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A Review on Drugs Used in Shrimp Aquaculture

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ABSTRACT

Many drugs are used in hatchery and grow-out operations of shrimp industry. Antimicrobial resistance, short term efficacy of antibiotics and environmental factors make the disease management difficult in shrimp aquaculture. Florefenicol, Sarafloxacin, Oxytetracycline and Enrofloxacin are the frequently used antibiotics in shrimp aquaculture. The use of antibiotics may cause development of antibiotic resistance among pathogens infecting cultured animals and humans. It is important that therapeutic regimes are designed to maximise efficacy and thereby minimise the risk of the development of the resistant pathogens. The design of pharmacokinetic studies in fish and shellfish is necessary prior to use of drugs in aquaculture.

Key words: *Antibiotics, Aquaculture, Shrimp, Drugs.*

INTRODUCTION

In India, brackishwater aquaculture in coastal areas mainly involves shrimp culture and it is widely practised along the costs of West Bengal, Andhra Pradesh, Orissa and Tamil Nadu. But recently, diseases caused by bacteria which belong to genus Vibrio are causing economic damage to shrimp culture industry. During the production cycles many antimicrobial agents are used in grow-out and hatchery operations. But in shrimp culture, disease management becomes complicated due to problems such as resistant pathogens, short term efficacy of antibiotics and environmental factors[1,2]. So it is important to conduct susceptibility test and efficacy test of a particular antibiotic against the pathogens before we use them in shrimp culture activities.

Shrimp culture

Aquaculture, the production of aquatic plants and animals is the fastest-growing food producing industry[3]. During the last 30 years aquaculture has expanded 12 fold with an annual growth rate of 8.8% and has in 2010 reached a total volume of 60 million tonnes[4]. Shrimp is the most traded seafood internationally and its culture has been accounted for about 28% to the internationally traded seafood production[5]. In India, brackish water aquaculture is concentrated around the giant tiger prawn (*P. monodon*) as the single most important species.

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But due to its fast growing rate, low incidence of native diseases, availability of Specific Pathogen Free (SPF) domesticated strains and culture feasibility in wide salinity range, *Litopenaeus vannamei* has attracted the farmers attention. With the production levels of 10–12 tonnes/ha/crop of 3-4 months duration the production of this species has reached to a level of 10,470,516 tonnes during 2012–13[4].

Bacterial diseases in shrimp culture

The intensification of shrimp culture has led to rise of many problems in production of shrimp in 90's due to massive disease outbreaks especially during 1995-96. Shrimp culture is affected by both bacterial and viral diseases. Bacterial diseases have emerged as a serious problem in aquaculture and represent the most important challenge [6,7]. In cultured penaeids, especially in the larval, post larval and juvenile stages a number of bacteria have been implicated as causes of disease and mortality [8, 9]. Bacterial micro organisms can also cause destructive infections such as the disease caused by bacteria of the Vibrio genus and the bacteria that cause necrotizing hepatopancreatitits[10].

Vibriosis

Vibriosis is ubiquitous throughout the world and all marine crustaceans including prawns are susceptible. It is caused by several Vibrio species and responsible for mortality of cultured shrimp worldwide[11, 12, 13, 14]. Vibrio species are part of the natural microflora of wild and cultured shrimps[15]. They become opportunistic pathogens when natural defence mechanisms are suppressed[16].*Vibrio parahaemolyticus*, pathogenic bacteria have been reported to be a part of their normal microflora[17].

Clinical signs of vibriosis

Vibriosis can cause mass mortalities when shrimps are stressed by the factors such as poor water quality, crowding, high water temperature and low water exchange [12, 16,18]. Shells become melanised with lesions, darkening or reddening of the body, tail rot and discolouration of the gills also seen. In case of juveniles high mortalities are found [19]. The clinical signs may range from gastroenteritis to wound infection, otitis and septicaemia depending on the bacterial species which cause disease [20].

Early mortality syndrome (EMS)

Early mortality syndrome (EMS) is also called as acute hepatopancreatic necrosis disease (AHPND). It was first reported in southern China in 2010 and subsequently in Vietnam, Thailand, and Malaysia. It is an emerging disease caused by bacteria. Forty days old or younger shrimps that are not yet marketable size are typically affected by EMS. Humans do not get affected but is often fatal to shrimp. Upto 100% mortalities can be observed in shrimp ponds which are affected by EMS. The causative agent of EMS has been reported to be a bacterium-*Vibrio parahaemolyticus* [21]. EMS is known to affect both *Penaeus monodon* and *Litopenaeus vannamei* and is responsible for the acute mortalities reported within the first 30–35 days of culture period leading to significant production losses in the affected areas [22, 23, 24,25].

