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Comparison of milk residue profiles after oral and subcutaneous administration of benzimidazole anthelmintics to dairy cows

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Abstract

The current experimental work reports on the comparison of the milk residue profile of the benzimidazole (BZD) anthelmintics after their administration by the oral and subcutaneous (SC) routes to dairy cows. The cows were distributed in four groups and treated as follows—Group 1: oxfendazole (OFZ) by oral route (5 mg kg^{-1}); Group 2: albendazole (ABZ) by oral route (5 mg kg^{-1}); Group 3: albendazole sulphoxide (ABZSO) by SC administration (3 mg kg^{-1}); Group 4: OFZ by SC route (3 mg kg^{-1}). After drug administrations milk samples were collected and frozen at −20 °C until analyzed by liquid chromatography (LC). A complete validation of the analytical methodology was accomplished. Regression curves were linear over the concentrations examined and the correlation coefficients (r) ranged between 0.994 and 0.999. The mean extraction recovery range between 77 and 97%. Residual concentrations of OFZ, fenbendazole sulphone ($FBZSO_2$) and FBZ were recovered in milk after OFZ oral administration. OFZ reached the highest concentration in milk (0.39 ± 0.10 μg ml^{-1}) at 12 h post-treatment, being detected up to 72 h post-treatment. In contrast, FBZ was not detected in cow milk and $FBZSO_2$ was the main analyte recovered from the milk with the maximum milk residues (0.042 ± 0.003 μg ml^{-1}) achieved at after 36 h following the SC injection of OFZ. ABZSO and $ABZSO_2$ were the metabolites recovered in milk following oral (ABZ) and SC (ABZSO) treatments in dairy cows. $ABZSO_2$ was the analyte recovered at the highest residual concentration (0.86 ± 0.33 μg ml^{-1}) at 12 h after oral administration of ABZ. However, ABZSO was the main compound measured in cow milk following its SC injection (0.18 μg ml^{-1}) at 12 h post-treatment. Overall, the total milk residue levels (sum of parent drug and metabolites) were higher after oral compared to parenteral treatments in dairy cows. These results reported here are discussed according to the acceptable maximum residue limits (MRLs) established for BZD compounds in cow milk.

Keywords: Milk residues; Albendazole; Albendazole sulphoxide; Oxfendazole; Oral administration; Subcutaneous administration

1. Introduction

It has been shown that cattle may develop protective immunity against parasites in the first or the second grazing seasons. However, adult cows can still be infected with several gastrointestinal (GI) nematodes [1]. These infections are normally sub-clinical but they have been associated with decreased levels of milk production [2]. In addition to this, several reports have demonstrated that treatment of infected dairy cows can advantageously influence milk production. Enhancement of milk production of ≈0.35–0.63 kg day^{-1} after anthelmintic treatment of naturally infected lactating dairy cows has been shown [3,4].

Anthelmintic drugs are widely used in veterinary medicine for prevention and treatment of animals mainly against gastrointestinal nematodes and lungworms. Benzimidazole (BZD) compounds currently marketed as broad-spectrum anthelmintics for use in ruminants, include albendazole (ABZ), albendazole sulphoxide (ABZSO), fenbendazole (FBZ), and oxfendazole (OFZ). It is well known that BZD anthelmintics

