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Invited review

Health concerns and management of select veterinary drug residues

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ABSTRACT

The aim of this manuscript is to review the potential adverse health effects in humans if exposed to residues of selected veterinary drugs used in food-producing animals. Our other objectives are to briefly inform the reader of why many of these drugs are or were approved for use in livestock production and how drug residues can be mitigated for these drugs. The selected drugs include several antimicrobials, beta agonists, and phenylbutazone. The antimicrobials continue to be of regulatory concern not only because of their acute adverse effects but also because their use as growth promoters have been linked to antimicrobial resistance. Furthermore, nitroimidazoles and arsenicals are no longer approved for use in food animals in most jurisdictions. In recent years, the risk assessment and risk management of beta agonists, have been the focus of national and international agencies and this manuscript attempts to review the pharmacology of these drugs and regulatory challenges. Several of the drugs selected for this review can cause noncancer effects (e.g., penicillins) and others are potential carcinogens (e.g., nitroimidazoles). This review also focuses on how regulatory and independent organizations manage the risk of these veterinary drugs based on data from human health risk assessments.

Contents

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1. Introduction

Risk assessment and regulation of veterinary drug residues in animal-derived food commodities, such as muscle, liver, kidney, fat, milk, and eggs, follow similar principles throughout the world. In the United States of America (USA), the Food and Drug Administration (FDA) is the regulatory body that sets maximum permitted concentrations for veterinary drug residues, known as tolerances. In the European Union (EU), the equivalent regulatory body is the European Medicines Agency (EMA), which publishes maximum residue limits (MRLs) that have been set by the Committee for Medicinal Products for Veterinary Use (CVMP). There are also independent risk assessment bodies, such as the Joint Food and Agricultural Organization/World Health Organization Expert Committee on Food Additives, (JECFA) which also recommends MRLs. JECFA advises the Codex Alimentarius Commission (CAC), which as risk manager, determines whether or not to establish international standards for residues of veterinary drugs in terms of MRLs. The term tolerance is used by the FDA while other countries and organizations use MRLs. Other developed countries that are not part of the EU develop their own MRLs. Most developing countries adopt EU or Codex MRLs. For these reasons, this review will focus on approaches adopted by the USA, EU, and Codex. Readers are advised to consult the guidance documents from these national and international agencies for details on how these tolerances and MRLs are derived. The safety evaluations of these compounds are described in public documentation provided by the USA and EU and through the JECFA reports and monographs. The FDA, EMA, and JECFA conduct similar risk assessments in their safety evaluation of veterinary drug residues as described in more detail in the next paragraph. The EU has since 2009 adopted MRLs established by CAC without requiring an additional MRL application and evaluation by EMA provided that the EU delegation at the CAC did not object to the MRLs. For the most part, the risk assessment methods are indeed very conservative by making allowance for the most sensitive member of the human population. However, when residue levels in the above food animal commodities exceed the tolerance or MRL, the consumer could develop adverse health effects. Potential adverse health effects can include allergic reactions to several antimicrobial drug classes, blood dyscrasias, carcinogenicity, and cardiovascular toxicity, to mention a few, but reflect several of the potential adverse health effects associated with exposure to the drugs selected for this review.

A residue at or below tolerance or MRL is considered safe when food at that level is consumed daily for a life-time. Derivation of the tolerance or MRL requires algorithms and several toxicological, pharmacological, and microbiological data packages which will be briefly described. This is a risk assessment process where a standard battery of safety studies in animals and/or humans as well as *in vitro* studies are used to determine the acceptable daily intake (ADI). The resulting toxicological ADI is often determined from the lowest no-observable-adverse-effect level (NOAEL) and/or lowest-observable-adverse-effect level (LOAEL) gleaned from the animal and/or human studies. These NOAELs and LOAELs are often adjusted by uncertainty factors to account for species differences (1–10 for animal to human extrapolations) and intra-species differences (1–10 for variability within a population). The ADI is then adjusted with food consumption values for various tissues (300 g for muscle, 100 g for liver, 50 g form kidney, 50 g for fat, and if a dairy approval, 1500 g for milk) to obtain MRLs or tolerance for each tissue. This requires kinetic data for each tissue and this is used to ensure that the total food basket of residues at each tissue MRL or tolerance results in less than the ADI. Different jurisdictions may use slight modifications such as allocations of ADIs in how MRLs and tolerances are calculated (Baynes et al., 1999), and a comparison is briefly discussed at the end of this review.

This paper focuses on several veterinary drugs that are (1) more likely to cause adverse health effects in humans consuming these drug residues in livestock products and/or (2) not approved or no longer approved for use in food producing animals because of their presence in food put human health at risk. We have focused on the antimicrobial drug class because they are among the most widely used drugs in the livestock industry. The drugs from this antimicrobial class that is the focus here include the penicillins, tetracyclines, aminoglycosides, sulfonamides, chloramphenicol, arsenicals, and nitroimidazoles. While there are several nonsteroidal anti-inflammatory drugs approved or used off label in food animals, this paper focuses on a nonsteroidal anti-inflammatory drug, phenylbutazone, because it is of high regulatory concern although not approved for use in food animals. The third drug class we focused on is the beta-agonists, which are known to have caused acute adverse health effects and deaths in humans following exposure to related residues in animal meat.

There are several other drug classes that are used in food-