Antibiotics in shrimp farming

In aquaculture, antibiotics are frequently used during the production cycle both in the larval and growth phases to control bacterial diseases. Most frequently used antibiotics in aquaculture to control bacterial diseases include florfenicol, sarafloxacin, oxytetracycline and [11,26]. Along with these antibiotics, other antibiotics such as quinolones, chlortetracycline, oxolinic acid, ciprofloxacin, norfloxacin, perfloxacin, sulfamethazine, gentamicin, and tiamulin are used[8]. Luminous bacteria showed higher resistance rates to nalidixic acid and oxytetracycline when compared to chloramphenicol and ciprofloxacin[27]. Oxytetracycline is widely used to treat bacterial infections in aquaculture farms such as Vibriosis and Furunculosis[28,29]. According to Roque *et al*[10]., the most common way in Mexico to resolve the Vibriosis problem is by the use of feed plus antibiotics in shrimp aquaculture, freshwater fish farms or directly applied to the water in case of the hatcheries[11].

The use of antibiotics in aquaculture may cause development of antibiotic resistance among pathogens infecting cultured animals and humans. The rapid development of antibiotic resistant bacteria and resultant devastation of the hatchery operations has been observed due to the regular prophylactic use of low concentration of antibiotics has induced [30,31]. It is reported that only 20-30% antibiotics are ingested by fish and the remaining 70-80% reach the environment. Even the antibiotics ingested by aquatic animals may be excreted as such or as metabolites which might sometimes be harmful to the animals as well as human consumers. Resistance to antibiotics in pathogens such as *Vibrios* and *Aeromonas* can develop very quickly[32]. According to Dixon[33]., resistance emerges by two known genetic mechanisms i.e., mutation on the bacterial chromosome or extra chromosomal transfer mediated by plasmids[33]. In shrimp culture, the extensive use of antibiotics contributes to the development of antibiotic resistant pathogens and that these microbes can infect both humans and domesticated animals[34]. The chemical residue from the antibiotics or pesticides used at the farm level can be accumulated in fish and could cause a chronic health effects to consumers and potentially to cause certain organ or system malfunction such as cancer, nerve problems and immunological problems in human[35]. Residual antibiotics present in the sediments will promote resistance and may have human health implications if this resistance is passed on to potential human pathogens[32]. It is important that therapeutic regimens are designed to maximise efficacy and there by minimise the risk of the development of the resistant pathogens. So the study of pharmacokinetic properties of drugs, in combination with susceptibility test is important to minimize human risk associated with drug residues and the environmental impact of the drugs.

Table 1: Antimicrobial agents used in global aquaculture

Antimicrobial agent	Bacterial disease controlled
Oxytetracycline	Acinetobacter disease, bacterial fin erosion, carp erythrodermatitis, coldwater disease, columnaris, edwardsiellosis, emphysematous putrefactive disease, enteric redmouth, enteric septicaemia, furunculosis, gill disease, haemorrhagic septicaemia, redpest, salmonid blood spot, saltwater columnaris, streptococcosis, ulcerative dermatitis, pseudomonas disease, gaffkemia
Penicillin dihydrostreptomycin Penicillin G, Piromidic acid	Bacterial kidney disease
Rifampin	Mycobacteriosis
Spiramycin	Bacterial kidney disease
Streptomycin	Haemorrhagic septicaemia, mycobacteriosis
Sulfadiazine- trimethoprim	Entericredmouth, furunculosis,*Plesiomonas shigelloides* infection, vibriosis
Sulfadimethoxine-ormetoprim	Furunculosis, enteric septicemia of catfish
Sulfamerazine	Bacterial kidney disease, coldwater disease, columnaris, enteric redmouth, furunculosis, haemorrhagic septicaemia
Sulfamethazine, sodium salt	Bacterial kidney disease, coldwater disease, columnaris, furunculosis, vibriosis
Sulfamonomethoxine Sulfamonomethoxineormetoprim Sulfisoxazole	Bacterial kidney disease, coldwater disease, columnaris, enteric redmouth, furunculosis, haemorrhagic septicaemia
Sulfonamides	Nocardiosis
Tetracycline	Carp erythrodermatitis, columnaris,furunculosis, streptococcosis
Thiamphenicol Tiamulin	Enteric red mouth

Table 2: Approved Drugs for Use in Aquaculture

Sl No.	Drug Name
1	Chorionic Gonadotropin
2	Formalin
3	Hydrogen Peroxide
4	Oxytetracycline Hydrochloride
5	Tricaine Methanesulfonate
6	Florfenicol
7	Oxytetracycline Dihydrate
8	Sulfadimethoxine & Ormetoprim

Oxytetracycline

Oxytetracycline (OTC) is one of three antibiotics currently available and approved by the U.S. Food and Drug Administration (FDA) for used as a chemotherapeutic agent in food fish and is widely used in the aquaculture industry. It is a yellow amphoteric crystalline compound with a molecular weight of 460.44. Injections of oxytetracycline are often formulated as hydrochlorides because it is unstable in solution form[36]. It is widely used to treat the bacterial infections like vibriosis and furunculosis[28,29,37,38]. Oxytetracycline has only been approved by the FDA to treat bacterial hemorrhagic septicaemia and pseudomonas in catfish and salmonids[39], it is often used to treat numerous other diseases in a variety of fish. Due to its broad antibacterial spectrum and high potency, it has potential for use in farm raised shrimp for the treatment of vibriosis and necrotizing hepatopancreatitits infections[28].

