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Pharmacokinetics of tulathromycin on plasma and semen of beef bulls

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| 1 | Pharmacokinetics of tulathromycin on plasma and semen of beef bulls |
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| 2 | |
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| 18 | |

19 <u>Abstract</u>

| 20 | The objective of this investigation was to evaluate the pharmacokinetic parameters of |
|----|---|
| 21 | tulathromycin in plasma and semen of beef bulls after administering a single sc dose at two |
| 22 | different sites in the neck. Four Simmental bulls with excellent temperament received a |
| 23 | comprehensive physical exam that included breeding soundness examination. In addition, blood |
| 24 | was collected and analyzed for CBC and chemical panel in order to rule out any subclinical liver |
| 25 | or kidney disease. All bulls were diagnosed as healthy and satisfactory potential breeders. The |
| 26 | mean plasma levels of tulathromycin for the two neck sites of sc administration were not |
| 27 | different between posterior aspect of the ear where it attaches to the head (RP; regio parotidea; |
| 28 | 77.9 ± 43.3 ng/mL; X \pm SD) and to the middle of the neck (RC; regio collis lateralis; 73.7 ± 39.7 |
| 29 | ng/mL; P=0.84). The mean seminal plasma levels of tulathromycin after administration in the RP |
| 30 | was 608 ± 374 ng/mL and for RC was 867 ± 599 ng/mL without differences between both sites |
| 31 | (P=0.29). The mean level of tulathromycin in plasma was 75.8 ± 40.2 ng/mL, which was lower |
| 32 | than mean seminal plasma levels of 781 ± 482 ng/mL (P=0.001). The plasma peak tulathromycin |
| 33 | concentration (C _{max}) was 160 ± 27 ng/mL at 21 ± 6 h (T _{max}) post-administration. The seminal |
| 34 | plasma C_{max} was 1,539 \pm 44.4 ng/mL at 33.00 \pm 18.00 h (T_{max}) post-administration. The C_{max} |
| 35 | between plasma and seminal plasma were different (P=0.008) without any differences in T_{max} |
| 36 | between plasma and seminal plasma (P=0.35). The terminal half-life for plasma tulathromycin |
| 37 | $(81.4 \pm 27.6 \text{ h})$ showed a tendency to be shorter than in seminal plasma (114.7 ± 21.7; P=0.10). |
| 38 | The plasma area under the curve concentration time from the first to the last sample (AUC _{0-last}) |
| 39 | was $15,440 \pm 1,717$ ng/mL/h, which was significatively smaller compared with $171,071 \pm 58,556$ |

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| 40 | ng/mL/h for seminal plasma AUC _{0-last} ($P=0.01$). The plasma means residence time from the first | | | | | | | | |
|----|---|--|--|--|--|--|--|--|--|
| 41 | to the last sample (MRT _{0-last}) was 89.3 ± 5.1 h and it was shorter than for seminal plasma of 96.6 | | | | | | | | |
| 42 | \pm 5.0 h (P=0.05). From the present investigation, it was concluded that tulathromycin is a | | | | | | | | |
| 43 | suitable antibiotic based in its pharmacokinetic properties that could be used for treatment of bull | | | | | | | | |
| 44 | genital infections when its application is indicated. | | | | | | | | |
| 45 | | | | | | | | | |
| 46 | Keywords: Bull, tulathromycin, pharmacokinetics, plasma, semen | | | | | | | | |
| 47 | | | | | | | | | |
| 48 | 1. Introduction | | | | | | | | |
| 40 | The use of optihistics is required in many nonneductive elimical conditions of hulls [1, 2] | | | | | | | | |

49 The use of antibiotics is required in many reproductive clinical conditions of bulls [1-3]. One of the most common reproductive diseases in young and old bulls is seminal adenitis 50 syndrome [3,4]. One of the recommendations to treat this disorder is the administration of either 51 local or systemic antibiotics [3,5,6]. Antibiotic selection for this clinical condition and other 52 53 genital infections (orchitis, epididymitis) is based on personal experience, anecdotal, extrapolation from other species, or on the results of microbiological culture and sensitivity tests. 54 55 The chosen antibiotic needs to be used at the correct dose, route and frequency for an acceptable period (antibiotic stewardship) [7]. Furthermore, a judicious use of antibiotics remains critical for 56 minimizing risk of microbial resistance. Unfortunately, information on antibiotic levels in the 57 bull's genital tract or in semen is not available. Hence, new information on this subject is 58 paramount not only to design an appropriate treatment regimen and preclude the uses of 59

