SESSION I: Pharmacology and Therapeutics in Aquaculture

The Salmonid Industry and Drug Delivery Problems

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INTRODUCTION

Aquaculture is like agriculture, involving many species of animals and plants, all with their own requirements and special idiosyncracies. Raising Brahmas or Zebu cattle is quite different from raising the familiar Herefords for the same product; i.e. beef. Raising eels in a contained recirculation system, bears little resemblance to raising catfish or shrimp in shallow ponds and both are quite different from raising salmon in net pens in the ocean, though each occurs in a well defined feedlot system. All fish are ectotherms, animals whose body temperature is always close to the surrounding ambient temperature. Ectothermia to those accustomed to mammals is a foreign and complicating factor. Nutritional requirements, feeding, social behaviour, predators, and optimal temperatures for their bodily functions (including drug metabolism) all vary immensely between species of fish and seasonally. We need to adapt to the advantages of ectothermia, capitalizing on this concept in treatment strategies, control of residue depletion, and in rearranging our perceptions of drug storage. The immune capabilities vary for each species, depending on which "immune tools" were maintained from their evolutionary development. Salmon are very old in terms of evolution. Vaccine development as a disease control strategy, therefore, has been slower than might be expected due to the lack of any passive immunity and the variation in response to antigens depending on temperature and immune capability. In this presentation, I hope to acquaint you with the salmonid industry (mostly Atlantic Salmon) as it exists today and to provide enough information to analyze the problems encountered in currently available drugs and therapy delivery systems.

A COMMODITY SYNOPSIS

Salmonid rearing is not new. For generations, governments were the main producers, culturing fish for river enhancement and for the recreational fishery. Commercial aquaculture put a unit price on each fish, contained the fish throughout their life cycle for close observation, and further intensified production standards. Before that additional step, there was little demand for the development of therapies. As production sites grow and the economic risks increase, the demand for new and innovative approaches to treatment rises, treatments that are more efficacious and more cost effective. Delivery of treatments is a major concern in their use and their real cost.

The world production of farmed salmonids rose rapidly during the eighties, now estimated at 270,000 tonnes. The main players in the industry are Norway, the leader in production and experience; Scotland, an experienced long term producer; Chile, the recent large scale developer; and North America. There are salmon being raised in a variety of places in the Northern and Southern temperate zones wherever water temperatures allow. In Canada, New Brunswick farm raised salmon exceeds 9000 tonnes and in B.C.production exceeds 16000 tonnes. Many provinces have continuously increased their production of rainbow trout; eg. Ontario at over 2500 tonnes. A current market "correction" (Salmon prices have dropped from over $7.00 per pound to less than $3.00) is increasing the push for efficiency and increasing the overall demand for support services and products. The size of the market continues to grow making the future look promising. Salmon creates a high profile product. In part it is a popular game fish and brings with it the connotation of a pristine environment or *that* fishing trip. The marketing strategy has until recently capitalized on the ability of this fine fish to compete in the gourmet markets. The recent decline in salmon prices has expanded the product into the larger everyday type of market. Lower returns have required lower margins and higher productivity to survive. Culture of Atlantic Salmon has played a role in aquatic farming success on both Canadian coasts, as this species is robust, more efficient to farm and commands a higher prices than most West Coast salmonids. The intensity of fish farming varies regionally. Sites with the best water quality parameters, essential for successful large scale production are often isolated and located in environmentally sensitive areas increasing the awareness of appropriate drug delivery and elimination criteria.

