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Research Article

Antibacterial drugs in products originating from aquaculture: assessing the risks to public welfare

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Abstract

As aquaculture expands to meet human demand and compensate for pessimistic forecasts of fisheries catches, use of antibacterial agents to combat or forestall bacterial diseases is still a necessity, although effective vaccines and improved hygiene have aided drastically in this battle. The hazards for the consumer perspective arising from the imprudent use of such chemicals can be detrimental, especially if the residues persist above legal tolerance. These may include selection and dissemination of resistant bacteria, disruption of the colonization barrier in the human intestinal flora and allergic reactions. In cases that unlawful drugs reached the consumer via consumption of aquatic products, human health may be jeopardized even further. The present review article assesses these risks to human health.

Keywords: Aquaculture; Antibacterials; Risks; Resistance; Human welfare.

Introduction

Nowadays, aquaculture is considered to be the fastest growing food production industry, boosted by governmental and technological impulsion, thus reducing the world's dependence on fisheries and offering financial relief to developing countries, which are the main contributors to this tremendous increase (GOLDBURG & NAYLOR, 2005). In particular, aquaculture participation in global supplies of aquatic products (fish, mollusks, crustaceans and aquatic plants) has quadrupled in comparison to its production in the 70's (38% of total fisheries production in 2004, accounting for 59.4 million tonnes and US$ 70.3 billion; FAO, 2007). Although aquaculture initially emerged as a benign industrial sector, its accelerated growth seems on some occasions to have proceeded ahead of adequate care for environmental and public welfare, even in the face of accumulated evidence of side effects. As intensive aquaculture involves farming where large numbers of animals are kept together in a confined space, outbreaks of disease are common, regardless of the quality of the hygiene practised. Bacterial diseases remain a major cause of mortalities and therefore a potential source of significant financial loss for the industry. Where vaccine application is not available, bacterial pathogens are dealt with by antibacterials, the administration of which is complicated due to the fact that the substances inevitably enter the aquatic environment either via the feed or directly into the water. Various registered antibacterial agents such as tetracyclines, (fluoro)quinolones, potentiated sulfa, penicillins, macrolides and amphenicols are used globally to treat bacterial outbreaks in aquatic farms (COSTELLO, 2001; SHAO, 2001). Several studies have stressed the implications of the use antibacterials in aquaculture throughout the world on human and environmental welfare (ANGULO, 2000; HAYA *et al.,* 2000; ANGULO *et al.,* 2004; BOXALL *et al.,* 2004; CABELLO, 2004; RIGOS & TROISI, 2005).

Legislation enforcing the use of chemotherapeutics varies among countries throughout the world (SERRANO, 2005). International organizations, including the Food & Agriculture Organization (FAO), the World Health Organization (WHO), the International Office of Epizootics (OIE), the Committee for Veterinary Medicinal Products (CVMP) and national agencies such as the U.S. Food and Drug Administration (FDA) have all raised issues associated with heavy use of antibacterials in all animal production sectors, with particular concern for potential risks to public health. Guidelines such as the acceptable daily intake (ADI), maximum residue levels (MRL) and withdrawal times have been established to protect the consumer from side effects. Unfortunately, antibacterial drugs have not always been used in a responsible manner to confront bacterial diseases. The urgency of the farmer's response to an outbreak, often results in ill-informed decision-making based on a rushed diagnosis and possible use of inappropriate drugs and dosing regimens. Thus, the marketing of aquatic products with residual drugs above the legal tolerance level, occasionally containing even banned substances, (chloramphenicol, nitrofurans) is not uncommon (WILLIS *et al.,* 1999; JOHNSTON & SANTILLO, 2002; PUBLIC CITIZEN, 2004; FOOD AND WATER WATCH, 2007). Although it is generally accepted that the use of antibacterials follows a decreasing pattern in relation to aquaculture production growth, antibacterial therapy has been challenged by specialist groups such as environmentalists and public health experts on the basis that it may threaten human welfare by inducing: a) development and transfer of bacterial resistance b) accidental contamination of the consumer with antibacterial residues, possibly affecting human intestinal flora c) toxic effects resulting from the consumption of unlawful substances and d) emergence of allergic reactions.

Development and dissemination of bacterial resistance

Development of bacterial resistance as a result of antibacterial use is of high concern in all culture environments and has raised considerable debate in human and veterinary medicine, including aquaculture (SMITH *et al.,* 1994; ALDERMAN & HASTINGS, 1998; ANGULO, 1999; SORUM, 1999; ANGULO, 2000; ANDERSON *et al.,* 2003; ANGULO, 2004; CABELLO, 2004; 2006). Several important fish pathogens have revealed their ability to develop resistance as a consequence of antibacterial exposure including *Aeromonas salmonicida, A. hydrophila, Edwardsiella tarda, Yersinia ruckeri, Photobacterium damselae subsp. piscicida, Vibrio anguillarum, V. salmonicida, P. psychrophilum and Pseudomonas fluorescens* (SERRANO, 2005; SORUM, 2006).

