (Vet)	0.01–0.025 mg/kg	Goldfish (IM)	—	MAC reduction	76

—, no pertinent information reported; MAC, minimum anesthetic concentration; Nd, no data; OTC, over the counter; Rx, not restricted but prescription required; vet, for veterinary use only; W, in the ambient water

Schedule information is provided for restricted drugs. Binomial nomenclature for fishes is given in the text at their first mention. The frequency of administration is not mentioned because repeated administration of analgesic drugs has not yet been investigated

medetomidine have been studied, although much less frequently. Rainbow trout, zebrafish, koi, and goldfish have been the main fish species used for research involving analgesics in fish.

Routes of administration include those commonly used in veterinary medicine (intramuscular, intraperitoneal) but also include bath immersion—that is, adding the drug to ambient water to achieve a particular concentration. An analgesic added to ambient water might affect skin receptors or act centrally after being absorbed across the gills. To our knowledge, no published reports address infiltrating local anesthetics. In addition, all tests used a single injection or application of the tested drug, whereas analgesics are often dosed repeatedly in veterinary and human medicine. In this regard, one needs to know the pharmacokinetics of the drug for each drug in each species at the temperature of concern, but very little pharmacokinetic information is available for fish. The reports available indicate that kinetics in fish are about an order of magnitude slower than in mammals and that substantial differences between fish species exist.

Opioids. Opioid agents interact with μ, δ, or κ opioid receptors, where they mimic the actions of endogenous opioid peptides.[7,38] These agents increase postsynaptic K^+ efflux or reduce Ca^{2+} influx, thus impeding nociceptive neurotransmitter release. Opioids have many potential side effects, including sedation, nausea, vomiting, constipation, dependence, tolerance, and cardiorespiratory depression.[5] To date, opioid administration in fish has resulted in few side effects, with those reported mainly associated with the cardiovascular and respiratory systems. Opioids are currently the most studied analgesics in fish, particularly morphine, butorphanol, buprenorphine, and tramadol. Opioids are Schedule II controlled drugs, requiring strict record-keeping.[40] Morphine is a full agonist, eliciting a maximal response from opioid receptors and providing profound analgesic effects in dogs and cats. Butorphanol is an agonist at κ receptors and an antagonist at μ receptors and provides modest analgesic effects in dogs and cats. Buprenorphine is a partial μ agonist and provides an analgesic effect less than that of full agonists in dogs. Tramadol is unique in that it binds to μ receptors but also inhibits reuptake of norepinephrine and serotonin. Tramadol is a Schedule IV controlled drug.

Morphine. Morphine is the most studied analgesic and the drug that has shown the most beneficial effects in fish. Morphine was shown to have antiinflammatory properties in carp.[12] In some cases, administration of morphine significantly reduced behaviors that might be associated with pain in common goldfish (*Carassius auratus*),[55,57] carp (*Cyprinus carpio*),[4] rainbow trout (*Onchorynchus mykiss*)[69,70] and zebrafish (*Danio rerio*).[20] Physiologic parameters also were favorably affected by morphine, as it blocked the cardiac response to a noxious stimulus in winter flounder[51] and reduced the respiratory rate that was otherwise elevated by the administration of a noxious stimulus in rainbow trout.[70,72] Morphine decreased the minimum anesthetic concentration (MAC) of the general anesthetic MS222 (tricaine methanesulfonate) needed to prevent a response to a noxious stimulus in goldfish.[76] MAC is used as a measure of anesthetic potency and is defined as the minimum concentration of anesthetic necessary to prevent purposeful movement in response to a noxious stimulus in 50% of animals.[42] Furthermore, morphine added to ambient water at a dose of 48 mg/L prevented the reduction of activity induced by acetic acid and hot water in larval zebrafish.[45,46] However, a lower dose of 1 mg/L showed a paradoxical increase in activity, which might indicate unforeseen side effects.[45] Such hyperactivity associated with low doses of morphine has also been reported to occur in goldfish, koi, and paradise fish (*Macropodus opercularis*) as

well as mammalian species.[4] This adverse effect was previously reported in fish after the administration of low doses of morphine[21,35] as well as a low dose of buprenorphine.[74] Other reported side effects include marked bradycardia, followed by a prolonged increase in cardiac output and heart rate, after the administration of morphine to winter flounder.[51] Furthermore, morphine (48 mg/L in ambient water) did not ameliorate the behavioral response to cold in larval zebrafish.[46]