Florfenicol

Florfenicol is one of the three antibiotics approved by FDA to use in aquaculture. It is used in shrimp aquaculture to control bacterial diseases[10,26]. In Mexico, florfenicol is commonly used in larval and grow-out facilities[40]. A dosage of 10 mg florfenicol per kg fish per day for 10 days is recommended is catfishes and freshwater reared salmonids by FDA.

Enrofloxacin

ENRO is a fluoroquinolone (FQ), nalidixic acid derivative with broad-spectrum activity against Gram-negative bacteria. It inhibits prokaryotic topoisomerase II (DNA gyrase) which is an important enzyme for bacterial replication[41]. It has broad spectrum activity and especially very effective against gram negative bacteria, such as *Aeromonas salmonicida*, *Renibacterrium salmoninarum*, *Vibrio anguillarum* and intracellular organism, such as rickettsia, chlamydia and mycoplasma[42].

Oxolinic acid

Oxolinic acid is a synthetic quinolone antibiotic, which is used in veterinary medicine for the treatment of cattle, pigs, poultry and fin fish. Quinolones are broad spectrum antibacterial agents which act especially on gram negative bacteria. In several European Union member countries, oxolinic acid (OA) is a licensed antibiotic that displays a broad spectrum of antibacterial activity especially against Gram negative bacterial fish pathogens[43]. It is accepted for use in aquaculture in Japan and some countries in Europe, being widely used in Norwegian aquaculture to treat numerous diseases including furunculosis[44]. Oxolinic acid is administered orally via medicated feed with a recommended dose for finfish of 12 mg/kg b.w /day for up to 7d [45]. A significantly decreased mortality was observed in fish offered oxolinic acid-medicated feed versus the controls after a *Vibrio anguillarum* immersion challenge [46].

Sarafloxacin

Sarafloxacin is a fluoroquinolone antibiotic which works by inhibition of bacterial DNA-topoisomerase II. Its molecular weight is 385 and its solubility is 0.034 mol/L at pH 1 [47,48]. It is used in fish feeds to treat diseases such as furunculosis, vibriosis and enteric red mouth. Ten mg/kg is the normal dosage used in farmed animals and the drug is administered in drinking water. Maximum residue level (MRL) has not been established for cow's milk or chicken muscle [47,48].

Antibiotic susceptibility test

When using antimicrobials it is essential to ascertain that the drug being considered will be effective in treating a particular disease causing agent. This may require antimicrobial susceptibility testing (AST) of the microorganism. The Kirby-Bauer method[49] is the most commonly used disk diffusion method for determining the susceptibility of aquatic bacteria to antimicrobial agents[50]. Among pathogenic vibrios, *Vibrio parahaemolyticus* is the leading cause of seafood-associated bacterial gastroenteritis in the United States [51] and the most common food borne pathogen in Asian countries [52]. *Vibrio parahaemolyticus* showed good susceptibility to most of the antimicrobial agents that are commercially available for the treatment of causing disease [53]. Chloramphenicol, sulfamethaoxazole and nitrofuranation were the most effective and possessed widest inhibitory spectrum against bacteria including *V. alginolyticus, V. cambpelli, V. parahaemolyticus* and other marine vibrios. *V. parahaemolyticus* which caused red leg disease in *Panulirus orientalis* was highly sensitive to erythromycin and chloramphenicol.

Pharmacokinetics

Pharmacokinetics is a branch of pharmacology and it is the use of mathematical models to quantitate drug concentrations in an animal[54]. The word phramacokinetics is derived from Greek word "pharmakon" which means "drug" and "kinetikos" which means "to do with motion" and is proposed to study the absorption, the distribution, the biotransformation and the elimination of drugs in man and animals[55]. It describes how the body affects a specific drug after administration through the mechanisms of absorption and distribution, the chemical changes of the substance in the body and the effects and routes of excretion of the metabolites of the drug. The site of administration and the dose of administered drug may affect the pharmacokinetic properties of drugs. These may affect the absorption rate. Absorption of antimicrobial agents range from 0 to 100% and is the process by which the compound transfers from the site of administration into the systemic circulation (central compartment)[56]. Intravenous or intramuscular administration of most antimicrobials results in a percentage bioavailability of 100%. However, absorption after oral administration is always less than 100%. Bioavailability refers only to the extent of absorption and provides no indication of the rapidity of absorption or the degree of protein binding. Many times pharmacokinetics is often studied in conjunction with pharmacodynamics, which means the study of a drug's pharmacological effect on the body.