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antibiotics that cannot be effective, but also to avoid their unnecessary use. One of the 60 recommendations to reduce medication errors and harm is to use the "five rights"-the right 61 patient, the right drug, the right dose, the right route, and the right time [8]. 62 63 Most information about the pharmacokinetic of antibiotics in the male genital tract is derived from human and dog models [9–11]. However, the anatomy and physiology of these two 64 65 species are different from ruminants [12]. As a result, extrapolation of the information from such different species should only be done when no other data is available. 66 67 Tulathromycin is a macrolide triamilide antibiotic that has been approved for use in the treating and preventing respiratory diseases in cattle, swine and other animals [13,14], infectious 68 69 bovine keratoconjunctivitis and interdigital necrobacillosis [14]. Like other macrolides, it binds 70 to the 50S subunit of bacterial ribosomes and inhibits protein synthesis, leading to inhibition of cell division and cell death. Tulathromycin's spectrum of activity includes Gram-negative, 71 Gram-positive, and Mycoplasma microorganisms [13,15], and it exhibits a mixed bacteriostatic 72 and bactericidal concentration [13]. The minimum bactericidal concentration (MBC) was found 73 to be the same as the minimum inhibitory concentration for 70% of M. haemolytica and 74 75 Pasteurella multocida isolated [13]. In cattle, this antibiotic presents unique pharmacokinetic characteristics such as rapid absorption from the injection site, extensive tissue and high-volume 76 distribution, elevated and sustained drug concentration in the lungs, and slow elimination [13]. 77 78 Studies have shown that the level of tulathromycin in plasma did not correlate with the therapeutic level in tissues of the respiratory system [13,15]. On the other hand, when 79 80 tulathromycin was administered parenterally, the concentrations in the synovial fluid were higher

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and persisted longer than in plasma [16]. Moreover, treatment with tulathromycin resulted in
clearance of Leptospira hardjo-bovis organisms from the urine and kidney tissue of all positive
heifers [17].

84 The pharmacokinetic of tulathromycin in the bull's genital tract or semen has not been investigated. Due to their known above-mentioned characteristics, this drug is the prime 85 86 candidate for further investigation in semen. The availability of an antibiotic with long-acting effects would limit the frequency of administration and animal handling with the consequent 87 reduction in animal stress while also improving compliance. Research on the pharmacokinetic 88 89 parameters of a second site of injection in the neck is not only valuable "per se" but also for practical reasons. Bulls are heavy animals that require high volume doses of medications. In the 90 case of tulathromycin, it is recommended to inject not more than 10 ml per injection site with a 91 distance not less than 10 cm between administration places. Therefore, tulathromycin 92 93 administration will require two or more sites of administration. The objective of this investigation was to evaluate the pharmacokinetic of tulathromycin 94

95 in plasma and semen in beef bulls by administering a single sc at two different sites.

96

97 <u>2. Material and methods</u>

98 <u>2.1. Animals</u>

99 Six Simmental bulls with excellent temperament and healthy appearance were selected100 for the study. Each one had a comprehensive physical examination including breeding soundness

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examination according to the guidelines by Society for Theriogenology [18]. In addition, blood 101 was collected from the tail vessels and analyzed for CBC and chemical panel in order to rule out 102 any subclinical liver or kidney disease. None of these showed any abnormalities. All bulls were 103 diagnosed as healthy and satisfactory potential breeders. Four of these bulls were randomly 104 selected for this investigation. The age of the bulls was 15 ± 0.2 mo (range: 15–16). The weight 105 106 was 639.3 ± 32.9 kg (604–681 kg). The body condition score was 6.1 ± 0.5 (5.5–6.50) [19]. The bulls were maintained in individual pens and received a ration of corn silage, mixed hay, and 107 alfalfa with water ad libitum. In addition, each bull received 2.5 kg of pellet concentrate once a 108 day containing 14% crude protein. 109

