REVIEW

Antibiotic Resistance: A Concern to Veterinary and Human Medicine

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Abstract

Bacterial resistance to antibiotics occurs even without the use of antibiotics. Antibiotic use exerts a selective pressure to the bacterial flora that help in the emergence and development of antibiotic resistance. Antibiotics are used worldwide both in veterinary and human medicine. The wide spread use of antibiotics in human and animal has raised the concern about the development of resistant and multi resistant bacteria that possess a potential danger to animals and men, as resistance may cause treatment failure. Resistance may be natural or acquired. Acquired resistance is due to transfer of extrachromosomal genetic material (R-plasmids) and is very important. The R-plasmids are spread to other bacterial cells by transformation, transduction, conjugation and transposition. Transmitted antibiotic resistance in disease causing bacteria may cause zoonotic infections and resistant non-infectious bacteria may serve as a reservoir of R- plasmids for the pathogenic organism(s). This paper highlights the mechanism of development of resistance in bacteria and means to minimize it.

Key words: Antibiotic resistance, bacteria, extrachromosomal material, resistance, R-plasmids

Introduction

The use of antibiotics in veterinary practice started soon after it became available for the treatment of human diseases in mid 1940s. Use of penicillin was started before world war II to treat mastitis. Antibiotic resistant strain of bacteria was recognized in the late 1950s and became evident that microorganisms resistance to one or more antibiotics can transfer it to other bacteria (Stalheim, 1987). The problem of antimicrobial resistance has become common today, especially in the area of bacterial chemotherapy (Nandivada and Amyes, 1990; Davies, 1994). A large amount of drugs are being used worldwide annually to secure sufficient quantities of food to feed fast growing world population (WHO, 1985). The wide spread use of antibiotic in human and animals has been followed by the increased emergence of bacteria resistance to these antibiotics, particularly in Enterobacteriaceae (Prescott and Baggot, 1993). A casual relationship between increased use of antibiotics and increased prevalence of resistant bacteria has been demonstrated (Holmberg et al., 1987). Transmission of resistance has been reported from person to person (Linton et al., 1972), animal to animal and animal to person (Levy et al., 1976). Diseases caused by drug-resistant strains of bacteria may transfer their resistance to the drug susceptible strains of bacteria that ultimately may act as reservoir of resistance to pathogenic organisms. Thus, the occurrence of antibiotic resistant bacteria is a great concern in both human and animal medicine.

Types and mechanism of resistance

Resistance to an antibiotic may be an inherent property of the infecting organism or it may be acquired. Acquired resistance may result from mutation or from transfer of an extrachromosomal genetic material followed by selection of resistant organisms during therapy (Davis et al., 1980). Mutations that result in antibiotic resistance are spontaneous events involving changes in chromosomal nucleotide sequences. The development of mutational resistance is favored by low and intermittent drug dosage (Prescott and Baggot, 1993).

R-plasmids (R-factors) are the extrachromosomal substances responsible for antibiotic resistance. In recent years, there has been increasing recognition of the role of extra chromosomal material of heredity for antibiotic resistance (Davis et al., 1980). These R-factors or R-plasmids are spread to other bacterial cells by transformation, transduction, conjugation and transposition (Timoney et al., 1988; Prescott and Baggot, 1993). The most common and important of them is conjugation in which two organisms exchange R-plasmids by contact through sex pilus. R-factors may also be released by one bacterium and take in through the cell wall of another (transformation). R-factors, therefore, can circulate in humans, in animals and in the environment and possibly between animals and humans (Landicho, 1996). Transmitted antibiotic resistance in disease-causing bacteria may cause zoonotic infections, while resistant non-infectious bacteria may serve as a reservoir of R-plasmids for other virulent organisms. R-factors encode at least four different biochemical mechanisms. These involve either enzymatic degradation or alteration of the antibiotic by the cell, alteration of the target site of the antibiotic and synthesis of a resistant form of an essential metabolic enzyme that is normally sensitive to different antibiotics (Timoney et al., 1988).