In addition to its analgesic effect, morphine might have an anxiolytic effect, given that reduced neophobia was reported after the administration of morphine during a novel object test in Atlantic salmon (*Salmo salar*)[56] and a novel tank test in zebrafish.[80] However, the opposite response was reported in another study,[72] where morphine administration to rainbow trout restored neophobia to a novel object. In that study,[72] neophobia to a novel object was normally present in control fish and had been significantly reduced after injection with a noxious stimulus. Only the species involved differed between the 2 studies involving salmonids,[56,72] and both used a very high dose of morphine (300 mg/kg IM). Furthermore, morphine (5 to 10 mg/L ambient water) decreased the amount of territorial aggression in cichlid fish (*Cichlasoma nigrofasciatum*).[3]

Currently, morphine is one of the few analgesics for which pharmacokinetic information for fish is available. This information was obtained from studies involving rainbow trout, winter flounder, and goldfish.[52,53,55] Morphine is eliminated much more slowly in fish than mammals, and marked interspecies variation occurs. For example, rainbow trout eliminated morphine significantly faster than winter flounder.[52] Morphine uptake in goldfish was very slow when administered in the water, therefore injection appeared to be a more appropriate administration route.[55] A dose–response curve was calculated for morphine when administered intraperitoneally in rainbow trout.[36] This experiment showed that morphine's antinociceptive action was dose-dependent, with an ED_{50} (the dose that produces an effect for 50% of the population) of approximately 6.7 mg/kg. Naloxone inhibited this antinociceptive effect.[36] Furthermore, morphine withdrawal has been studied by using zebrafish, and various anxiogenic effects were reported when morphine was withdrawn after a week of chronic administration.[9]

Morphine has been reported to have beneficial effects in multiple situations, although some results have been questioned.[54,64] Because very few side effects have been reported, the addition of morphine to surgical protocols involving fish could be beneficial. However, the original review[71] exaggerated morphine's benefits in fish when it stated in its summary table that the drug is "very efficient at 5 mg/kg." Moreover, the origin of this 5 mg/kg dose is unclear, given no studies referenced in the 2012 review[71] used morphine at that dose. A single dose–response study reported an ED_{50} of 6.7 mg/kg IP, but a dose of 10 mg/kg or greater was required to get a positive response in all fish.[36] Furthermore, important interspecies variability in the response to morphine occurs, and we advise caution when extrapolating from one species of fish to another.

Butorphanol. Butorphanol is 1 of only 2 agents studied in an elasmobranch, the chain dogfish (*Scyliorhinus retifer*); most other agents have been studied in teleosts (that is, bony fish) only. Butorphanol has not yet shown clear analgesic effects in fish, because no beneficial effect occurred in chain dogfish[23] or zebrafish,[65] and only mild behavior-sparing effects were reported in koi.[33] In addition, conflicting results were reported when the MAC of MS222 needed to prevent a response to a noxious stimulus in goldfish was assessed,[76] given that the lowest dose of butorphanol tested decreased MAC, but higher doses increased MAC instead. Butorphanol (10 mg/kg IM) had beneficial effects on food consumption in koi after abdominal surgery, but some important side effects, such as decreased ventilation rate and buoyancy problems, were seen.[4] No side effects of butorphanol were reported in other studies, but one report,[33] referring to unpublished data, indicated that butorphanol (1 mg/kg IV) caused death in a tilapia (*Oreochromis mossambicus*).