Nowadays, transfer of antibacterial resistance between veterinary and human medicine has become a global issue and has stimulated intense criticism (SMITH *et al.,* 1994; ALDERMAN & HASTINGS, 1998; ANGULO *et al.,* 2004). It is unfortunate that antibacterials commonly used for veterinary purposes, including aquaculture therapy (eg. quinolones, tetracyclines and potentiated sulfa), are also employed in human medicine (SERRANO, 2005). Inevitably, the use of antibacterials in the aquaculture industry can favour the occurrence of antibacterial resistance in another therapeutic field, such as human medicine. It has been indicated that dissemination of antibacterial resistance may be facilitated by the horizontal transfer of R plasmids between related and diverse bacteria (WATANABE *et al.,* 1977; AOKI, 1988). These resistance genes have no phylogenetic, geographical or ecological barriers (OIE/FAO/WHO, 2004). Thus, fish pathogens which may have developed acquired resistance as a result of drug usage and the continuous presence of residual levels in the fish body, can act as a host for resistance genes that can be transferred to human pathogens (e.g. the spread of a resistance gene from *Aeromonas* spp. to *E. coli* and the resistance acquisition of *V. cholerae* and *Vibrio parahemolyticus;* ANGULO, 1999), even moving from one producing country to another (OIE/FAO/WHO, 2004). This is considered as an indirect transfer of resistance from aquaculture to human medicine caused by horizontal gene transfer and has been demonstrated also *in vitro*. For example, plasmids carrying resistance determinants have also been transferred from fish to human pathogens including *V. cholerae* (AOKI, 1988), *V. parahemolyticus* (NAKJIMA *et al.,* 1983) and *E. coli* (SON *et al.,* 1997).

Moreover, the use of antibacterial drugs in aquaculture may also select for resistance bacteria that are not fish pathogens, which is regarded as a direct pathway of resistance from aquatic practices to humans. Bacterial pathogens resistant to drugs have been isolated from the intestinal contents of farmed and wild fish species captured around fish farms (ERVIK *et al.,* 1994). This indicates that wild inhabitants of farming sites subjected to medication can also act as a reservoir of resistance dissemination. Antibacterial resistant bacteria may be transmitted to humans when the aquacultured products (primary or secondary) are improperly cooked and eaten (eg. *Aeromonas* spp, *Edwardsiella tarda, E. coli, Plesiomonas shigelloides, Salmonella* spp., *Shigella spp., V. cholerae, V. parahaemolyticus,* and *V. vulnificus)* (IASR, 1999; WHO, 1999).

Residual antibacterials in aquatic farmed items; possible effects on human intestinal microflora

The possible presence of residual antibacterials in commercialized farmed aquatic products and the associated risks to the consumer has been the subject of several investigations (GOLDBURG *et al.,* 2001; JOHNSTON & SANTILLO, 2002; CABELLO 2003; 2004; ANGULO *et al.,* 2004; HASTEIN *et al.,* 2006). Another hidden threat from drug pollution from aquatic farms is the potential accumulation of drug residues in the aquatic food chain (from uneaten medicated feed, fish excretions, baths) leading to direct or indirect exposure of biota around farm sites. Secondary farmed items including scavengers and wild-caught fish destined for human consumption and harvested from areas around farm sites, have been found to be contaminated with antibacterial drugs to levels beyond the safety factor (BJORKLUND *et al.,* 1990; 1991; SAMUELSEN *et al.,* 1992; ERVIK *et al.,* 1994; CAPONE *et al.,* 1996 ; COYNE *et al.,* 1997). In these studies, drug concentrations (oxolinic acid, flumequine, oxytetracycline) ranging from 0.1 to 12.5 μg/g tissue were measured in wild fauna (mussels, crabs, fish) inhabiting the adjacent areas of farming sites subjected to medication.