110 <u>2.2. Experimental design</u>

These bulls had no history of tulathromycin administration. Each bull received a single sc 111 dose of tulathromycin (Draxxin, Zoetis Italy, Rome) at the dose of 2.5 mg/kg of body weight 112 (day 0 time 0). Two of the bulls received the dose posterior aspect of the left ear where it 113 attaches to the head (RP; regio parotidea sinister) and two in the middle of the left side of the 114 neck (RC; regio collis lateralis sinister)[20]. The order of sample collection was blood and 115 116 semen, collected at 0, 12, 24, 48, 72, 96, 144, 192, and 240 h after tulathromycin administration. Blood was collected from the tail vessels using vacuum tubes containing lithium heparin (10 117 mL). Semen was collected from each bull by electroejaculation by using an electro-ejaculator in 118 119 automatic mode; the same set-up was used for all the bulls (Pulsator V, Lane Manufacturing, Denver, CO, USA) using a two-electrode rectal probe of 60 mm diameter. All the samples were 120 immediately refrigerated, then centrifuged at 600 g for 30 minutes, processed within the first h, 121

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and stored at -80° C. Procedures used in this investigation were approved by the Committee for

123 Animal Welfare, University of Bologna (Prot. n.0005783).

124

125 <u>2.3. Tulathromycin analysis</u>

Liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) was used 126 to measure tulathromycin concentrations in bull plasma and seminal plasma, with an approach 127 128 similar to the technique described by Zhou et al. [21]. Two hundred µL of thawed sample was placed in a microcentrifuge tube, then 180 μ L of acetonitrile and 20 μ L of internal standard 129 tulathromycin-d7 (Toronto Research Chemicals, North York, ON, Canada) in acetonitrile were 130 added. The tube was agitated in a vortex mixer for 30 sec, centrifuged at $21,000 \times g$ for 10 min at 131 4 °C and the supernatant was filtered through a 0.22 μm nylon syringe filter. A 100 μL aliquot of 132 133 the purified sample was diluted in a vial with an equal amount of 0.1% formic acid aqueous solution, and, finally, 10 µL from each vial was injected in the LC-MS/MS system. 134

The apparatus consisted of a Waters Acquity UHPLC binary pump (Waters, Milford, MA, 135 136 USA) and thermostated autosampler, kept at 20 °C. Chromatographic separation was obtained with a Waters Acquity BEH C18 ($50 \times 2.1 \text{ mm}$, $1.7 \mu \text{m}$) column (Waters, Milford, MA, USA), 137 maintained at 40 °C to lower system backpressure. The mobile phase was a mixture of 0.1% formic 138 acid in water (A) and acetonitrile (B) flowing at 0.3 mL/min during a 5 min run: its composition 139 changed from 90% to 50% A in the first 2 min, then was kept at 50% A for 1.75 min, brought back 140 to 90% A in 0.5 min and finally kept at 90% A for 0.75 min to allow column equilibration. The 141 detector was a Waters Quattro Premier XE triple quadrupole mass spectrometer (Waters, Milford, 142

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MA, USA), equipped with an electrospray ionization source (ESI), with capillary voltage set at 143 +3.0 kV, source temperature at 120 °C and desolvation temperature at 400 °C. Desolvation and 144 cone gas flow were 600 and 100 L/h, respectively, and argon was used as collision gas. The 145 retention time was 1.23 min for both tulathromycin and tulathromycin-d7. The instrument operated 146 in MRM mode, monitoring the 403.7>576.9 m/z (quantification) and 403.7>229.9 m/z 147 148 (confirmation) transitions for tulathromycin and the 407.3>236.9 m/z transition for the internal standard. Data acquisition and processing were carried out with MassLynx 4.1 software (Waters, 149 150 Milford, MA, USA).