Buprenorphine. Buprenorphine was shown to have analgesic properties in zebrafish larvae, because its administration reversed thermal aversion and prevented the behavioral changes induced by acetic acid (buprenorphine dose, 5 µM and 0.1 µg/mL in the water, respectively); these effects of buprenorphine were reversed by naloxone administration.[22,74] Buprenorphine (0.01 to 0.1 mg/kg SC) did not show any clear beneficial effects on rainbow trout.[49] However, buprenorphine (0.05 mg/kg IM) showed considerable side effects in rainbow trout, in which it decreased both ventilation and heart rates for 4 to 5 d after anesthesia.[29]

Tramadol. Tramadol (25 µg/fish IM; 10 to 15 mg/kg) resulted in adverse side effects in zebrafish (hyperactivity and surface respiration); and the elimination half-time from brain was approximately 117 min.[82] The dose tested (25 µg/fish IM) was probably too high, because doubling it resulted in 100% mortality within 5 min.[82] The effects of long-term exposure to tramadol on the early development of zebrafish (10 to 200 µg/L for 144h) and carp (10 to 200 µg/L for 32 d) have been investigated;[68] tramadol had deleterious effects on hatching as well as early ontogeny and affected antioxidant enzyme activity. Tramadol has shown a beneficial effect in carp, where its administration increased the nociceptive threshold in response to an electric shock in a dose-dependent manner with an ED_{50} of 50 µM/kg (that is, approximately 13 mg/kg).[16] Dermorphine and β-casomorphin were tested in a similar manner by the same authors and shown to increase the nociceptive threshold in cod and rainbow trout as well.[15,17]

NSAID. The analgesic action of NSAID is mainly due to their inhibition of the enzymes that synthesize prostaglandins, although other mechanisms appear to be involved.[11] These drugs have known side effects involving the digestive and renal systems in dogs,[39] but those side effects have not yet been reported during clinical trials in fish. However, nephrotoxicity, hepatotoxicity and other toxic effects have been reported after chronic administration of some NSAID during ecotoxicologic studies.[28,30,61,66,73,79] Few studies have investigated the use of NSAID in fish;[14] to date, only 7 agents have been tested—ketoprofen, meloxicam, ibuprofen, carprofen, flunixin, ketorolac, and aspirin

Ketoprofen. In addition to butorphanol, ketoprofen is the only other agent studied in an elasmobranch, the chain dogfish. The MAC of MS222 needed to prevent a response to a noxious stimulus was used in the chain dogfish; the experiment was unsuccessful, however, in that no difference could be seen between the control animals and fish that received ketoprofen (1 to 4 mg/kg IM).[23] This same parameter was assessed when ketoprofen was used in goldfish (0.5 to 2 mg/kg IM), and it was beneficial in this species because it significantly decreased MAC.[76] In addition, a dose of 2 mg/kg IM of this agent was studied in a surgical model of koi[33] and rainbow trout.[63] No clear signs of behavior-sparing effects occurred in either species, although postsurgical muscle damage was reduced by the administration of ketoprofen in koi and healing of the incision site was not altered in rainbow trout. Furthermore, no adverse side effects were reported in any of the species investigated.

Meloxicam. No clear beneficial effects of meloxicam in fish have been reported. The pharmacokinetic properties of meloxicam (1 mg/kg IV and IM) were investigated in the Nile tilapia (*Oreochromis niloticus*); this study showed that Nile tilapia eliminates the drug considerably faster than their mammalian counterparts.[27] This finding suggests that multiple daily administrations of meloxicam would be necessary to maintain clinically valuable plasma concentrations in this species, thus making the use of meloxicam at this dosage rather impractical, because it would require numerous handling events, which are highly stressful for fish. Meloxicam (0.1 to 0.2 mg/kg IM) reportedly has been used clinically, but its efficacy was not tested.[78]

