Winter School on

'RECENT ADVANCES IN DIAGNOSIS AND MANAGEMENT OF DISEASES IN MARICULTURE'

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Course Manual

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DRUG DELIVERY SYSTEMS

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Drug delivery systems are designed based on the action of the drug in the body, reaction of the body to these drugs and the active drug available in the body for therapeutic action. The way a drug is made to reach the destination and act at the appropriate site is the drug delivery systems.

In USA, the Food and Drug Administration controls the use of drugs and chemicals for food fishes. Six categories are used to classify uses: 1. therapeutants, 2. anaesthetics, 3. disinfecting agents, 4. water treatment compounds, 5. herbicides and algicides, and 6. fish control agents. The US Environmental Protection Agency (EPA) controls the release of chemicals into the environment and is concerned about the release of pharmaceuticals and chemicals from fish farms and aquaculture facilities.

Routes of Delivery

Drugs can be given orally, intramuscularly, intraperitoneally, intravenously or topically as baths or dips. Selection of the proper route depends on the environmental situation, the species and condition of the patient, and the drug being delivered. Failure to consider any of these factors can result in unsatisfactory treatment.

Intravenous Administration

The small size of most tropical fish precludes effective intravenous dosage. Cannulation of small vessels in the mouth is possible on anaesthetized patients of reasonable size, but the procedure requires microsurgical skills and equipment as well as the physiologic impact of anaesthesia. The caudal vein is suitable in sharks for delivery of a variety of drugs including steroids and antibiotics. Other sites include veins running laterally behind the head just above the lateral line. These veins are accessible on larger animals. Prepping shark skin with alcohol is very irritating and results in local erythema and induration.

Intraperitoneal Administration

This route of administration is the most common substitute for the intravenous route. The drug should be nonirritating and capable of crossing endothelial barriers. It may not be practical in situations involving very large numbers of fish. The procedure is relatively safe and simple even in very small fish. Once the abdomen is located and defined, a small needle (22 to 30 gauge) is inserted under the scales in the caudoventral aspect of the abdomen, directed cranio-dorsal. The posterior ventral site of insertion minimizes the chance of injuring the liver, spleen or kidney. Use sterile syringes and needles and observe all practices to reduce cross-infection between patients or contamination of mutidose drug containers.

Intramuscular Administration

Intramuscular injections are generally administered into the dorsal muscle mass under the dorsal fin. A site roughly halfway between the lateral line and the dorsal fin is usually selected and the needle directed cranially under scales as in the IP injection. This

route eliminates any risk of abdominal organ injury and is more readily administered without use of sedatives or anaesthetics. Objections to the use of the IM route include the belief that fish muscle is less well vascularized than mammalian muscle. This would lead to poor distribution of drugs, formation of sterile abscesses and increased local impact of irritating drugs. In practical application, this does not seem to be the case when drugs are properly selected and administered.

Oral Administration

If fish are still eating when they are presented for treatment, oral administration is usually the route of choice. This is particularly true in production systems where large numbers of fish must be medicated. Exceptions to this general statement include the delivery of drugs intended for systemic treatment that will not be absorbed the digestive system such as aminoglycosides. The dose interval can also present problem. If a fish feeds normally every third day but needs drug delivery at least daily, effective levels will not be reached unless the feeding schedule is modified.

Topical Administration

Four basic forms of topical treatment must be considered on fish therapeutics. They are

1. Direct topical application
2. Short duration dips
3. Long duration baths and dips
4. Tank treatments.

1. Direct topical application

   Localized application of antiseptics, antibiotics, steroids and dressings can be done by this method. The most common use of this application is to cauterize or disinfect a localized lesion.

2. Short duration dips

   This is used to achieve systemic levels of drug. Some drugs are absorbed across gill and other mucous membranes. It is best to consider short dips of 1 second to 1 minute to be purely topical administrations.

3. Long duration baths and dips

   This requires handling the fish but have the major advantage of sparing the environment from damage and increasing the predictability of drug delivery. To carry out this, another container is required that can be filled with a known volume of water from the tank where the fish to be treated are housed. Drug is added to this separate container and the fish are then exposed to it for varying periods of time.

4. Tank treatments

   It is the most frequently used method of treating small tropical fish. In this treatment drug is put directly into the pond where the fish lives. The entire environment is saturated with the drug. Advantages are ease of administration, since the fish need not be handled and the extension of the treatment to the environmental substrates, successfully destroying the pathogenic organisms not yet on the fish.

Modified Release Drug Delivery System.