151 Aliquots (200 µL) of each matrix were fortified with tulathromycin (Toronto Research Chemicals, North York, ON, Canada) at different concentrations to obtain matrix-matched calibration curves 152 at suitable ranges (10-1000 ng/mL) for plasma and 50-5000 ng/mL for seminal plasma and quality 153 control (QC) samples at three different levels for each day of the analysis. Tulathromycin/internal 154 standard peak area ratios were plotted against the correspondent concentrations and a linear least 155 156 square regression model was applied; the good linearity of the method was proved by the correlation coefficient (R2) always ≥ 0.99 and all the calibration standards within $\pm 15\%$ of the 157 nominal value. The lower limit of quantification (LLOQ), that is, the lowest tested concentration 158 159 of tulathromycin showing a signal/noise ratio ≥ 10 , was 10 ng/mL for plasma and 20 ng/mL for seminal plasma. Accuracy and precision, intended as measured value-expected concentration 160 161 relative difference and coefficient of variation (CV%), respectively, were always within $\pm 15\%$ at 162 all QC concentration and all the three matrices.

163 <u>2.4. Pharmacokinetic parameters.</u>

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| 164 | Noncompartmental analysis was used to estimate the pharmacokinetic parameters in |
|-----|--|
| 165 | plasma and seminal plasma for each individual animal. Standard software, PK-Solver add-in for |
| 166 | Excel [22] was used to estimate the pharmacokinetic parameters. The following variables were |
| 167 | calculated for plasma and seminal plasma of each animal: time of peak drug concentration |
| 168 | (T_{max}), peak drug concentration (C_{max}), apparent elimination half-life (t1/2), calculated as ln |
| 169 | (2)/ λz , λz being the first order rate constant associated with the terminal portion of the time- |
| 170 | concentration curve as estimated by linear regression of time versus log concentration, area |
| 171 | under the time-concentration curve from time zero to the last observed concentration (AUC $_{0-last}$), |
| 172 | calculated by the linear trapezoidal rule, area under the time-concentration curve from time zero |
| 173 | extrapolated to infinity (AUC $_{0-inf}$), calculated by adding the last observed concentration divided |
| 174 | by λz to the AUC _{0-last}), area under the moment curve from time zero to last observed |
| 175 | concentration (AUMC _{0-last}), area under the moment curve from time zero extrapolated to infinity |
| 176 | (AUMC _{0-inf}), mean resident time estimated using time zero to last observed concentrations |
| 177 | $(MRT_{0-last}, calculated as AUMC_{0-last}/AUC_{0-last})$, and mean residence time estimated using time |
| 178 | zero to infinity (MRT 0-inf, calculated as AUMC 0-inf/AUC 0-inf) |
| 179 | |

180 <u>2.5. Statistical Analysis.</u>

Statistical software [23] was used to determine parameters such as mean, standard
deviation, and range. Student "t" test for paired samples was used. In addition, a software
program (PK-Solver) for pharmacokinetic parameters as previously mentioned was used [22].
An alpha error of 5% was used to accept the alternative hypothesis.

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186 <u>3. Results</u>

187 All bulls remained clinically healthy throughout the study period.

| 188 | Mean plasma levels of tulathromycin for the two sc neck injection sites were not different |
|-----|--|
| 189 | between RP (77.9 \pm 43.3 ng/mL) and the RC (73.7 \pm 39.7 ng/mL; P=0.84). Mean seminal plasma |
| 190 | levels of tulathromycin after administration on the RP were 608 ± 374 ng/mL and 867 ± 599 |
| 191 | ng/mL for RC without differences between both sites (P=0.29). Because no significant |
| 192 | differences were noticed at the two sites of administration, the means for plasma and seminal |
| 193 | plasma were combined. The mean level of tulathromycin in plasma was 75.8 ± 40.2 ng/mL |
| 194 | which was lower than mean seminal plasma level of 781 ± 482 ng/mL (P=0.001). The ratio for |
| 195 | mean plasma/seminal plasma of tulathromycin levels was 10.3. Mean (\pm SD) plasma and seminal |
| 196 | plasma of tulathromycin concentration (ng/mL) throughout the investigation period is presented |
| 197 | in Fig 1. |

