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Review

Antimicrobial growth promoter use in livestock: a requirement to understand their modes of action to develop effective alternatives

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ABSTRACT

Antimicrobial agents (AMAs) have been used in agriculture since the 1950s as growth-promoting agents [antimicrobial growth promoters (AGPs)]. They have provided benefits to the agricultural industry by increasing production efficiencies and maximising livestock health, yet the potential risks surrounding resistance to AMAs in medically important pathogenic bacteria have enhanced public and government scrutiny regarding AMA use in agriculture. Although it is recognised that AGP administration can select for resistance to AMAs in enteric bacteria of livestock, conclusive evidence showing a link between resistant bacteria from livestock and human health is lacking (e.g. transmission of resistant zoonotic pathogens). Livestock production output must be increased significantly due to the increase in global population, and thus the identification of non-AMA alternatives to AGP use is required. One strategy employed to identify alternatives to AGPs is an observational empirical methodology, but this approach has failed to deliver effective alternatives. A second approach is aimed at understanding the mechanisms involved in AGP function and developing alternatives that mimic the physiological responses to AGPs. New evidence indicates that AGP function is more complex than merely affecting enteric bacterial populations, and AGPs likely function by directly or indirectly modulating host responses such as the immune system. As such, a more comprehensive understanding of the mechanisms associated with AMA function as AGPs will facilitate the development of effective alternatives.

1. Introduction

The global human population is projected to reach 9.6 billion by 2050 [1]. This will increase demand for high-quality livestock products and necessitate the development of strategies to optimise livestock production and maintain animal health. The sustainability of livestock production has been greatly improved with the in-feed administration of non-therapeutic concentrations of antimicrobial agents (AMAs), which are known as antimicrobial growth promoters (AGPs) [2]. Unfortunately, there exists potential for the emergence of antimicrobial resistance (AMR) in human pathogenic bacteria as a result of AGP administration [3], potentially compromising the therapeutic effectiveness of AMAs in veterinary (VAMAs) and human (HAMAs) medicine. As a consequence of widespread public health concerns regarding AGP use in livestock, the European Union (EU) gradually banned all AGPs, an act that has been linked to production losses in the livestock industry [4] and has been proposed to have unexpected detrimental effects on human and livestock health [5]. Given the loss of AGPs in some jurisdictions and the impending loss of AGPs in others, the identification and development of alternatives to AGPs is an urgent issue for the global livestock industry. However, our lack of knowledge regarding the mechanisms of AGP action has hampered the development of efficacious alternatives. Here we review the use of AMAs as AGPs as well as the benefits and risks associated with AGP use, and the effects of AMAs on the enteric microbiota and the host with regard to potential mechanisms of AGP action. Understanding the roles of each of these factors is a necessary step in developing effective alternatives that mimic the action of AMAs.

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2. Use of antimicrobial agents in agriculture

2.1. Antimicrobial agents as growth promoters

An AMA is considered an AGP when it is administered to livestock feed to promote growth and to enhance feed efficiency. AMAs used as AGPs span several antibiotic classes with different bactericidal or bacteriostatic mechanisms of action (Table 1). Growth promoters are usually administered in relatively low concentrations, ranging from 2.5 mg/kg to 125 mg/kg (ppm), depending on the drug type and animal species [6]. Indications of the beneficial effect of AMAs on host health and nutrition were reported as early as 1946 [7], and the use of AMAs as feed additives for livestock without prescription was first approved by the US Food and Drug Administration (FDA) in 1951 [8]. Subsequently, the use of AGPs in livestock has become common practice worldwide, increasing by 10- to 20-fold since the 1950s.

