SYMPOSIUM: ANTIBIOTIC RESIDUES IN MEAT AND MILK

Use of Antibiotics in Livestock and Human Health Concerns

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ABSTRACT

Animal feed additives have for many years constituted the largest and most controversial category of antimicrobial use. The primary concerns addressed have been the generation of antibiotic resistance in animal bacteria and the influence of such resistance on human health. Studies designed to shed light on the controversy generally have yielded information leading to ambiguous conclusions. A 1989 report from the National Academy of Sciences was the latest of a long collection of assessments that have been meant to provide expert guidance to regulatory authorities on this matter. The FDA has been trying for some time to determine whether a regulatory decision on existing products is warranted. After several decades of research directed at this question, most qualified study groups have reported a paucity of appropriate information necessary to judge the reality of a public health risk.
(Key words: antibiotic residues, antibiotic resistance, feed additives)

Abbreviation key: CDC = Centers for Disease Control, CVM = Center for Veterinary Medicine, NAS = National Academy of Sciences,

INTRODUCTION

Soon after antibiotics became available for the treatment of human bacterial disease, they were also introduced into veterinary practice. Before the end of World War II, infusions of penicillin in saline were used to treat mastitis in lactating dairy animals. Injectable products also became available to the veterinarian for companion and food animals and various formulations of streptomycin, the tetracyclines, and chloramphenicol joined penicillin and the sulfa drugs on the veterinarian's shelf in the years following World War II. It was the introduction of antibiotics into animal feeds in the early 1950s that ushered in a new era in livestock management and meat production.

Antibiotics have been used in animal feeds for about 40 yr. For more than half of that period, their uses have been questioned by some observers, who pointed to the possibility of a public health risk. In the most simplified division by function, feed antibiotics may be thought of as products to control disease or to enhance performance. The reality of the situation is that products whose spectrum and pharmacokinetics allow the prevention or treatment of systemic bacterial diseases may also improve performance, that is, growth rate and feed efficiency. Conversely, some growth-promoting antibiotics, not absorbed and bearing only gram-positive activity, may also have limited claims against specific enteric infections. In the United States, the controversial use of antibiotics in animal feeds centers primarily on the tetracyclines and penicillin. The two tetracyclines used in feeds are chlortetracycline and oxytetracycline. It was chlortetracycline that was first used as a feed additive in 1950, and this antibiotic continues to occupy a large share of the feed antibiotic market. Although the tetracyclines were originally introduced at very low feed concentrations to enhance performance, reductions in manufacturing costs in the 1950s allowed uses in feed at higher concentrations. It was quickly learned that, at these higher concentrations, tetracyclines played a significant role in the control of livestock diseases. In the 1960s, scientists became aware of plasmid-mediated resistance and learned that clinical bacterial isolates resistant to several gram-negative antimicrobial products could transfer the genetic information encoding these

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resistances to other bacteria. This became the central point of the focus on feed antibiotics and human health risks. It was postulated that the use of certain antibiotics in animal feed could generate large numbers of resistance plasmids in the enteric flora of livestock, and that this genetic material might eventually encode antibiotic resistance in human pathogens. It was argued that the use of antibiotics in livestock feeds could ultimately induce a significant loss of antibiotic efficacy in human medicine, particularly those uses in animals that are considered to be subtherapeutic or prophylactic.

There were, however, compounding factors that interfered with an easy resolution of the questions that had been raised. Key questions needed to be answered. For example: 1) What influence do therapeutic antibiotic uses in animals have on the total resistance genes in animals compared with the subtherapeutic uses in animal feeds? 2) What influence does use of antibiotics in humans have on the development of antibiotic resistance? 3) To what extent do animal bacteria pass through the food chain and become resident in human flora? 4) To what extent does such resistant flora from animals transmit genetic information to human pathogens? 5) To what extent, if any, do feed antibiotics reduce the availability and transfer of zoonotic pathogens from animals to humans (*Salmonella* sp., *Campylobacter* sp.)? 6) If subtherapeutic uses of antibiotics were significantly reduced in animal agriculture and if all other uses were continued, what changes in antibiotic resistance could be anticipated? These are just a few of the questions that needed to be addressed in order to judge the reality of a public health risk.