All pharmacokinetic parameters calculated for non-compartmental analysis of plasma and 198 seminal plasma are presented in table 1. The plasma C_{max} was 160 ± 27 ng/mL at 21 ± 6 h (T_{max}) 199 after administration. The seminal plasma C_{max} was $1,539 \pm 444$ ng/mL at 33.00 ± 18.00 h (T_{max}) 200 after administration. The C_{max} between plasma and seminal plasma was different (P=0.008) 201 without any differences in T_{max} between plasma and seminal plasma (P=0.35). The ratio C_{max} 202 between plasma/seminal plasma was 9.6. The terminal half-life for plasma (81.4 ± 27.6 h) 203 showed a tendency to be shorter than in seminal plasma (114.7 \pm 21.7; P=0.10). The plasma for 204 AUC_{0-last} was $15,440 \pm 1,717$ ng/mL/h, significantly smaller compared to $171,071 \pm 58,556$ 205

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ng/mL/h for seminal plasma AUC_{0-last} (P=0.01). The ratio AUC_{0-last} plasma/seminal plasma of tulathromycin levels was 11.9. The plasma means residence time from the first to the last sample (MRT_{0-last}) was 89.3 ± 5.1 h and it was shorter than for seminal plasma of 96.6 ± 5.0 h (P=0.05).

210 4. Discussion

211 No side effects at the dose used such as hypersalivation, head shaking, pawing the ground 212 or decreased feed intake as previous reported were observed [14,24]. Only a mild swelling at the 213 site of injection was detected, especially at the RP, which disappeared in 5 days. The two neck locations of administration did not present any difference either in plasma or seminal plasma 214 215 concentrations of tulathromycin; therefore, this could be considered an extra benefit in which an 216 additional site of administration could be used without affecting the beef quality assurance. Bulls 217 are big animals that require a high volume dose. It is recommended not more than 10 ml per injection site a distance not less than 10 cm between administration places. Therefore, bull 218 treatment will require two or more injections sites of tulathromcyin. 219

In cattle, the parenteral administration of tulathromycin at label dose (2.5 mg/kg) was characterized by rapid rate of absorption, early maximal plasma concentrations, extensive distribution, and slow elimination [13,15,25,26]. In plasma, tulathromycin has a long terminal half-life, ranging across studies from 64 h [26], 90 h [13,15], 110 h [25], 112 h [27], and up to 189 h [28]. In the current study, a terminal half-life of 81.4 ± 27.6 h (range: 71–96 h) was obtained in agreement with some of aforementioned reports.

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| 226 | The plasma C_{max} obtained was 160 ng/mL (range 121–180 ng/mL) a low value compared |
|-----|--|
| 227 | with former findings which reported 277 ng/mL [26], 300 ng/mL [25], 500 ng [13,15], 718 |
| 228 | ng/mL [28]. However, the current evaluation agrees with two recent reports using 10 mo |
| 229 | Holstein steers and bisons in which levels of 154 ng/mL [27] and 195 ng/mL [29], respectively |
| 230 | were reported. One possible explanation for this difference with those studies could be that the |
| 231 | first blood sample collection was performed 12 h after tulathromycin administration; therefore, |
| 232 | due to rapid rate of absorption and quick systemic distribution, the plasma concentration of |
| 233 | tulathromycin was already in a descending phase. This is supported by two reasons. First, in |
| 234 | those studies the first the T_{max} , time of C_{max} , was obtained at 0.25 h [29], < 1 h [13], 0.7 h [26], 1 |
| 235 | h [28], 1.8 h [15], or 3 h [26]; second, when the present values from 24 to 240 h were compared |
| 236 | with the results obtained by Nowakowski et al. [15] or Evans [13], similar profiles were |
| 237 | obtained. These, therefore, supported and confirmed the current plasma outcomes. |
| 238 | The plasma AUC_{0-last} in the present study was 18,382 ng/mL/h in conformity with the |
| 239 | results of 17,885 ng/mL/ h by Rivera et al. [28] and 16,700 ng/mL/h by Evans [13] but higher |
| 240 | than previous stated by other investigators [15,25-27]. The MRT for plasma was 134.3 h agreed |
| 241 | with 146 h reported by Nowakowski [15] and it was in between results from other two studies of |
| 242 | 65 h [27] and 171.5 h [29]. Differences in plasma pharmacokinetic parameters compared with |
| 243 | previous investigations were detected; they were, however, within the normal range. Therefore, |
| 244 | the present outcomes permit to be confident that not only the plasma analysis was appropriate, |
| 245 | but it also supported the seminal plasma results. |