Bacterial resistance to antibiotics

The development of bacterial strain resistant to antibiotics was recognized in the late 1950s. It later became evident that microorganisms such as *Salmonella typhimurium* and *S. dublin*, which are resistant to one or more antibiotics can be transferred to other bacteria (O' Brien et al., 1982; Gracey, 1986). Studies have shown that the use of antibiotics as feed additives results in an increase in both proportion and persistence of antibiotic resistant bacteria (Langlois et al., 1984). The feeding of low levels of antibiotics creates a selection pressure to the bacterial flora of livestock. The effect of this selection pressure has been the appearance of numerous resistant strains of *Escherichia coli*, *Salmonella* spp., S*taphylococcus aureaus*, *Pasteurella hemolytica*, *P. multocida*, S*treptococcus agalactiae*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Haemophilus pleuropneumoniae*, *Clostridium perfringens* and many other bacterial species (Timoney et al., 1988). The Swann Committee (cited by Gracey, 1986) reported that the use of antibiotics as growth promoter in livestock and poultry has led to the development of resistant strains of microorganisms. These resistant microorganisms can transmit resistance to the non-resistant bacteria. Threlfall et al. (1978) reported that the use of antibacterial drugs to control bovine salmonellosis in Britain facilitated the emergence and establishment of 204 multi-resistant types and 193 strains of *Salmonella typhimurium*. Lee et al. (1993) in a nationwide survey in the USA found that 57% of isolates from broiler chickens after slaughter were resistant to one or more antimicrobial agents, while 45% were resistant to two or more agents with higher resistance to tetracycline (45%) and streptomycin (41%), sulfixazole (19%), gentamycin (10%) and trimethoprim/ sulfamethoxazole (8%). In a study, in India, Mahipal et al. (1994) found 63.2 % strains of *E. coli* was singly or multi-resistant to different antibiotics isolated from various infections to man and animals.

Similarly, increasing drug resistance has been observed in human patients from different clinical cases. In a national survey in the USA, Riley et al. (1984) found increasing resistance to *Salmonella* isolated from human patients. He attributed this to increasing frequencies of anti-microbial drug-resistant *Salmonella* infections to animal reservoirs. Antibiotic resistance in opportunist pathogens is a major problem in human hospital practice but there has been little information about veterinary hospitals.

Multiple antibiotic resistance

R-factors were first found in members of the genus *Shigella* in Japan (Watanabe, 1963). Since then, they have been found in all other genera of the family Enterobacteriaceae and in the genera of *Pasteurella*, *Vibrio*, *Camphylobacter*, *Haemophilus*, *Neisseria*, *Staphylococcus*, *Streptococcus*, *Clostridium* and *Pseudomonas* (Temony et al., 1988). R-plasmids possess regions with the resistance genes and resistance

to a number of different antibiotics can be mediated by the same R-factor and is known as multiple antibiotic resistance (Prescott and Baggot, 1993). The prevalence of multiple drug resistance bacteria itself is a serious problem, but transfer of multiple drug resistance to other members of the family Enterobacteriaceae, particularly *E. coli*, *Salmonella* and *Shigella* makes it even greater concern to clinicians in curbing infections in medical and veterinary practice (Mahipal et al., 1994).

R-plasmids in human and animals

Persons who carry the largest number of R-plasmids are the individuals who are in direct contact with antibiotic such as sick people under treatment, workers in antibiotic factories and farms where antibiotics are incorporated into animal feedstuffs (Linton et al., 1972). However, individuals, who are not in contact with antibiotics also carry R-plasmids, but in minimal amounts (Pohl and Lintermans, 1986) and R-plasmids also develop and disseminate in the environment as well as in humans and animals even in the absence of any selective pressure of antibiotics (Huber, 1986).