Ibuprofen. Ibuprofen (370 to 470 µg/L for 24 to 72 h) showed antiinflammatory effects in fish, in which it decreased prostaglandin E metabolite levels in fathead minnows (*Pimephales promelas*)[59] when administered in the water. This effect was related to dose, although no dose–response curve could be established in this study; large interindividual variations were reported. In another study, ibuprofen (400 µM) did not show benefits, given that it was ineffective at reversing thermal aversion in larval zebrafish when administered via the water.[22]

Others. Carprofen,[49] flunixin,[63] and ketorolac[63] have been the subjects of experiments involving rainbow trout. Carprofen administration might have induced some analgesic effects at a dose of 2.5 mg/kg IM, but the sample size was very small, limiting the repeatability of the conclusions.[14,64] In the same study,[41] fish were reported to have decreased activity after administration of the highest dose tested (5 mg/kg IM). Flunixin (0.5 mg/kg IM) and ketorolac (0.5 mg/kg IM) did not show any clear signs of analgesia in rainbow trout.[63] In addition, flunixin (8 or 20 mg/L) administered in the water did not show any beneficial effects in larval zebrafish when exposed to acetic acid or heat as noxious stimuli.[45,46] Studies using larval zebrafish[45,46] showed that aspirin (2.5 mg/L) prevented the reduction of activity induced by acetic acid but did not show clear benefits in response to high temperatures. In addition, the administration of aspirin (1 or 2.5 mg/L) in the water showed beneficial effects in adult zebrafish after fin clipping.[65]

At the doses tested, NSAID have not yet proven to be particularly beneficial to fish, however these drugs appear to be safe. Their administration has not resulted in any adverse side effects, except for an increase in total phosphorus after administration of flunixin (0.5 mg/kg IM);[63] no biologic explanation was reported for this change. Furthermore, flunixin (0.25 to 0.5 mg/kg IM) is routinely used for analgesia in fish at the New England Aquarium without any apparent problems.[77] Further studies are needed to evaluate the effects of NSAID in fish species, so that their use can be recommended in light of stronger evidence of efficacy.

Local anesthetics. Local anesthetics interrupt nerve conduction by inhibiting the influx of sodium ions at voltage-gated sodium channels in axonal membranes. The mechanism involves binding of the drug to the H-gate, also known as the inactivation gate of the channel.[67] Local anesthetic use can reduce the amount of anesthetic required as well as the overall requirements for systemic analgesia, in addition to providing sufficient localized desensitization for many minor surgical procedures.[43] Although rare, side effects are associated with accidental intravenous administration[44] with the CNS and cardiovascular systems affected. Side effects have not yet been reported in fish during clinical trials. It should be noted that a local anesthetic, tricaine methanesulfonate or MS222, is regularly used to produce and maintain general anesthesia in fish.[50,71] In veterinary and human medicine, lidocaine is often used in combination with other drugs but insofar as we know combinations for analgesia have not been tested in fish.

Local anesthetics used as analgesics in fish[14] have been the subject of the fewest number of studies of the 3 main groups of drugs presented in this review. Subcutaneous injection of novocaine reportedly "fully blocked up nociceptive responses"[15] after an electrical stimulus in cod (*Gadus morhua marisalbi*), but "this alone is not considered sufficient evidence to recommend its use in vivo."[71] The only experiment assessing the efficacy of a local anesthetic as an injection was a study in which the author of the original review was involved.[49] This experiment tested lidocaine by using acetic acid injection as the noxious stimulus and the lips as the tested site. The original 2012 review[71] presented some inconsistencies in regard to this experiment. First, the reported dose range is incorrectly reported as 0.1 to 2 mg/kg SC (injected in the 'lips'), whereas the source paper actually used 3 doses reported as 0.5, 1, and 2 mg per fish.[49] Given that the average fish weight reported in the source is 111.2 ± 49.1 g, the doses tested were approximately 4.5, 9, and 18 mg/kg. Second, the summary table[71] mentions zebrafish as a species on which lidocaine has been tested, yet there was no published data on this species for lidocaine or any other local anesthetic administered for analgesia at the time. Third, the summary table[71] states under "efficacy" that lidocaine is "very efficient at 1 mg/kg" (actually 9 mg/kg). However, none of the metrics used (delay in feeding, activity 30 min after the stimulus, ventilation rate 30 min after the stimulus, rate of recovery of respiration after the stimulus) in the source material differed significantly after the noxious stimulus in the presence compared with absence of lidocaine treatment for any of the 3 doses.[14] Furthermore, the sample size of the study was small (5 fish per group), and the statistical tests not always appropriate; the *P* values were not corrected for the large number of comparisons.[14,64]