DISCUSSION

Committee Reviews

Assessments of the public health questions on animal feed antibiotics have been carried out by distinguished bodies of experts for nearly three decades. The first studies were done in England where the Netherthorpe Committee issued a report in 1962, declaring that no alteration in the use of antibiotics was warranted (9). A major salmonella epidemic in calves in the mid-1960s provoked the formation of a committee of inquiry under the chairmanship of Sir Michael Swann. A report was issued in 1969 recommending that feed antimicrobials used for animals in England should be regulated differently according to category of use (13). Products that were used for performance enhancement, that is, growth promotion and feed efficiency, should continue to be used at the descretion of the meat producer. Antimicrobials with claims for disease prophylaxis or therapy would be used only on the order of a veterinarian. Both types of product would be licensed by the Ministry of Agriculture, Food and Fisheries, following review by the Veterinary Product Committee. This procedure was implemented in 1971 and continues to be used today. Similar regulations were implemented in other European countries in the early 1970s. What effect did these regulations have on the use of antibiotics and on antibiotic resistance? In general, the tetracyclines continue to be used in livestock in England but usually at dosages higher than those employed before 1971. No measurable overall reduction in antibiotic resistance has been reported, and this would be expected, because many observers think, based on proprietary company sales information, that the total use of antibiotics has not been reduced since these new regulations were implemented.

The expert groups in the United States that have issued reports on the antibiotic controversy in the past 20 yr include a Food and Drug Administration Task Force in 1971, a subcommittee of the National Advisory Food and Drug Committee in 1976, the Office of Technology Assessment in 1979, the National Academy of Sciences (NAS) in 1980 (8), the Council of Agricultural Science and Technology in 1981, and the NAS once again in 1989. In addition to the extensive literature examination by these groups, the Center for Veterinary Medicine (CVM) technical staff has maintained close surveillance of the emerging literature in this area. The Agency also funded research in the late 1970s and early 1980s to answer specific questions on the subject.

The Natural Resources Defense Council filed a petition of "imminent hazard" with the FDA in late 1984 (12). This was the first time that such an action had been taken against an agricultural product. Arguments on both sides of the issue were presented at a 1-d hearing in January 1985. A year after the petition was submitted, it was rejected by the Secretary of

Health and Human Services, Margaret Heckler. She followed the recommendations of FDA Commissioner Young and his staff.

Estimation of Risk

In late 1987, the FDA signed a contract with the NAS to study old and recent data on the feed antibiotic controversy and to attempt to develop a risk assessment model. A blue ribbon panel was set up by NAS Institute of Medicine and the task was undertaken during 1988. It was decided that the risk assessment model would utilize salmonella deaths in humans as the primary endpoint to be judged. The overall question of general antibiotic resistance in human bacterial disease would have been far too difficult and diffuse to yield reasonable conclusions from a risk model. The report issued to FDA in December 1988 and to others in January 1989 was distributed on request to interested parties (4). Those who wished to issue opinions on the report had until May 4, 1989, to do so. The report cautioned that the risk model presented could not yield hard and useful figures because the data that were available as inputs were in many cases sketchy and unreliable. The committee recognized and stated that *Salmonella* was used only because it was traceable, and that far less than 1% of the antibiotics used in the United States are directed against infection by *Salmonella*. They concluded: "The Committee was unable to find a substantial body of *direct* evidence that established the existence of a definite human health hazard in the use of subtherapeutic concentrations of penicillin and the tetracyclines in animal feeds" (p. 11). Currently the CVM is studying the NAS Institute of Medicine report, as well as the submitted comments from interested parties. The FDA is expected to issue a statement on the subject in 1990.

University of Kentucky Research

I have presented a good deal of the political and regulatory aspects of the antibiotic controversy but have said very little of the biological data necessary to help in making a public health decision. Some of the important research has been conducted at the University of Kentucky. Central to the issue is the question about proposed changes in antibiotic practices and what effects could be expected if subtherapeutic antibiotic use were significantly reduced or eliminated in livestock. Langlois and his colleagues (5, 6) addressed this question by raising two swine herds at separate facilities 200 miles apart. One of the herds, the University of Kentucky's Coldstream herd, has been provided since 1972 with chlortetracycline at 50 to 100 g/909 kg in feed. This was compared with a herd raised since 1972 without either subtherapeutic or therapeutic exposure to antibiotics. Coliforms were monitored for many years, and the prevalence of antibiotic resistance and multiresistance was determined using disk sensitivity of random isolates. Pigs deprived of regular feed antibiotics, the Princeton herd, showed a gradual decline of antibiotic resistance. They also showed a concomitant decline in performance as measured by reduced litter size, litter weight, conception rate, increased incidence of joint problems, staphylococcal skin lesions, and other problems. When Princeton pigs were separated from the herd and given a single course of therapy, their resistance immediately increased to that of the Coldstream herd in Lexington. It was apparent that established resistance in swine coliforms did not quickly revert to sensitive when the animals were deprived of all exposure to antibiotics. These experiments, which have continued for approximately 17 yr, are important because they suggest strongly that a significant reduction in the current uses of these antibiotics would not quickly restore antibiotic sensitivity to the enteric flora of pigs and that any potential long-term reduction in resistance would probably be prevented by occasional therapeutic uses.