Likewise animals raised with frequent use of antibiotics have more R-plasmids containing colibacilli flora (Pohl and Lintermans, 1986). However, R- plasmids were also observed on farms where antibiotics are not used either for treatment or for growth promotion (cited by Pohl and Lintermans, 1986). Therefore, in animals as well as in humans, R-factors are observed in the absence of any selective pressure by antibacterial agents (Pohl and Lintermans, 1986).

Public health significance of antibiotic resistance in animals

Many antibiotics that are used in animal feed are also used to treat diseases in man. Such use of antibiotics in feed raised the concern among public health authorities and consumers because such level of the drug use may occur bacterial resistant in the gastrointestinal tract of these animals (WHO, 1985). Such resistance can be transferred to bacterial inhabitants of the gastrointestinal tract (McCapes et al., 1991) through food chain. The feeding of low levels of antibiotic such as tetracycline and penicillin in poultry, swine and calves to promote growth has resulted in a great increase in the reservoir of resistant bacteria (Timoney et al., 1988). These resistant bacteria from animals may reach the human population. This is well established with *Salmonella* infections (Prescott and Baggot, 1993). Likewise there is considerable evidence that some antibiotic resistant *E. coli* can colonize the intestines of humans long enough for transfer of antibiotic resistance to occur (Wells and James, 1973). However, the colonization of the digestive tract by a foreign strain is generally very difficult as the conditions in the intestinal environment are unfavorable for foreign strain.

The danger of passing antibiotic resistance from animals to man or vice-versa through their donor bacteria, as some of their serotypes are of zoonotic nature, has got the importance in present day chemotherapy (Linton, 1986). A potential health hazard to consumers can be expected from resistant bacteria. If the organism is resistant to antibiotics, then initial treatment may be ineffective both in man and animals and an alternative treatment need to be applied (McCapes et al., 1991).

Control of antibiotic resistance

A number of approaches can be taken to limit the development and spread of antibiotic resistance. All our efforts should be directed towards reducing the selection pressure as much as possible. Antibiotics should be administered at therapeutic doses only for short periods, prolonged use may select resistant strains (Prescott and Baggot, 1993). Price and Sleight (1970) mentioned that decreased use or withdrawal of certain drugs followed by dramatic reduction in resistance to these and other antibiotics. It is commonly assumed that misuse and inappropriate use of antibiotics is the main cause of antibiotic resistance. Thus, the control of antibiotic resistance depends on the careful and appropriate use of antibiotics.

Conclusion

Resistant and multiresistant organisms may develop even without the use of antibiotics, however, their indiscriminate and prolonged use in human and animal practice may enhance the emergence and development of resistant and multiresistant bacteria. These resistance can be transferred between animal and man and vice versa. Thus, prudent use of antibiotics both in human and animals is needed.

References

Davies, L. 1971. Inactivation of antibiotics and the dissemination of resistance genes. *Science* 264:375-82.

Davis, BD, R Dulbecco, HN Eissen and HS Ginsbeg. 1980. *Microbiology*. Harper and Row Publishers, Inc., Maryland 21740, pp.111-126.

Gracey, JF. 1986.Chemical residues in meat. Meat hygiene. Baillere Tindall. The Bath Press, London, pp.191-211.

Holmberg, SD, SI Soloman and PA Blake. 1987. Health and economic importance of antimicrobial agents. *Rev. Inf. Dis.* 9:1065-78.

Huber, WG. 1986. Allergenicity of antibacterial drug residues. Pp.33-39. In: *Drug Residues in Animals* (AG Rico, ed.). Academic Press, Inc., London.

Landicho, EF. 1996. *Veterinary drug residues in food*. College of Veterinary Medicine, University of the Philippines, Los Banos, pp.1-30.

Langlois, BE, KA Dawson, TS Stahly and GL Cromwell. 1984. Antibiotic resistance of fecal coliforms from swine fed subthrapeutic and thrapeutic levels of chlortetracycline. *J. Animal Sci.* 55(3):666-674.