The risks of antibacterial residues to human welfare, with particular reference to intestinal microflora, have been stressed by several authorities (FDA, 1993; CVMP, 1995). Although residual drugs may be degraded by cooking procedures to some degree (XU *et al.,* 1996; UNO *et al.,* 2006) and inactivated to a variable extent in the intestines by decomposition of bacterial enzymes and by binding to bacteria and other faecal components, the possibility of inducing alteration of the intestinal flora and disruption of the colonization barrier is not unlikely (VAN DER WAAIJ, 1982; EDLUND & NORD, 1993; VOLLARD & CLASENER, 1994; CERNIGLIA & KOTARSKI, 1999; EDLUND & NORD, 1999). Human intestinal microflora constitute a balanced and complex community inhabited by hundreds of bacterial species (CERNIGLIA & KOTARSKI, 1999) which are vital for the maintenance of a healthy human gastrointestinal tract since they inhibit colonization of pathogenic bacteria (VOLLARD & CLASENER, 1994) and intervene in the digestion and processing of various substances (CHADWICK *et al.,* 1992). Although the side effects of drugs on human intestinal microflora can be more apparent during therapeutic applications where the tissue levels to be targeted are high, however, prolonged unwanted exposure to antibacterial residues may also disturb the equilibrium of the gut microflora by changing the population density and composition (antibacterials may reduce total numbers of some bacteria or selectively kill some vital species), by altering enzyme activity for the metabolism of endogenous and exogenous substances and by impairing colonization resistance (CERNIGLIA & KOTARSKI, 1999). This may have serious consequences for the consumer, including increased susceptibility to infection by exogenous potential bacterial pathogens (eg. *Salmonella* sp.), favouring the colonization of new resistant pathogenic bacteria and the outgrowth of indigenous opportunistic inhabitants which may be part of the normal flora (eg. *Escherichia coli* and yeasts) (TANCREDE, 1992; GORBACH, 1995; NORD & EDLUND, 1991; VOLLARD & CLASENER, 1994; CABELLO, 2004).

Residual unlawful antibacterials

During the last decade, the detection of illicit antibacterials (chloramphenicol and nitrofurans) in aquaculture products has not been an uncommon issue (FOOD STANDARDS AUSTRALIAN NEW ZEALAND, 2004; PUBLIC CITIZEN, 2004; FOOD AND WATER WATCH, 2007). The detection of chloramphenicol and nitrofuran residues in exported Asian aquatic farmed products, has alarmed national and international authorities, resulting occasionally in a slowdown or shutdown of imports in the consuming countries, thus causing financial loss in the producing countries and reducing the credibility of the aquaculture industry at a global level (PUBLIC CITIZEN, 2004; FOOD AND WATER WATCH, 2007). The initiation of these episodes took place during 2001-2002 when EU food authorities detected unacceptable levels of chloramphenicol and nitrofurans in imported shrimp from several Asian countries (China, Vietnam, Indonesia, Thailand and India; PUBLIC CITIZEN, 2004). During the same period, the discovery of chloramphenicol levels in crawfish and shrimp (China, Vietnam) was also the case in several states in the USA (MCGOVERN, 2002; SEAFOOD, 2002;). FOOD STANDARDS AUSTRALIAN NEW ZEALAND (2004) reported that imported prawns were contaminated with nitrofurans (mainly represented by furazolidone; a commonly used illegal nitrofuran) during the production cycle.

Chloramphenicol can be used only as a therapeutic last resort in life-threatening cases in human medicine (for typhoid fever and meningitis when no other drugs are available, and for conjunctivitis). The substance is highly toxic and potentially fatal for humans even at trace levels. Therefore, national authorities and international organizations have established zero tolerance, indicating no acceptability of detectable residues in food products (PUBLIC CITIZEN, 2004). Evaluations performed by GESAMP (1997) stressed that the compound is capable of producing genetic damage, allergies, anemia and cancer. Moreover, the drug may cause aplastic anemia, an irreversible condition affecting bone marrow causing it to stop producing red and white blood cells (YOUNG & KAUFMAN, 2008). Nitrofurans are also very dangerous for human health due to their potential carcinogenic properties (WHO, 1993). It was also stressed by the same review meeting that furazolidone induced a variety of tumours in mice and rats and was positive in *in vitro* genotoxicity tests.

Chloramphenicol and nitrofurans are also banned in the respective producer countries, however the non-compliance of particular farmers with these guidelines may have caused uncontrolled contamination of local consumers with illicit substances when the treated aquatic products reached the local markets. The lack of an immediate response to these issues in the importing countries and/or the employment of insensitive analytical methods during the inspection procedure may indicate that hazardous unlawful drugs may have already been consumed via imported aquaculture products with unknown consequences.

Allergic reactions

Accidental consumption of antibacterial agents in aquacultured products can generate allergies in sensitive consumers. Such cases, however, are of lesser concern, are also difficult to monitor and consequently are underestimated.

Conclusion

At least for the immediate future, antibacterials should be the last resort when dealing with bacterial outbreaks in aquaculture practices, regardless of the improvement of disease management and vaccine development. Use of antibacterials especially in developing countries may jeopardise human health if inappropriate drug selection, treatment schedules and safety guidelines are considered. Given that antibacterial resistance is a serious global issue with obvious, devastating consequences on human health, it is mandatory that therapy in the rapidly developing aquaculture sector receives special additional attention from federal agencies in order to eliminate its contribution to this crisis. Residues of banned substances in aquacultured products originating from the Orient are also of significant concern and thus an increased inspection effort from authorities of both producing and importing countries must be applied to increase protection of consumers.

Alternative preventive and therapeutic methods must be seriously considered to reduce the use of drugs.

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