LIVING IN WATER

Fish live in a medium that is 775 times more dense than air. Small skeletons and immense muscle masses have evolved to suit this medium. They float, easily drifting to any selected depth in the water column creating and accommodating to a three dimensional social hierarchy, selecting a space both by depth and area. Their entire strategy of survival is based on the efficient use of food. Utilising their natural advantages, due in part to no waste of energy stores to control body temperature and no need to expend energy on posture, fish can convert scrap protein into a gourmet product at an efficiency of less than 2:1 on a dry matter basis. Fish continue to grow muscle fibres throughout their lives as long as adequate food is available. Farmed salmonids increase their birth weight (weight at hatching) 7000 to 10000 times in as little as three years. Poultry can grow quickly and efficiently, but to a more defined genetic limit. In the same time period, a one ounce chick would have to be over 600 pounds or a 60 pound calf would be 200 tons. This perspective on growth alters the normal thinking about the value of therapy versus the ease of eradication for disease control. Obviously, volume of therapeutants consumed in an aquaculture system increases during the later life stages. The consequence of disaster in early life is not so economically devastating except when there is insufficient progeny to sustain the industry production goals.

Fish metabolism remains efficient through a specified range of body temperatures which vary depending on species. For salmon the lower lethal temperature is -0.75° C and the upper lethal temperature is 27° C if sustained for any length of time. Food consumption below 4° C is slow, but there is evidence that the longer residence time in the gut promotes efficient use of the nutrients. At lower than optimal temperatures, salmonids are able to withstand long periods of starvation and demonstrate no adverse modification of subsequent regrowth, but residue times are prolonged with many therapeutic compounds. Cold water fish held at temperatures in the upper range (greater than 20° C), require more food at regular intervals to prevent severe emaciation as their basal metabolic rate is very high. The assumption is that any drug residues are also metabolized more quickly. Delivery mechanisms and therapeutic compound formulations will need to adapt to these profound shifts in target animal metabolism.

Salmon are a "schooling fish" and being low on the evolutionary tree, tolerate crowding well. In fact, true stocking density is a difficult concept in the raising of fish as all calculations pertaining to holding capacity of an enclosure must three dimensional and include fluctuations of the water flow responsible for all life support necessities such as oxygen and waste removal. Accurately estimating the biomass during periods of rapid growth relies on a subsample estimate (convenience sample taken by dip net) that can be quite inaccurate and often represents the only information available for formulating prescriptions. Recently developed automated grading systems allow more access to individual fish and may change the way we view therapy. Evenly distributing the medication is no easy job either. Behavioral studies have shown that 25% of a population of caged salmon eat about 60% of the feed supplied. Delivery of drugs, therefore, requires changes in feed management to better access the sick fish for appropriate therapy.

The fish hatchery industry knows they can increase the virtual size of the containment system (i.e. hold more fish in the same tank) without any physical alteration by increasing the water flow or the amount of oxygen supplied to the water. They deal with large numbers (hundreds of thousands) of tiny fish which grow rapidly in tanks that are stocked to capacity. Bath treatments are most common and to stop water flow for an hour for therapy, limits the oxygen available complicating this type of delivery mechanism. The large population numbers make the logistics of injection difficult, though recent developments have allowed economical injection of vaccine to large populations of hatchery fish.

There is considerable difference between the fish's life in the fresh water and in saltwater. In the fresh water environment, fish are hyperosmotic to their environment; water tries to gain entry at every pore. They utilize a semi-waterproof cuticle to help maintain their internal integrity and drink virtually no water. Water is continuously excreted via voluminous urine formation. Na^+ is lost from the kidney and specialised ionocytes in the gill try to recover Na^+ from the water used for respiration. When transferred to salt water the fish enters an aquatic desert; losing water from each and every unprotected cell. The process by which these fish prepare for saltwater transfer is a complex endocrine, physiologic, cellular, photoperiod and temperature induced event called smoltification.

In the natural state, these changes are allowed to take place over a time suitable to the animal, but in aquaculture they take place in a matter of hours and can induce a series of stresses that leave the population at risk to any available disease agent. Following transfer, there is a rise in serum Na+ with a subsequent reduction over a three to seven day period in those individuals that can handle the osmotic change.

Fish in salt water drink! Salt is exuded from the body by the same ionocytes in the gill that change the direction of the Na+ pumping when salt water transfer occurs. In saltwater, a harsh desert, which is laden with divalent cations can affect the availability of any therapeutant delivered in bath or oral form. "Carry over" diseases, those that occur in carrier states from the hatchery and express themselves at stressful times tend to show at this point. These include Bacterial Kidney Disease and Furunculosis.

