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Evaluation of the effectiveness of intrauterine treatment with formosulphathiazole of clinical endometritis in postpartum dairy cows

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Abstract

In cattle, elimination of bacterial contamination from the uterine lumen after parturition is often delayed or compromised, and pathogenic bacteria can persist, causing uterine disease and infertility. The aim of this study was to compare the clinical and bacteriologic recovery following a single intrauterine administration of formosulphatiazole, cephapirin or placebo in cows with clinical endometritis. Cows (n = 80), no less than 28 days postpartum, with clinical endometritis were enrolled in the study. Endometritis was diagnosed by a complete reproductive examination, including rectal palpation, ultrasonography, vaginoscopy and uterine swab. All cows were randomly assigned to receive one of three intrauterine treatments (T0): 2500 mg of formosulphatiazole (Group A); 500 mg of cephapirin (Group B); placebo (4250 mg of propylene glycol; Group C). Cows were examined at the first estrus after treatment or no more than 30 days after (T1). Bacteria isolated were *E. coli*, *A. pyogenes*, *Pasteurella spp.* and *Streptococcus* spp. After treatment, in Group A and B only 6/30 (20.0%) and 6/24 (25.0%) cows showed a positive bacteriologic culture ($P > 0.05$), while in Group C the number of positive animals was significantly higher (19/26; 73.1%; $P < 0.05$). At T0, total clinical scores were similar between the three groups (Group A: 5.84 ± 1.07; Group B: 5.91 ± 1.0; Group C: 5.62 ± 1.17; $P > 0.05$) and indicative of clinical endometritis. At T1, endometritis scores were significantly lower than those reported before uterine infusion ($P < 0.05$); however, Group A and B score, 0.4 ± 0.9 and 1.0 ± 2.1, respectively, correspond to no and slight endometritis, while animals in Group C reported a total endometritis score significantly higher (4.6 ± 3.5; $P < 0.05$) corresponding to endometritis. In the present study, a commercial formosulphatiazole preparation was as effective as cephapirin and more effective than placebo for the treatment of clinical endometritis.

Keywords: Dairy cows; Endometritis; Postpartum; formosulphathiazole

1. Introduction

Uterine diseases related to microbial infection represent the main cause of reduced fertility in dairy cow farming in Europe; the economic losses related to these diseases are double to those caused by ovarian disorders, with a great impact on the economy [1]. In Italy, the incidence of uterine infection in dairy cows ranges between 10 and 40% [2]. The uterus is routinely contaminated with bacteria in the early postpartum period: approximately 80 to 100% of cows have intrauterine bacterial contamination in the first 2 wks postpartum

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[3–5], but often clinical disease does not develop because the normal uterus is able to efficiently clear bacterial infection. There is a wide range of bacteria isolated from the lumen of the postpartum uterus: the most common are *Escherichia coli, Arcanobacterium pyogenes Streptococcus spp, Pasteurella spp, Prevotella* spp, *Fusobacterium necrophorum*, [3,4,6–12]. Development of uterine infection depends on the immune response of the cow, as well as species and number of bacteria. Retained placenta, dystocia, twins and stillbirth could be predisposing factors, determining a concomitant delay in uterine involution and expulsions of *lochia*, disruption of neutrophil function and tissue damage [13–15]. Establishment of uterine bacterial infection may also depend on metabolic disease, such as milk fever, ketosis and displacement of abomasum, although the specific mechanisms are not clear [16]. Finally, the endocrine environment affects the likelihood of elimination of bacteria [15]: bacterial growth is facilitated by progesterone [17,18], while administration of estrogens or estrus induction enhances elimination of bacterial infection [19]. Bondurant [20], in 1999, defined endometritis as a superficial inflammation of the endometrium, extending no deeper than *stratum spongiosum*. Clinical endometritis is characterized by the presence of purulent vaginal discharge 21 days or more postpartum, or mucopurulent exudates 26 days postpartum without systemic signs [20,21]. Treatment of endometritis is controversial. Antimicrobial agents and hormones have been used to treat uterine infections, but hormones are of limited value three wks or more after parturition [22]. Antimicrobial therapy can be administered locally, by infusion into the uterus, or systemically, with the first one allowing to achieve higher concentrations at the site of infection [23,24]. A wide range of antimicrobials could be used for treating endometritis. Thurond, et al, in 1993 [25], showed no differences in subsequent reproductive performance in cows treated with oxytetracycline or procaine penicillin in uterus and control cows. Although oxytetracycline is widely used, Cohen, et al, in 1996 [26], demonstrated that intrauterine infusion of this drug may be inappropriate because of the lack of sensitivity of the bacteria isolated. Recently, Sheldon, et al [27] showed that oxytetracycline had the highest minimum inhibitory concentrations values compared with other antibiotics frequently used in treatment of uterine infections, such as cephapirin, a first-generation cephalosporin. Cephalosporins resemble penicillins in that they interfere with cell-wall formation, particularly with terminal stages of peptidoglycan synthesis of cells in growth phase: an alteration in cell-wall construction determines entry of water into the cell and cell death [28,29]. Since the cell-wall is specific to the prokaryotic cell, this antimicrobial activity does not interfere with mammal cells, a key feature in the use of an antibacterial agent in the therapy of bovine endometritis [30]. Several authors showed that intrauterine infusion of cephalosporin could provide good clinical recovery and reproductive performance in cows affected by bacterial endometritis [31–34]. As reported by Sheldon, et al. [27], cephapirin is effective against Gram-positive and anaerobic bacteria. Other authors [35] showed that, because of the β-lactamase production, some pathogens, such as *A. pyogenes* and *E. coli*, most frequently involved in bovine endometritis, are resistant to this drug. Instead, sulfonamides have a wide spectrum of activity, having effect against both Gram-positive and Gram-negative organisms [28,36]. The mechanism of action of these bacteriostatic drugs, used since the mid-1930s, is based on their interference with intracellular biosynthesis of folic acid from *p*-aminobenzoic acid (PABA) [28,36], thus they act on organisms that use only folic acid synthesized in-house, and do not interfere with mammalian cells that use preformed folic acid [36]. Among sulfonamides, sulphatiazole is considered one of most effective compounds: formosulphatiazole is a long-chain sulfonamide, derived from the condensation of sulphatiazole and formaldehyde, effective against a wide range of bacteria and viruses [28]. This molecule is used successfully to treat bacterial enterocolitis in human and animals [37,38] because its low intestinal absorption and good clinical effectiveness. Because the competition of sulfonamides with PABA is quantitative, the presence of excessive amounts of the latter, as in the presence of tissue exudates, pus or necrotic material, may result in reduction or cancelation of sulfa activity [36]. In the postpartum uterus, with necrotic tissue debris and dead leukocytes, most of the metabolites derived through PABA pathways are readily available for the bacteria; consequently, sulfonamides could be ineffective [39]. Because of the mechanism of action and the importance of protein synthesis during bacterial growth, the efficiency of sulfonamides is higher during the acute phase of disease and after metabolite stocks have been exhausted [36]. As in the intestine, formosulphatiazole is poorly absorbed in the uterine lumen, persisting at high concentrations for a long period, and could, therefore, be very efficient in purulent infections [40]. To our knowledge, only Dobson and Noakes [40], in 1990, used this drug to prevent uterine infections in cows after parturition; the authors