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Integration of Pharmacokinetic and Pharmacodynamic Approach of Meropenem against *Staphylococcus aureus* Isolated from Mastitis in Ewes

A Dissertation
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Abstract

The study was carried out to study each of pharmacodynamics and pharmacokinetics of Meropenem then integrating both studies via a suitable pharmacokinetic-pharmacodynamic approach to design a suitable dosage regimen as a part of therapy against experimental clinical mastitis in Awassi ewes that induced by field isolate of pathogenic *Staphylococcus aureus*, then after tracking of Meropenem residues in milk and determining of withdrawal period after application of the proposed dosage regimen.

To select bacterial isolate that had been used for evaluation of Meropenem pharmacodynamics and induction of mastitis; milk samples were obtained from 50 halves that primarily identified as mastitis positively prevalent according to the case history report, clinical signs, and physicochemical properties of the produced milk; these samples had been submitted to microbiological and biochemical tests followed by molecular identification of the elected *S. aureus* isolate that recorded in the National Center for Biotechnology Information (NCBI) GenBank sequence database as *S. aureus* (strain LOC-M2020).

To evaluate Meropenem pharmacodynamics; the elected *S. aureus* isolate had been subjected to Minimum Inhibitory Concentration (MIC), Minimum bactericidal concentration (MBC) by utilizing of Time kill curve, Post antibiotic effect (PAE), Mutant prevention concentration (MPC), and Minimum biofilm inhibition concentration (MBIC); results found that the value of MIC of Meropenem against *S. aureus* (strain LOC-M2020) was 4 μg/ml, the values of MBC, MPC and MBIC were 8 μg/ml for each of them, while the post-antibiotic effect of Meropenem against *S. aureus* was remaining for 0.61 h.

To study pharmacokinetic parameters of Meropenem in plasma and milk of ewes after intravenous bolus administration, five healthy milking ewes had been received a 20 mg/kg of Meropenem as a single intravenous bolus to characterize both of distribution and elimination of Meropenem in plasma and milk, concentrations of Meropenem in plasma and milk had been analyzed by the microbiological method and pharmacokinetic data had been analyzed by compartmental and noncompartmental methods, results of mean ± standard deviation for half-life, the volume of distribution and total body clearance for plasma samples were 0.67 ± 0.09 h., 0.169 ± 0.01 and 0.3 ± 0.02 L/hr/kg, respectively, the plasma protein binding

ratio was 7.27 ± 0.22 %; while the half-life, C_{max} and drug penetration ratio for milk samples were 9.56 ± 3.13 h, 3.91 ± 0.99 μg/ml and 0.86 ± 0.23 respectively.

The time that Meropenem concentration spent over its MIC (*f* T>MIC) against *S. aureus* (strain LOC-M2020) was utilized to propose a suitable dosage regimen which was 20 mg/kg every 8 hrs. The efficacy of the proposed Meropenem dosage regimen was evaluated against experimentally induced mastitis in ewes where the counting of bacterial colonies that recovered from milk throughout the treatment period showed a significant decrement in number with no growth after 24 hrs. after treatment in comparison to the untreated ewes.

Meropenem residues and withdrawal period from milk were calculated by microbiological assay; where the microbiologically active Meropenem residues had not been detected in milk after 48 hrs. of last administered dose, while the calculated withdrawal time of Meropenem from milk was after 39 hrs. of last administered dose.

In conclusions, Meropenem possesses an efficacious profile against *S. aureus* as same as other sensitive bacteria which qualifying it to be a potential candidate to be one of the preferred parenterally administered antibacterial agents to encounter the acute cases of mastitis that ought to be treated hastily depending on Meropenem approval state in veterinary therapy.