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Review Article

Drugs and Fish

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Abstract

The present review discusses the effects of pharmaceutical drugs on aquatic ecosystem, in particular the fish to be precise. The focus is on roles of multiple drug types like antimicrobial, antipsychotic, analgesic, and anti-inflammatory; and the toxicity induced by them towards growth and development of the fish present in the aquatic ecosystem. Few studies either in the wild or in *in vivo* have discussed these impacts of drugs. Interactions of drugs such as tilmicosin (TMS), tylosin (TYL), clarithromysin (CLR), azithromycin (AZM), Xanax, valium, and others, impacting fish physiology, metabolism, growth and development, have been highlighted. The toxicity of drugs on various fish models and possible modes of management in alleviating such situations are discussed.

Keywords: drug, ecosystem, fish, pharmaceuticals, toxicity

1. Introduction

The biological and environmental risks of pharmaceuticals such as antibiotics in aquatic ecosystems are a major cause of concern across the world (Ranjitha & Sharath, 2020). These detrimental molecules are released from human bodies, homes, and industries, entering the waterways and segregating and accumulating in fish and other water beings such as bugs, mollusks, and so on (Chandra & Sukumaran, 2020; Hatami, Banaee, & Haghi, 2019). Ecological zones around drug manufacturing plants have become considerable hotspots for the above-mentioned ecological impacts. Waterways contain several traces of drugs, including antibacterial, antifungal, analgesic, and other antipsychotics (Sharath, Raghava & Sharada, 2014) which target pain, fertility, sleeplessness, and other neurodegenerative diseases. If the present situation persists, scientists expect that these pharmaceutical agents in the aquatic ecosystems will increase by two thirds by 2050. Moreover, fish are consumed extensively worldwide, and pharmaceuticals affecting these living beings are a major cause of concern in the ecological food chain and as regards bioaccumulation (Banaee, Sureda, Taheri, & Hedayatzadeh, 2019, Chandra & Sukumaran, 2020). Monitoring the impacts of the drugs in the natural ecosystems is extremely strenuous; however, toxicologists consider that their impacts on aquatic animals like fish may happen at low concentrations, not in correlation with the effective dose levels for human beings (Mirghaed *et al*., 2018; Rashmi, Ranjitha & Sharath, 2019).

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2. Observations

2.1 Antipsychotic drugs

Many observations have been made in this direction. Amphetamines determine the timing of development of aquatic insects. Antidepressants disturb the learning and memory processes in cuttlefish. Antidepressants also cause the peeling off the rocks of marine and freshwater snails. Antipsychotic drugs lead to distorted behavior in crabs. Atlantic salmon smolts, when exposed to benzodiazepines derivative drugs like xanax and valium, which are used to treat anxiety, are prone to increased migrations compared to the non-affected ones. When exposed to pharmaceuticals, juvenile fish are more likely to arrive to the sea in immature condition and earlier than the favorable seasonal conditions. Aquatic pollution by drugs unfolds the psychobiological impacts on smolts and their feeling of stress (Abhijith, Ramesh & Poopal, 2016).

2.2 Antibiotics

Macrolide antibiotics (MALs) are extensively used for both humans and animals (Yan *et al*., 2019). Most macrolide antibiotics and their metabolites enter the aquatic ecosystem causing deleterious effects. Studies on Zebra fish embryos when exposed to four different MALs, namely tilmicosin (TMS), tylosin (TYL), clarithromysin (CLR) and azithromycin (AZM) have reported cardiotoxicity. The zebrafish heart rate exhibited comparable biphasic distribution when exposed to any of the four MALs separately, at two days after fertilization. The heart rate was elevated remarkably at low doses of MALs and lowered at high concentrations. Studies of TMS for its acute and developmental toxicity reported pericardial edema and spinal curvature in zebrafish embryos four days after fertilization. Moreover, TMS also induced oxidative stress (Chandra, Puneeth, Mahadimane, & Sharada, 2017; Puneeth and Chandra, 2020), with lowered superoxide dismutase (SOD) activities and elevated malondialdehyde (MDA) levels. Apoptosis was reported in zebrafish embryos when treated with TMS, followed by up-regulation of apoptosis associated genes, namely bcl2, caspase 3, p53, and caspase 9, which established an elevated protein expression. These results confirm the MALs having toxicity in the growth and development phases of zebrafish.