2.2. Antimicrobial resistance associated with antimicrobial agent use

Administration of AGPs has been increasingly scrutinised due to concerns over selection for AMR and potential transmission of antimicrobial-resistant bacteria to human beings. The risk posed depends on whether the AMA registered for use in livestock belongs to the same class as AMAs registered for use in human medicine. Importantly, certain classes of AMAs used in livestock as growth promoters are also administered therapeutically in human beings (e.g. tetracyclines, penicillins, aminoglycosides), whilst others (e.g. ionophores) are used only in livestock (Table 1). To reduce the risk of losing AMA efficacy in people, most regulatory agencies are currently focused on controlling the non-therapeutic administration of HAMAs to livestock. However, some HAMAs are registered for prophylactic (i.e. disease prevention) and metaphylactic (i.e. group treatment of infected and non-infected animals) administration in livestock, thereby representing significant challenges for regulators (i.e. balancing livestock welfare, economical production and risks posed due to AMR development). It is noteworthy that at the height of their use, ca. 90% of AMAs used in agriculture in the USA were administered as AGPs and as prophylactic agents [9]. Concerns over AMA use in livestock have primarily focused on AMR development in zoonotic pathogens, as livestock are reservoirs of important bacterial pathogens of humans [10–19]. Although administration of HAMAs as AGPs is considered to be a primary administration strategy responsible for AMR development (i.e. administration of low concentrations of HAMAs for prolonged periods), therapeutic, metaphylactic and prophylactic administration of HAMAs in livestock can also result in resistance development in zoonotic pathogens. Although often overlooked, resistance development in commensal bacteria is also a concern to public health, since these bacteria provide a pool of resistance genes [20]. Bacteria can transfer genes by bacteriophage transduction, plasmid transfer and natural transformation, and via these mechanisms resistance determinants in commensal or human pathogenic bacteria in livestock treated with HAMAs could be transferred [21]. Evidence of interspecies transfer of resistance determinants has been obtained in vitro [22], and the high density and diversity of bacteria found in the gastrointestinal tract (GIT) of both livestock and human beings is a highly conducive environment for the transfer of mobile genetic elements [23]. The degree to which commensal enteric bacteria serve as a reservoir of AMR genes, and the mechanisms and selection pressures governing transmission of resistance genes from commensals remains largely unexplored.

2.3. Implications of reduced use of antimicrobial agents in agriculture

Management strategies aimed at minimising adverse human health consequences due to AMR have focused primarily on decreasing selection pressure on bacteria in livestock by restricting the use of HAMAs including common classes previously used as AGPs. The World Health Organization (WHO) has recommended the prohibition of AMAs that are administered as AGPs, and has released recommendations to limit group medication livestock, to restrict the use of antimicrobials to prescription only, and to implement risk assessments to monitor AMR levels in bacteria in livestock [6,24]. Several countries are adhering to these recommendations. In this regard, Sweden banned the use of all AGPs in 1986, a change that has now been implemented throughout the EU [5]. In Canada, guidelines were released in 2009 calling for the immediate elimination of growth-promoting antibiotics that are used in human medicine and a proposal to phase out all antibiotics used for enhancing livestock production and feed efficiency by 2015 [25].

Whilst the implications of the AGP ban in the EU both to livestock and human health are difficult to define and subject to different interpretations [26], the European ban on AGPs has provided a model to evaluate the potential impacts of reduced AGP use on livestock production and human health. Despite the implementation of strategies designed to compensate for the restrictions on HAMA usage, there are reports that the ban on AGPs in the EU has had a negative impact on livestock health [27]. After the AGP ban was implemented, an initial increase in therapeutic HAMA administration that resulted in an overall increase in AMA use was observed [28]. However, this appears to have been temporary as HAMA use has subsequently decreased [29]. Based on the Swedish and Danish experiences, it was estimated that an AGP ban in the USA would increase the cost of production by US$700 million in the pork industry over a 10-year period [30]. Conversely, an economic analysis of the US poultry industry concluded that the production benefits associated with AGP do not compensate for the costs of the HAMAs added to the feed [26].

The primary impetus of the EU AGP ban was to decrease the prevalence of infections by bacterial pathogens resistant to AMAs in humans, yet the benefits of the AGP ban are not equivocal [31]. Vancomycin-resistant enterococci have been relatively well studied in this regard, and a modest decrease in vancomycin resistance in enterococci isolated from asymptomatic human carriers was observed in some instances [32], but the overall prevalence of enterococcal infections did not diminish [4,33]. Despite the lower prevalence of AMR in some pathogens, resistance levels in *Salmonella* spp. and *Campylobacter* spp. have remained constant in Denmark [34], possibly because the HAMAs banned primarily have a Gram-positive spectrum of activity. Although the AGP ban in Denmark was associated with a decrease in the prevalence of AMR in enterococci isolated from human and livestock faeces [4,35], it is not known to what extent the observed increase in therapeutic administration of AMAs will contribute to the emergence of AMR. Despite a lack of incontrovertible evidence linking VAMA use in livestock and AMR in human pathogenic bacteria, the precautionary principle has prevailed in the majority of jurisdictions. The movement to eliminate AGPs globally coupled with the increasing requirement for livestock protein in diets makes the development of alternatives to AGPs increasingly important.

3. Possible mechanisms of antimicrobial agent action as growth promoters

The challenge of demonstrating the mode(s) of action of AGPs is attributable to the complexity within the mammalian GIT, including interactions amongst environmental, bacterial, and host