The efficacy of any antimicrobial is determined by both its pharmacokinetic and 246 pharmacodynamic properties. Antibiotics have been classified in two major groups-those with 247 bacteriostatic antimicrobial action that exhibit time-dependent killing action or those with 248 bactericidal antimicrobial action that behave with either time-dependent or concentration-249 dependent killing [15]. Tulathromycin has shown to have bacteriostatic antimicrobial action and 250 251 also bactericidal antimicrobial time-dependent action [13] with a bioavailability after parenteral administration more than 85% for cattle and swine [13,30,31]. Antimicrobial having time-252 253 dependent action is associated to the exposure to pathogens to an appropriate amount of time. 254 Therefore, concentration of antibiotic above the minimum inhibitory concentration (MIC) of each specific pathogen is one accepted method of evaluation [13]. In a recent report, the AUC 255 above the minimum inhibitory concentration (MIC) for a specific microorganism (AUC/MIC) 256 was considered the primary pharmacokinetic/pharmacodynamics predictor for tulathromycin 257 clinical effectiveness [32]. In vitro studies of tulathromycin in the bacteriostatic and bactericidal 258 259 activity were both affected by pH, carbon dioxide, and serum, which have a possible significant relevance in vivo [13]. Unfortunately, correlation between in vitro susceptibility test and clinical 260 effectiveness is undetermined for certain clinical conditions. 261

The ejaculate consists of spermatozoa suspended in a fluid medium called seminal plasma (SP). The components of SP are produced from rete testis, epididymis, and accessory sex glands (AG) of the male reproductive tract [12,33,34]. In the bull, the AG are seminal glands (vesicles), prostate (compact and disseminate), and Cowper glands that contribute to the major portion of SP at ejaculation [12,35]. The spermatozoa present in the ejaculate collected either by

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artificial vagina or electroejaculation come from the tail of epididymis and ampulla [12.33-35]. 267 Therefore, the presence of tulathromycin in the seminal plasma could be considered a strong 268 indication that the antibiotic was released from the tail of epididymis, and/or accessory sexual 269 glands. In multiple previous independent investigations, high and extended concentrations of 270 Tulathromycin in lung tissue feature have been reported. Lung concentrations were many times 271 272 higher than plasma concentration with lung plasma area under the concentration-time curve ratios being more than 50 times with a long half-life values than plasma [13,26]. In vitro studies 273 274 show that tulathromycin accumulates in neutrophils and blood macrophages, pulmonary epithelia 275 lining cells from normal cattle [26,36]. In a recent study, the parenteral administration of tulathromycin resulted in synovial fluid concentrations that were higher with a longer duration 276 that previous reported plasma values [16]. To the best of the authors' knowledge, this is the first 277 study that shows pharmacokinetic of tulathromycin in bull semen after a standard dose of this 278 antibiotic as recommended for cattle. The seminal plasma Cmax of tulathromycin was almost 10 279 280 times higher than in plasma with a tendency of longer half time compared with plasma. Moreover, the seminal plasma AUC_{0-last} was almost 14 times higher contrasted with AUC_{0-last} in 281 282 plasma. Finally, both mean residency times (MRT_{0-last} and MRT_{0-inf}) for seminal plasma were 283 extended compared with MRT_{0-last} and MRT_{0-inf} of plasma. In the case of seminal plasma, MRT₀₋ inf was 43% longer than plasma MRT_{0-inf}. Therefore, it appears that tulathromycin elimination 284 285 from male's genital tract was slower, probably because of delayed exposure in the organs of 286 elimination, and this can be considered an advantage for male reproductive treatments. Based on the present pharmacokinetic findings, the sc administration of tulathromycin at 2.5 mg/kg body 287 288 weight in bulls produced rapid absorption with higher levels in seminal plasma that continue