In most teleost, pharmacokinetic studies are carried out as single dose drug exposures, where the drug is administered intravascularly (IV), intraperitoneally (IP), intramuscularly (IM) and per os (PO) [57,58]. At pre-determined time interval, blood and tissue samples are collected to establish a drug concentration versus time curve. From these studies many pharmacokinetic parameters can be estimated such as: the absorption rate constant (ka), maximum serum concentration (Cmax), time to maximum serum concentration (Tmax), the area under the curve (AUC), total bioavailability (F), the apparent volume of distribution (Vd), the total body clearance (Cl), the elimination rate constant (kel), half life (T½) for absorption (extravascular administration), distribution and elimination[57].

Pharmacokinetic studies may be designed as either population-based or individual-based compartmental investigations [57, 59]. In fishes, compartmentalization of drug distribution is influenced by species of fish, route of drug administration, drug and drug formulation, experimental design and environmental factors [60]. In pharmacokinetic data analysis, application of compartments is a method to model data and to derive pharmacokinetic parameters and the body is viewed as having a number of "equilibrium compartments" where each compartment represents, mathematically not necessarily anatomically or physiologically, a specific body area or tissue. In compartmental models we assume that after drug administration, elimination takes place from a central compartment and that the drug distribution and elimination rate constants obey first-order kinetics[61]. Non compartmental models are gaining popularity because they have the flexibility to estimate the same pharmacokinetic parameters (Vd, Cl and T½) as compartmental models while maintaining physiological relevance[54, 61]. Non compartment models differs from compartment models because the limitation of the non-compartmental models to estimate drug localization within the body or how long the drug resides in the body[54, 61].

Pharmacokinetics is important because it gives useful indications for drug research and development, supports the studies of preclinical toxicology in animals and gives the knowledge of the kinetics and of the effects (pharmacodynamics) of drugs [62]. The regular and continuous use of antibiotics in shrimp and fish culture has been associated with increased incidence of antibiotic resistant bacteria[29, 63, 64]. So the comparative studies of different aqua-drugs to assess their anti-bacterial potential and suitability for aquaculture applications are essential[65]. The design of pharmacokinetic studies in fish and shellfish is necessary prior to use of drugs in aquaculture.

Many pharmacokinetics studies have been reported by different scientists in both finfishes and shell fishes. But studies in shell fishes is very less when compared to finfishes. Pharmacokinetics of oxytetracycline was studied in *Litopenaeus setiferus* by using i.s dose of 11.1 mg/kg bw[28] and found extensive tissue distribution such as a long elimination half life and a high volume of distribution with the low potential for OTC in tail muscle tissue. Chiayvareesajja *et al*.[66] studied the pharmacokinetics of oxytetracycline in *Litopenaeus vannamei* by using single i.s dose of 10 mg/kg bw and found that OTC was thus not only distributed into the tissue compartment but also to the digestive gland, from where it was eliminated from the shrimp's body[66]. Faroongsamg[67] (studied the bioavailability and absorption analysis of oxytetracycline in *Litopenaeus vannamei* by using single i.s dose of 20 mg/kg of feed and found that bioavailability was 80.62% [67].

Uno studied the pharmacokinetics of oxolinic acid and oxytetracycline in *Penaeus japonicas* after intra-sinus (10 and 25 mg/kg) and oral (50 mg/kg) administration[68]. He reported that the distribution and elimination half-lives were found to be 0.59 and 33.2 h for oxolinic acid and 0.45 and 24.7 h for oxytetracycline and the bioavailability (*F*) was 32.9% for oxolinic acid and 43.2% for oxytetracycline. But still pharmacokinetics work on some antibiotics like oxolinic acid, gentamicin and sarafloxacin has not been reported in *Litopenaeus vannamei*. Antibiotics like oxolinic acid and sarafloxacin is mainly used to control vibriosis in shrimp culture. So it is very important to optimize the dose and study the pharmacokinetic parameters of these antibiotics[68].

CONCLUSION

Presently, many antibiotics are being used in shrimp aquaculture. Some of the drugs are not approved by FDA. Moreover, many drugs are not used according their optimum dosage regime. In many parts of the world, farmers use antibiotics indiscriminately without following the rationale of approved standard dose. This may lead to antimicrobial resistance and also residual accumulation in culture environment. In addition to this, overuse of antibiotic may result in bioaccumulation in fish tissue and thus cause health risks. Therefore, it is important that appropriate dosage regime must be determined and only permitted antibiotics to be used in shrimp aquaculture to prevent further complications.

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