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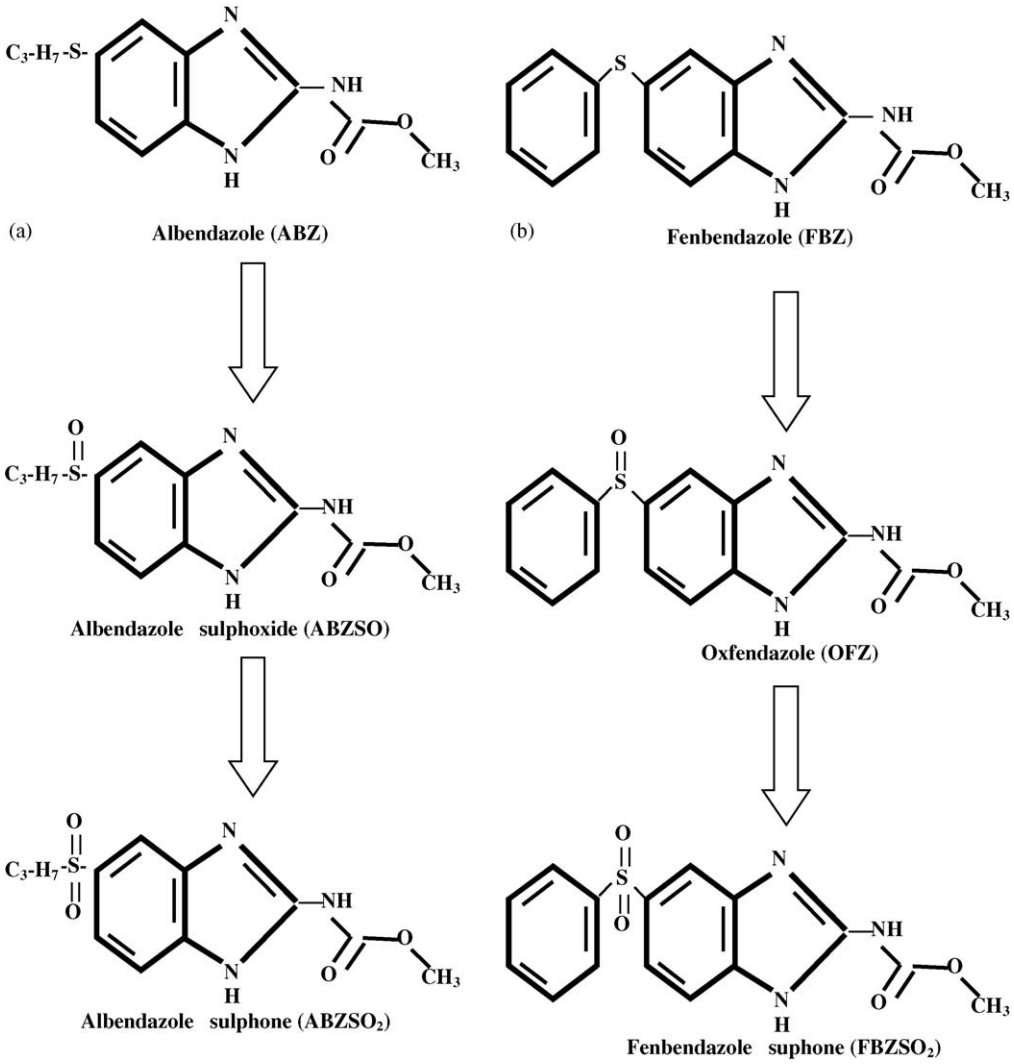

Fig. 1. Chemical structures of the benzimidazole compounds assayed in the current work: (a) albendazole (ABZ) and its metabolites, albendazole sulphoxide (ABZSO) and albendazole sulphone ($ABZSO_2$); (b) fenbendazole (FBZ) and its metabolites, oxfendazole (OFZ) and fenbendazole sulphone ($FBZSO_2$).

are extensively metabolized in all mammalian species studied [5,6]. Parent drugs are rapidly metabolized by two different microsomal enzymatic systems in the liver of sheep and cattle: flavin-containing monooxygenase (FMO) and cytochrome P-450 system. The sulphoxide (ABZSO) (active) and the sulphone ($ABZSO_2$) (inactive) metabolites are the main molecules recovered in plasma of sheep and cattle after treatment with ABZ parent drug (Fig. 1a). On the other hand, after FBZ administration to sheep and cattle, in addition to the sulphoxide (OFZ) (active) and the sulphone ($FBZSO_2$) (inactive) metabolites, FBZ parent drug was recovered from plasma [7,8] (Fig. 1b). Although these BZD anthelmintic have a wide safety margin in treated animals, a teratogenic effect has been described for ABZ in some animal species [9]. Currently BZD compounds can be used in dairy animals but required withdrawal times after treatment must be respected to avoid residual concentration above the defined maximum residues (MRL). MRLs for BZD anthelmintics have now been defined by regulatory agencies [10,11].

Low water solubility is an important limitation for the formulation of the most potent BZD methylcarbamate anthelmintics (ABZ, FBZ, etc.), restricting their formulation to suspensions for oral/intraruminal administration [12]. Poor and/or erratic gastrointestinal absorption is an inconvenience for the systemic availability and resultant efficacy of enterally administered BZD compounds. In an attempt to overcome this problem, injectable formulations (aqueous solutions) of ABZSO and OFZ have been developed to control helmint parasites in cattle. The milk residues of some orally given BZD compounds in dairy animals have been reported [13–16]. However, the pattern of milk excretion for parenterally administered BZD anthelmintic in dairy cows has not been described.

The goals of the work reported here were: (1) To develop and validate an alternative analytical method to quantify