2.3 Non-steroidal Anti-inflammatory drugs (NSAIDS)

Another study on toxicity of three drugs, namely diclofenac, carbamazepine, and metoprolol, on embryos of the fish *Danio rerio* has been reported (Brandhof & Montforts, 2010). The fish embryo toxicity test (FET) was performed to 2-h old zebrafish embryos, which were exposed for 72 h to diclofenac, carbamazepine and metoprolol in turn to observe the impacts on tail movement and detachment, gastrulation, mortality, somite formation, heartbeat, pigmentation, malformation of head, scoliosis, deformity of yolk, hatching success, and otoliths and heart rate, at 24, 48 and 72 h. The results exhibited retardation of growth above 30.6 mg/l carbamazepine, growth retardation and scoliosis above 12.6 mg/l metoprolol, and yolk sac and tail deformation and no hatching above 1.5 mg/l diclofenac. Thus, the toxicity to embryos was confirmed for the above-mentioned pharmaceuticals.

2.4 Psychoactive drugs

Another study (Huerta *et al*., 2016) reports the habitual presence of psychoactive drugs in aquatic ecosystems. The evolutionary conservation of gene level target sites of the psychotic drugs (Sumpter, Donnachie, & Johnson, 2014) in human and fish correlate with each other, but the pattern and dosage to impact fish is still uncovered. Huerta et al assessed the uptake and tissue distribution in *Pimephales promelas* (fathead minnow) of benzodiazepine oxazepam (Argyropoulos & Nutt, 1999; Brodin, Fick, Jonsson, & Klaminder, 2013), prescribed to treat anxiety along with insomnia and alcohol withdrawal (Facciolo, Crudo, Zizza, Giusi, & Canonaco, 2012). The studies were conducted and evaluated post 28 d exposure to 0.8 $\mu g\ L^{-1}$, 4.7 $\mu g\ L^{-1}$, and 30.6 $\mu g\ L^{-1}$ of benzodiazepine oxazepam. An association between oxazepam internal concentrations and the impacts on fish exploratory behavior was determined by performing shelter seeking test and a novel tank diving test (Stewart *et al*., 2011). Maximum levels of oxazepam were seen in brain, in comparison to plasma and liver, and negligible levels in muscle. Average contents reported in the plasma of *Pimephales promelas* were $8.7 \pm 5.7\ \mu g\ L^{-1}$, $30.3 \pm 16.1\ \mu g\ L^{-1}$, and $98.8 \pm 72.9\ \mu g\ L^{-1}$, respectively for the three dose levels tested. Noticeable relations between tissue and plasma levels of oxazepam were reported in all three treatment groups. When the fish were treated with 30.6 $\mu g\ L^{-1}$, the plasma levels were found to be just below human therapeutic plasma concentration (HPC) (Valenti *et al*., 2012). Remarkable behavioral impact was noted at a concentration of 4.7 $\mu g\ L^{-1}$ in the novel tank diving test. Thus, the effects of psychotic drugs on fish were once more confirmed.

2.5 Anticonvulsants

Brandão *et al*. (2013) reported the toxicological impacts of the three anticonvulsant (Fent *et al*., 2006) drugs phenytoin (Benotti *et al*., 2009), carbamazepine (Zhou, Dai, Zhang, Y. Surampalli, & Zhang, 2011) and diazepam (Calisto, Domingues, & Esteves, 2011) on pumpkinseed sunfish (*Lepomis gibbosus*). They observed alterations in oxidative stress variables like glutathione S-transferase (GSTs), lipid peroxidation (thiobarbituric acid reactive substances, TBARS), catalase (CAT), and glutathione reductase (GRed) in the gills, hepatic, and digestive systems of the treated fish.

Table 1. Table showing impacts of drugs on various species of fish

Drug	Test animal	Indications
Tilmicosin (TMS)	Zebra fish embryos	Cardiotoxicity
Tylosin (TYL)		Pericardial edema and spinal curvature (TMS)
Clarithromysin (CLR)		Up-regulation of apoptosis associated genes namely bcl2, caspase 3, p53 and caspase 9 (TMS)
Diclofenac (Df)		Retardation of growth (Df)
Carbamazepine (Cp)		Growth retardation and Scoliosis (Cp)
Metoprolol (Mp)	Zebra fish	Yolk sac and tail deformation and on hatching (Mp)
Benzodiazepine oxazepam	Fathead minnow	Oxazepam were seen in brain Impact on fish exploratory behavior
Phenytoin (Ph)	Pumpkinseed sunfish	Alterations in oxidative stress variables
Carbamazepine (Cp)		Scototaxis activity
Diazepam (Dz)		Raise in glutathione reductase and glutathione S-transferase activity. (Cp) Increased motion of fish. (Cp)