Lee AL, VL Threatt, ND Puhr, P Levine, K Ferris and RV Tauxe. 1993. Antimicrobial resistant *Salmonella* spp. isolated from healthy broiler chickens after slaughter. *J. American Vet. Med. Assoc.* 202(5):752-755.

Levy, SB, GB Fitzgerald and AB Macone. 1976. Spread of antibiotic resistance plasmids from chicken to chicken and from chicken to man. *Nature* 260:40-42.

Linton KB, PA Lee, MH Richmond, MA Gillepsie, AJ Rowland and VN Baker. 1972. Antibiotic resistance and transmissible R-factors in the intestinal coliform flora of healthy adults and children in an urban and rural community. *J. Hygiene* 70:99-104.

Linton, AH. 1986. Flow of resistance genes in the environment and from animals to man. *J. Antimicrobial Chemotheraphy* (Suppl.) 18:189-97.

Mahipal, S, SC Sanyal, MA Chaudhary and JNS Yadava. 1994. Plasmid mediated drug resistance in veterinary and human isolates of *Escherichia coli*: A potential threat to human and veterinary medicine. *Indian Vet. Med. J.* 18:131-141.

McCapes, RH, BI Osburn and M Riemann. 1991. Safety of foods of animal origin: Responsibilities of veterinary medicine. *J. American Vet. Med. Assoc.* 193(7):872-873.

Nandivada, LS and SGB. Amyes. 1990. Plasmid mediated B-lactam resistance in pathogenic gram-negative bacteria isolated in south India. *J. Antimicrobial Chemotheraphy* 26:279-90.

O' Brien, TF, JD Hopkins, ES Gilleece, AA Medeiros, RL Kent, BO Blackburn, MB Holmes, JP Reardon, JM Vergeront, WL Schell, E Christenson, ML Bissett and EV Morse. 1982. Molecular epidemiology of antibiotic resistance in Salmonella from animals and human beings in the United States, New England. *J. Medicine* 307:1-5.

Pohl P and P Lintermans. 1986. R-Plasmids reservoirs and circulation. Pp.51-53. In: *Drug residues in animals* (GR Andre, ed.). Academic Press Inc., London.

Prescott, JJ and DJ Baggot. 1993. *Antimicrobial therapy in veterinary medicine*. International Book Distributing Co., India, pp.564-565.

Price, DJE and JD Sleight. 1970. Control of infection due to *Klebsiella aerogenes* in a neurological unit by withdrawal of all antibiotics. *Lancet* 2:1213.

Riley, LW, ML Cohen and JE Seals. 1984. Importance of host factors in human Salmonellosis caused by multiresistant strains of Salmonella. *J. Infectious Dis.* 149:878-883.

Stalheim, OHV. 1987. Veterinary services in emergencies: Food safety and inspection. *J. American Vet. Medical Assoc.* 190:725-726.

Threlfall, EJ, LR Ward and B Rowe. 1978. Spread of multiresistant strains of *Salmonella typhimurium* phage types 204 and 193 in Britain. *British Med. J.* 2:997.

Timoney, JF, JH Gillespie, FW Scott and JK Barlough. 1988. The genetics of virulence and antibiotic resistance. Pp.24-32. In: *Hagan and Bruner's Microbiology and infectious diseases of domestic animals*. 8th ed. Cornell University Press, Ithaca and London.

Watanabe, T. 1963. Infective heredity of multiple drug resistance in bacteria. *Bacteriological Rev.* 27:87-115.

Well, DM and OB James. 1973. Transmission of infectious drug resistance from animals to man. *J. Hygiene* 71:209-215.

WHO. 1985. Report of a joint FAO/WHO expert consultation on residues of veterinary drugs in foods. *Food and Nutrition Paper No. 32*. World Health Organization, Geneva, pp.1-16.