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| 289 | longer when contrasted with plasma levels. The present pharmacokinetic information will allow | | | | | | | | |
|-----|--|--|--|--|--|--|--|--|--|
| 290 | establishing an adequate dose regime of tulathromycin for bull genital infections. | | | | | | | | |
| 291 | From the present investigation, it was concluded that tulathromycin is a suitable | | | | | | | | |
| 292 | antibiotic based on its pharmacokinetic properties that could be used for treatment of bull genital | | | | | | | | |
| 293 | infections when its application is indicated. | | | | | | | | |
| 294 | | | | | | | | | |
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| 302 | | | | | | | | | |
| 303 | Competing interests | | | | | | | | |
| 304 | All authors declare that there is no conflict of interest that could be perceived as prejudicing the | | | | | | | | |
| 305 | impartiality of the research reported. | | | | | | | | |
| 306 | | | | | | | | | |
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| | | Plasma | | Seminal Plasma | | | |
|--------------------------|----------------------|-----------|----------|----------------|------------|------------|-------------|
| Parameter | Unit | Mean | SD | | Mean | SD | Probability |
| Lambda z (Λ_z) | 1/h | 0.009427 | 0.003654 | | 0.006188 | 0.001002 | 0.16 |
| t1/2 | h | 81.4 | 27.6 | | 114.7 | 21.7 | 0.1 |
| T _{max} | h | 21 | 6 | | 33 | 18 | 0.35 |
| C _{max} | ng/mL | 160 | 26.5 | | 1,539 | 444.3 | 0.008 |
| AUC 0-last | ng/mL*h | 15,440 | 1,717 | | 171,071 | 58,556 | 0.01 |
| AUC 0-inf | ng/mL*h | 18,382 | 11,729 | | 247,892 | 89,099 | 0.01 |
| AUMC 0-last | ng/mL*h ² | 1,379,000 | 176,000 | | 16,442,000 | 5,274,000 | 0.01 |
| AUMC 0-inf | ng/mL*h ² | 2,479,756 | 673633 | | 47,130,701 | 15,873,682 | 0.01 |
| MRT 0-last | h | 89.3 | 5.1 | | 96.5 | 5.0 | 0.05 |
| MRT 0-inf | h | 134.3 | 32.4 | | 191.4 | 9.3 | 0.05 |

Table 1. Plasma and seminal plasma pharmacokinetics parameters of tulathromycin administered by sc route at 2.5 mg/kg.

 Λ_z being the first order rate constant associated with the terminal portion of the time-concentration curve; t1/2 : apparent elimination half-time calculated as $\ln(2)/\Lambda_z$; T_{max} : time of peak drug concentration; C_{max} : peak of drug concentration; AUC_{0-last}: area under the time-concentration curve from time zero extrapolated to infinity; AUMC_{0-inf} : area under the time-concentration; and the moment curve from time zero extrapolated to last observed concentration; AUMC _{0-inf}: area under the moment curve from time zero extrapolated to last observed concentration; AUMC _{0-inf}: area under the moment curve from time zero extrapolated to last observed concentration; AUMC _{0-inf}: area under the moment curve from time zero extrapolated to last observed concentration; AUMC _{0-inf}: area under the moment curve from time zero extrapolated to last observed concentration; AUMC _{0-inf}: area under the moment curve from time zero extrapolated to last observed concentration; AUMC _{0-inf}: area under the moment curve from time zero extrapolated to last observed concentration; AUMC _{0-inf}: area under the moment curve from time zero extrapolated to last observed concentration; AUMC _{0-inf}: MRT _{0-inf} : Mean resident time calculated as AUMC _{0-last} /AUC _{0-last}; MRT _{0-inf} : Mean (± SD) pharmacokinetics parameters in plasma and seminal plasma calculated via noncompartmental analysis after sc administration.

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Figure 1. Mean (\pm SD) plasma and seminal plasma of tulathromycin concentration (ng/mL) after single sc administration at 2.5 mg/kg in four Simmental bulls.