Subsequently, behavioral patterns like scototaxis glutathione reductase (GRed) in the gills, hepatic, and digestive systems of the treated fish. Subsequently, behavioral patterns like scototaxis activity were also observed and reported. Diazepam treated fish exhibited elevated GST activities in gill tissue and inhibition of glutathione reductase in digestive system, signifying antioxidant feedback. On the behavioral front it inflicted less refuge time and more swimming activity. Exposure of fish to carbamazepine led to raised glutathione reductase and glutathione S-transferase activities in the digestive system. Carbamazepine also led to increased mobility of the fish. Phenytoin treatment showed adaptive response in glutathione S-transferase and catalase activity in liver tissue, followed by negligible behavioral changes. All the three drugs clinically showed toxic accumulation in fish.

3. Prevention and Management

Drug exposures in an aquatic ecosystem are hard to prevent due to their odorless and tasteless characteristics, and also toxic effects on fish are very difficult to recognize based on behavior and appearance. Most of the drugs are heat stable and thus cannot be removed from fish by typical food treatments like cooking, boiling, or freezing. This highlights the importance of the management of drug-induced fish toxicity. Aquatic zones vulnerable to discharges of drug waste should be identified and measures to avert such major detrimental hazards to the fish should be made by concerned stakeholders. Measures should be taken to create awareness among fish consumers, particularly in toxic hotspots, to avoid consumption of fish organs like head, liver, or roe, where the enrichment and accumulation of xenobiotics can be particularly high (Perva *et al*., 2020).

References

Argyropoulos, S. V., & Nutt, D. J. (1999). The use of benzodiazepines in anxiety and other disorders. *European Neuropsychopharmacology*, *9*, S407-S412.

Abhijith, B. D., Ramesh, M., & Poopal, R. K. (2016). Responses of metabolic and antioxidant enzymatic activities in gill, liver and plasma of Catla catla during methyl parathion exposure, *The Journal of Basic and Applied Zoology*, *77*, 31-40.

Banaee, M., Sureda, A., Taheri, S., & Hedayatzadeh, F. (2019). Sub-lethal effects of dimethoate alone and in combination with cadmium on biochemical parameters in freshwater snail, *Galba truncatula*. *Comparative Biochemistry and Physiology Part C: Toxicology and Pharmacology*, *220*, 62-70.

Benotti, M. J., Trenholm, R. A., Vanderford, B. J., Holady, J. C., Stanford, B. D., & Snyder, S. A. (2009). Pharmaceuticals and endocrine disrupting compounds in US drinking water. *Environmental Science and technology*, *43*(3), 597-603.

Brandão, F. P., Rodrigues, S., Castro, B. B., Gonçalves, F., Antunes, S. C., & Nunes, B. (2013). Short-term effects of neuroactive pharmaceutical drugs on a fish species: biochemical and behavioural effects. *Aquatic Toxicology*, *144*, 218-229.

Brandhof, E. V., & Montforts, M. (2010). Fish embryo toxicity of carbamazepine, diclofenac and metoprolol. *Ecotoxicology and Environmental Safety*, *738*, 1862-6.

Brodin, T., Fick, J., Jonsson, M., & Klaminder, J. (2013). Dilute concentrations of a psychiatric drug alter behavior of fish from natural populations. *Science*, *339*(6121), 814-815.

Calisto, V., Domingues, M. R. M., & Esteves, V. I. (2011). Photodegradation of psychiatric pharmaceuticals in aquatic environments–Kinetics and photo degradation products. *Water Research*, *45*(18), 6097-6106.

Chandra, S. P., Puneeth, H. R., Mahadimane, P. V., & Sharada, A. C. (2017). Biochemical evaluation of Cordia dichotoma seed extracts. *Advanced Science Letters*, *23*(3), 1823-1825.

Chandra, S., & Sukumaran, S. (2020). Physiological, Biochemical and Neurochemical responses of Cirrhinus mrigala upon short term exposure to Cerium oxide. *International Journal of Aquatic Biology*, *7*(6), 368-373.

Facciolo, R. M., Crudo, M., Zizza, M., Giusi, G., & Canonaco, M. (2012). α GABAA subunit-orexin receptor interactions activate learning/motivational pathways in the goldfish. *Behavioural Brain Research*, *234*(2), 349-356.