Often a parallel is drawn between the way that poultry are raised and the way that fish are raised, but the only similarity is the large population numbers. Salmon remain in the feedlot about the same time as cattle, 12 to 18 months. It is an open "sea" system, so longer residence leads to greater exposure to disease possibilities. Pelagic wild fish from around the globe pass by constantly and when they can, inhabit the cages. Under most fish farm management schemes, animals of different ages are introduced into the system increasing the number of contact possibilities for the spread of disease. Disease profiles in the ocean feedlot tend to be seasonal. Most antibacterial treatments occur in late summer during the warmer water temperatures despite an immune system that becomes more effective at these higher temperatures. The increased survival of bacteria in warmer water likely accounts for the seasonality of diseases. Some bacterial diseases, like Hitra disease (*Vibrio salmonicida*), occur at colder water temperatures. Since elimination of antibacterials is temperature related, some innovative therapeutic strategies are required. Anorexia in sick fish complicates the evaluation of treatment success as those fish that do not eat continue to die after treatment. Treatment is often delivered so late in the disease process that fish only have a small window of opportunity to consume medicated feed. A strategy for single dose oral medication would be advantageous.

DRUG DELIVERY ALTERNATIVES

Increase the Number of Therapeutants Available

Much of the emphasis for therapy revolves around antibacterials and parasiticides. Other compounds such as hormones, disinfectants, and anesthetics are currently available and effective, although they may be complicated by registration problems. Volume of compounds used early in the life of the fish tend to be small compared with treatments used in the grow out stage. Most of the major diseases of farmed fish in feedlots are bacterial. Oxytetracycline and Romet 30, a potentiated sulphonamide, are the only two registered antibacterials for use on fish in Canada. There isn't much choice to help deal with difficult disease problems or antibacterial resistances. The first necessity is a greater variety of effective and well understood compounds. In this environmentally aware age it is essential that the pharmacokinetics of any compounds used be well known, yet too little information exists about the effect of parent compounds or the metabolites on the surrounding ecosystem.

Broodstock as a Delivery System for Progeny

Interference in the life cycle of vertically transmitted bacteria by injection of the broodstock with antibiotics is a system used to reduce Bacterial Kidney Disease. The brood stock become the vehicle of delivery as the compounds are readily deposited in the egg yolk. A similar acting fungicide would be highly regarded. As more of the base compounds come under scrutiny (such as malachite green) a market will exist for suitable fungicides and parasiticides to treat eggs and fry.

Utilising Egg Adhesion or Osmotic Uptake

With such a low overall biomass at egg and fry stages, the volume of drugs used globally is unlikely to amount to a suitably sized market unless the essence of a bath treatment is redefined to give lasting protection by adhesion to the cuticle of the egg, or the fish, or by uptake and distribution into the vascular compartment. Effective treatment would pay for itself in labour savings and reduced losses due to handling.

Flavour Enhancement and Prolonged Residues

Oral therapy in general (and for fingerlings in particular), needs to be palatable, even attractive, to the feeding fish. Contrary to the feedlot situation, longer residue times would be advantageous so prophylactic treatment could be delivered in advance of seasonally recurrent diseases. This concept is especially important at smoltification. Recognising that the salmon would be several months from any possible market, protection over that first summer in sea water administered before saltwater transfer would capitalize on the higher metabolic rate of the warmer temperatures and the reduced disease problems during the cold water times to allow for residue depletion.

CONCLUSION

Many differences exist between the intensive farming of ectotherms and mammals. These challenges need to be turned into opportunities for existing therapeutants and for compounds that were discarded from the traditional developmental process. Many of the concepts that form the foundations of our thinking need to be discarded or modified if we are to make significant progress in the treatment of sick fish. Presented here are some nontraditional approaches that may help to formulate productive discussion.