Modified release dosage forms are prepared by using designed substances to modify the rate of release of active ingredient in the body. The magnitude of the plasma drug concentration is influenced by a number of factors, viz., the dose, dosage interval, rate of drug absorption, biotrasformation, elimination, etc. Several types of drug delivery systems have been developed like

1. Delayed release, the drug is released at a time other than immediately after administration.
2. Repeat action, the drug is released in small amounts at intermittent intervals after administration.
3. Sustained release, the drug is released slowly at a rate governed by the delivery system.
4. Controlled release, the drug is released at a constant rate and the drug conc. obtained after administration of the system are in variant with time.

Mechanism of Drug Release

The principal mechanisms involved in controlling drug release are diffusion and dissolution. In general, the drug release is not zero-order due to difficulty of ensuring that release occurs from a constant surface area of drug. A drug with low aqueous solubility is likely to have an inbuilt potential for extended release in that the dissolution rate will be slower than the rate of absorption through a biological membrane. It is possible to modify a highly water-soluble drug to less water-soluble forms, thereby reducing dissolution rate and extending the period of release.

Two groups of oral delivery systems, the encapsulated and matrix systems rely on dissolution of the drug or components as the rate controlling process in release, whereas membrane reservoir system and special drug matrix systems are the two important types of delivery systems where drug diffusion is the rate limiting step. Prodrug formulations have been used for sustained release. Many of the prodrugs like prontosil, phenacetin and phenylbutazone were subsequently replaced by their active metabolites.

Limitations of Extended Release Systems

1. High cost 2. Dose dumping 3. Physiological tolerance due to continuous therapeutic conc. 4. Loss of clinical efficacy 5. Toxicity with drugs of low margin of safety.

Targeted drug delivery

The aim of targeted drug delivery is to deliver the therapeutic formulations specifically and efficaciously to the affected cells and tissues with minimum deleterious effects on the healthy cells, due to high drug conc. in plasma. The vehicles for the effective delivery of drug molecules are

1. Standard Liposomes
2. Long-circulation liposomes
3. Immunoliposomes
4. Immunonano particles and Immuno-conjugates
5. Magnetic immuno-microspheres
6. Targeted bacterial toxins and
7. Vitamin-mediated delivery.

Standard Liposomes

Aqueous dispersions of bilayer forming phospholipids are referred as liposomes. The liposomes may contain one or more aqueous compartments separated by lipid bilayers. The alternate order of the aqueous and lipid compartments in liposomes control the release of drug molecules entrapped in these vesicles.

Long-circulation liposomes

Polymer containing LC liposomes, Glycolipid containing LC liposomes and pH sensitive liposomes are some examples of this type. The advantages of LC liposomes are

a) A wide range of rate of drug release can be achieved by changing lipid composition.
b) They are able to cross the biological barriers in vivo.
c) Their use results in increased uptake of drugs at the site of infection and tumors with decreased toxicity.
d) Their decreased uptake by reticulo-endothelial system saves the host defence system.
e) Their prolonged half-life in blood maintains systemic delivery.
f) LC liposomes are useful in antibody mediated targeting of bioactive molecules.

Immunoliposomes

The immunoliposomal targeted drug delivery technique is based on the principle of rendering the antigen recognizing capacity of antibody to the liposomal vesicles, thus making it target oriented. Incorporation of cholesterol stabilizes vesicles by relaxing inter-chain packing constraints. Immunoliposomes fuse with the membrane of the specifically targeted cells and thus are capable of delivering their entrapped drug into the cytosol of target cells.

Immunonano-particles and immuno-conjugates.

Nanoparticles are 200-500 nm size colloidal particles prepared from sterilizable, nontoxic and biodegradable materials such as casein, albumin, gelatin and ethylcellulose. The drug is conjugated to the nanoparticles and their attachment to antibody leads to targeting of nanoparticles.

Magnetic immuno-microspheres.

Magnetomicrospheres coupled with monoclonal antibodies can be used as magneto-immunonano particles that can be manipulated by a magnet. Magnetic microspheres were bound to the malignant cells with the help of monoclonal antibodies, and then the bound cells were removed from the bone marrow using a magnet.

Targeted bacterial toxins.

Some gram-negative bacteria produce exotoxins. The toxin operates stepwise by getting adsorbed to its receptor, endocytosed by means of coated pits into endosomes, reduced and then processed so as to release traslocation and intoxication domains that are translocated into the cytosol

Vitamin mediated drug delivery.

The concept behind this technique is that cell surface receptors for vitamins such as folic acid and biotin mediate endocytosis of vitamin conjugated macromolecules.