Other studies investigated the use of lidocaine as a bath treatment for larval zebrafish.[45,46,65] In 2 studies, lidocaine's effects were investigated by using larval zebrafish and lidocaine in ambient water (5 mg/L for approximately 40 min before application of a noxious stimulus). In these studies lidocaine prevented the reduction in activity reported in response to acetic acid exposure and hot water.[45,46] In another study using adult zebrafish, immersion of fish in low doses of lidocaine (2 or 5 mg/L for 45 min) also showed beneficial effects on activity and ventilation.[65] The mechanism behind the effects of immersion in low-dose lidocaine is unclear, however, and might be more similar to desensitization of the skin or gills rather than analgesia. As such, internal injury might not be affected by lidocaine dosed by immersion instead of infiltration. Alternatively, the effects reported after lidocaine immersion might be caused by neuromuscular blockage or sedation. In fact, lidocaine and other local anesthetics such as benzocaine and MS222[18,71] are usually used in fish for general anesthesia and are administered in the water. When used as such, local anesthetic enters through the gills and act on the CNS instead of acting locally. The exact mechanism of this central action has not been completely explained,[81] and the pathway through which low doses of lidocaine act on fish is unclear as well. Therefore, using lidocaine as an infiltration in combination with general anesthesia—as currently done in mammals and other species[44]—for species of fish whose size permits it might be prudent. This practice of administering a constant infusion of an analgesic drug such as lidocaine in conjunction with a general anesthetic is termed 'balanced anesthesia.' The addition of the analgesic and anesthetic-sparing effects of the drug reduces the general anesthetic requirements during anesthesia, reducing cardiovascular depression.[37]

Local anesthetics have proven to be very beneficial in mammals, yet more research is needed to determine an effective dose of local anesthetic for analgesia in fish.

Others. Other drugs have been studied in regard to analgesia of fish, although quite infrequently. When administered in ambient water, clonidine (5 µM) and amitriptyline (0.5 µM) were shown to be effective at reversing thermal aversion in zebrafish,[22] but gabapentin (100 µM) was ineffective. Medetomidine (0.025 mg/kg IM) had some beneficial effects, in that its administration decreased the MAC of MS222 needed to prevent a response to a noxious stimulus in goldfish.[76]

Pain assessment. Assessing pain is still problematic in nonhuman animals,[26] especially in fish, for which no well validated and generally accepted parameters are available currently. Because animals cannot easily communicate with us, pain typically is assessed by measuring physiologic parameters and biologic markers, such as heart or respiratory rate and cortisol levels, and observing deviations from normal behavior.[2] Both methods can be problematic. An important drawback regarding physiologic parameters is that the normal physiologic values of most fish species are unknown, or when known, their measurement is often impractical. For example, collecting blood from a fish to assess physiologic parameters necessitates catching and handling it under general anesthesia. This process can be quite time-consuming, especially when multiple fish are involved, and can cause significant stress to the animal. Furthermore, the parameters are affected by several variables such as species, breed, sex, exercise, eating, restraint, and ambient noise.[2,19] In addition, the commonly used parameter cortisol is not a very sensitive indication of pain; a recent review[25] has specifically discussed this issue in fish. In addition, feeding rate has been found to be an unreliable parameter in some species[63] but not others,[4] whereas opercular rate and fish weight proved to be more reliable.[63]

Observing changes in behavior is a practical way to detect a problem in welfare. This method is frequently used for companion animals, and changes in behavior are well correlated with physiologic signs of distress in various farm animals.[48] However, behavioral assessment can be problematic:[24] it requires a thorough knowledge of an animal's normal behavior, it is often based on extrapolating from one species to another, and it is prone to anthropomorphic bias. Behavioral assessment in fish is particularly difficult, because we currently lack important information about the normal behavior of most fish species. In addition, extrapolation is arduous because fish are markedly different from other laboratory species, given that they do not share a terrestrial environment and lack facial expression.[34] Those problems, as well as the strong sentiments evoked by the debate concerning the presence of pain in fish, tend to increase anthropomorphic bias in the interpretation of fish behavior.