Salmonella Outbreaks

The general concerns about the large pool of antibiotic resistance in livestock is less often mentioned by people concerned with human health. The emphasis has shifted to a single genus: *Salmonella*. It is much easier to deal conceptually with this organism since it is zoonotic; it may transfer directly to humans where there is a potential to produce disease. With *Salmonella* there is no need to postulate the transfer of plasmids between animal commensal bacteria and pathogens in the human gut. In the 1980s, the literature on the subject empha-

sized *Salmonella* and publications from the Centers for Disease Control (CDC) have been the most prominent. Scott Holmberg of CDC (2, 3) was the guiding author on two of these papers. He reported an outbreak of *Salmonella newport* in the Midwest in which 18 cases of clinical salmonellosis were allegedly linked to a beef herd that had received tetracyclines in their feed. It is not clear whether the animals had received therapeutic or subtherapeutic amounts. This study received an exceptional amount of press coverage, and Holmberg was one of those who testified on behalf of NRDC at the imminent hazard hearings. The other publication by Holmberg and his colleagues concerned an assessment of mortality rate in a collection of salmonella outbreaks over several years. The authors proposed that mortality was significantly higher from resistant than from sensitive *Salmonella*, although they did not draw conclusions concerning the mechanism involved. This data collection preceded the very large 1985 *Salmonella* outbreak in Chicago in which the mortality rate was very low. The Chicago outbreak was caused by a resistant strain derived from contaminated milk. Another salmonella report from CDC described an outbreak of *S. newport* in California in which a clear line of transmission was shown from calves to humans (11). In that case, the primary drug used in sick calves was chloramphenicol, an antibiotic not approved for food animal use. Its use in California was thus illegal.

On several occasions, members of Congress have turned their attention to antibiotic uses and the public health questions related to antibiotic resistance. Congressman John Dingell (Democrat from Michigan) introduced a bill in 1980 seeking to severely restrict the uses of antibiotics in animal agriculture. The bill was considered at a hearing in which proponents and opponents of the bill presented views. It received little support in committee and the bill ultimately died. Other similar bills were introduced in subsequent years by Congressmen from Rhode Island, New Jersey, and California. Congressman Albert Gore (now Senator Gore, Democrat from Tennessee) held a 2-d hearing in late 1984. The first day was devoted to the agricultural uses of antibiotics and testimony was provided by a number of experts. Congressional attention to the subject in the past 15 yr has not resulted in new legislation or restrictions on antibiotic use. The ultimate responsibility for deciding the human health issue has remained the province of FDA, and it is not surprising that the FDA has found the controversy difficult.

Current Trends in Antibiotic Resistance

It now appears that antibiotic resistance in human clinical isolates is not increasing in the manner that was originally feared. Atkinson and Lorian (1) reported the results of a large data base of information on resistance to 16 commonly used antibacterials. They concluded that antibiotic resistance to most antibiotics against commonly encountered pathogens was not increasing. From 1971 to 1982, the incidence of resistance to ampicillin and tetracycline in coliforms slowly declined. Lorian (7) in a new study reported 2 yr later that the same trend with *Salmonella* was seen. O'Brien (10) and other members of an NIH sponsored task force confirmed that prevalence of antibiotic resistance to the older antibiotics was not increasing in most developed countries, but that resistance was possibly increasing to recently introduced antibiotics. They cautioned that genes encoding resistance to antibiotics could appear in new clinically important pathogens without increasing prevalence overall.

CONCLUSION

It appears that the solution to this large and lengthy riddle still eludes us. The FDA is hearing from many people that the Agency should settle the issue once and for all. Commissioner Young's tenure at FDA ended in December 1989 and any clear policy decisions on feed antibiotics are unlikely to be made soon. It is clear that whatever course of action is eventually proposed by the Agency, not everyone will be satisfied.

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