Fent, K., Weston, A. A., & Caminada, D. (2006). Ecotoxicology of human pharmaceuticals. *Aquatic Toxicology*, *76*(2), 122-159.

Hatami, M., Banaee, M., & Haghi, B. N. (2019). Sub-lethal toxicity of chlorpyrifos alone and in combination with polyethylene glycol to common carp (Cyprinus carpio). *Chemosphere*, *219*, 981-988.

Huerta, B., Margiotta-Casaluci, L., Rodríguez-Mozaz, S., Scholze, M., Winter, M. J., Barceló, D., & Sumpter, J. P. (2016). Anti-anxiety drugs and fish behavior: Establishing the link between internal concentrations of oxazepam and behavioral effects. *Environmental Toxicology and Chemistry*, *35*(11), 2782-2790.

Mirghaed, A. T., Yarahmadi, P., Craig, P. M., Farsani, H. G., Ghysvandi, N., & Eagderi, S. (2018). Hemato-immunological, serum metabolite and enzymatic stress response alterations in exposed rainbow trout (*Oncorhynchus mykiss*) to nanosilver. *International Journal of Aquatic Biology*, *6*(4), 221-234.

Perva, S., Swamy, K., Chandrashekar, N., Subramanian, R., Sukumaran, S., & Chandra SP, S. (2020). Physio-biochemical responses of Indian major carp *Catla catla* upon sub-chronic exposure to tin oxide nanoparticles. *Egyptian Journal of Aquatic Biology and Fisheries*, *24*(4), 509-520.

Puneeth, H. R., & Chandra, S. S. P. (2020). A review on potential therapeutic properties of Pomegranate (*Punica granatum* L.). *Plant Science Today*, *7*(1), 9-16.

Ranjitha, T., & Sharath Chandra, S. P. (2020). Biological and ecological impact of iron and iron nanoparticles across diverse array of fish models: A review. *Ecology, Environment and Conservation, 26*(1), 180-184

Rashmi, N., Ranjitha, T., & Sharath Chandra, S. P. (2019). Chromium and their Derivatives Causes Physiological and Biochemical Modifications in Diverse Fish Models: A Review. 2019. *Biomedical and Pharmacology Journal, 12*(4), 2049-2053.

Sharath Chandra, S. P., Raghava, B., & Sharada, A. C. (2014). Synthesis, characterization, molecular property prediction and antipsychotic activity of novel 6-fluoro-3-(piperidin-4-yl) benzo[d]isoxazole Deri vatives. *International Journal of Pharmaceutical Sciences Review and Research*, *29*(1), 302-308

Sharath Chandra, S. P., & Sukumaran, S. (2020). Magnesium chloride impairs physio-biochemical and neurochemical responses in cirrhinusmrigala (Hamilton, 1822) upon short term exposure. *Biointerface Research in Applied Chemistry*, *10*(1), 4934-4938.

Stewart, A., Wu, N., Cachat, J., Hart, P., Gaikwad, S., Wong, K., . . . Carlos, D. (2011). Pharmacological modulation of anxiety-like phenotypes in adult zebrafish behavioral models. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *35*(6), 1421-1431.

Sumpter, J. P., Donnachie, R. L., & Johnson, A. C. (2014). The apparently very variable potency of the anti-depressant fluoxetine. *Aquatic toxicology, 151*, 57-60.

Valenti Jr, T. W., Gould, G. G., Berninger, J. P., Connors, K. A., Keele, N. B., Prosser, K. N., & Brooks, B. W. (2012). Human therapeutic plasma levels of the selective serotonin reuptake inhibitor (SSRI) sertraline decrease serotonin reuptake transporter binding and shelter-seeking behavior in adult male fathead minnows. *Environmental Science and Technology*, *46*(4), 2427-2435.

Yan, Z., Huang, X., Xie, Y., Song, M., Zhu, K., & Ding, S. (2019). Macrolides induce severe cardiotoxicity and developmental toxicity in zebrafish embryos. *The Science of the Total Environment*, *649*, 1414–1421.

Zhou, X. F., Dai, C. M., Zhang, Y. L., Surampalli, R. Y., & Zhang, T. C. (2011). A preliminary study on the occurrence and behavior of carbamazepine (CBZ) in aquatic environment of Yangtze River Delta, China. *Environmental Monitoring and Assessment*, *173*(1-4), 45-53.