All of the difficulties mentioned markedly influence the results of the studies we have reviewed here. Because there have not truly been any validated parameters to assess pain or nociception in fish, authors are currently arbitrarily choosing parameters to assess whether the drugs tested are efficacious. Those parameters are either physiologic or behavioral—and often a combination of both—and there is great variability between studies. Therefore it is quite difficult for authors to interpret their results as changes in their parameters can be problematic to interpret considering the aforementioned lack of knowledge of normal parameters in fish. Furthermore, often only one, or very few, of the multiple parameters assessed show significant change, a situation that makes asserting that the drug tested is efficacious particularly challenging. For those reasons, absolutely confirming that the analgesics tested to date are efficacious has been impossible, but some beneficial effects have been noted, especially with opioids. The creation of validated behavioral and physiologic parameters to assess pain and nociception in fish could correct this situation and thus would be critically valuable to the study of analgesics in these species.

Conclusions

In summary, information available concerning the use of analgesic in fish remains sparse. To date, mainly opioids, NSAID, and local anesthetics have been investigated, primarily in rainbow trout and zebrafish. Of those drugs, only the pharmacologic properties of morphine, meloxicam and tramadol have been investigated. Contrary to the statement in "Clinical anesthesia and analgesia in fish,"[71] little evidence is available currently that any of those drugs are "very efficient" in the species investigated. Although this lack of efficacy might be explained by the fact that fish really do not feel pain, it is likely that we have simply not yet identified an appropriate drug or dosage to show a distinct analgesic effect in fish. A significant obstacle in this search is our current lack of a correct and useful set of indicators to assess for nociception in fish. This absence is mainly due to our still-limited knowledge of fish behavior and normal physiologic parameters. Therefore, research aimed at improving our knowledge of the various species of fishes is needed to increase our ability to determine whether and when the use of analgesic drugs can be beneficial in fish.

Although no overwhelming evidence of the efficacy of analgesics in fish is available presently, signs of beneficial effects have been reported in many instances, particularly in the case of opioids, especially morphine. Furthermore, most doses tested did not result in significant side effects in the species involved. Therefore, those agents potentially could be administered when there is any concern that an animal is experiencing pain, because they appear not to cause harm and may be beneficial. However, when administering any drug to any animal, both the potential costs and benefits must be weighed. For example, morphine leads to small long-term effects on the cardiovascular system in trout that could interfere with goals of some experimental paradigms. The costs of administering an analgesic to fish are small, but chasing and netting a fish to administer an analgesic may be more stressful than the drug is beneficial. Furthermore, caution is advised when extrapolating to other species, because fish species often differ greatly from one another. Those differences influence the way those animals respond to and metabolize drugs. Pilot studies are recommended to ensure that the analgesic drug used is not harmful to the specific species of fish or in the specific experiment in which it is used.

Analgesic use in fish potentially could improve fish welfare, as it has in other animal species. Further studies are needed to investigate analgesic use in fish. Such studies would be more beneficial if based on proven parameters to assess the efficacy of analgesics in fish. In addition, detailed pharmacodynamic information about analgesics in fish is needed. In the meantime, scientists must make educated decisions that are based on the available literature yet acknowledge the potential bias in the interpretation of results caused by the current debate concerning the presence of pain in fish. Here we have analyzed the literature to address those biases and to provide scientists with an updated and comprehensive review of information regarding analgesic use in fish.

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