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PLASMA AND TISSUES DISTRIBUTION KINETICS OF GENTAMICIN SULFATE IN MICE. LOCAL PHYSIOLOGICAL MODEL FOR LIVER, SPLEEN AND KIDNEY

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Pharmacokinetic/pharmacodinamic (pk/pd) modelling using drug in plasma has been reported as a powerful tool for describing and predicting the "in vivo" drug effects. In the case of antibiotic drugs where the biophase takes place in infected tissues and most the effects have been correlated with drug exposure in damaged organs, the use of physiological based (pb) pk models can improve the prediction and the understanding of both, therapeutic and adverse outcomes. In the current study a pbpk model has been developed for gentamicin sulfate in liver, spleen and kidney in control (healthy) mice, as a previous step towards the comparison with brucella infected mice under different gentamicin formulations (liposomal delivery systems). The disposition kinetics of gentamicin sulfate were characterised by compartmental models in plasma and a pbpk model in various tissues. For this purpose, the drug was administrated intravenously (40mg/kg) to 33 mice (Balb C). Plasma, liver, spleen and kidney samples were taken at 11 different times, from 0-48 h after administration of drug. The concentrations of gentamicin were determined by fluorescence polarized immunoassay. Plasma levels of gentamicin declined biexponentially and the data were analysed according to a two compartment open model. After a rapid decrease tissue concentrations tended to be constant, suggesting a limited flow model which includes active and passive transport for drug uptake. The predictions of this model described adequately the observed kinetics of distribution.

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PHARMACOKINETIC STUDY OF AN ASSOCIATION OF 0.03 MG ETHINYLESTRADIOL AND 2 MG DIENOGEST AFTER SINGLE AND REPEATED ORAL ADMINISTRATIONS IN SIXTEEN NORMAL HEALTHY YOUNG VOLUNTEERS.

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The aim of the present study was to evaluate the pharmacokinetics of new oral contraceptive containing ethinylestradiol 0.03 mg and dienogest 2 mg during multiple dose administration.

It was an open study composed of a pill free cycle followed by a second cycle with a single administration period between days 1 and 5, followed by three cycles with a repeated oral administration from day 1 to 21 of each cycle, followed by a 7-day pill free interval in sixteen healthy young women. Plasma samples were collected after single dose and after repeated dose :T0h (prior dosing) and until T48.0h after administration. *Ethinylestradiol was measured by GC/MS system. The experimental limit* of quantification was 10 $pg.ml^{-1}$. Dienogest was measured by RIA. The limit of quantification was $1ng.ml^{-1}$.

Under the conditions of the study, single and repeated administration by oral route, the clinical and biological tolerability was good with only weak effect on renin, thyroid and adrenocortical hormons. This study has also shown that there is a significant increase of the AUC_{ss0-24} of ethinylestradiol and dienogest after multiple oral administration of a combination of 0.03 mg ethinylestradiol with 2 mg dienogest compared to the $AUC_{0-\infty}$ after single dose. In addition when dienogest is administered with estradiol valerate instead of ethinylestradiol, the AUC_{ss0-24} after multiple dosing is not different from the $AUC_{0-\infty}$ after single dose.

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In vivo cutaneous water dynamical description through compartmental analysis

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Introduction. Trans-epidermal water loss and skin surface hydration are the most frequently used parameters to assess in vivo skin water balance changes. These are crucial indicators of some pathological processes or to quantify the efficacy of some specific therapeutics. However, data must be correctly interpreted in order to look deeper into the process. Recent research provided new variables such as SSWL (skin surface water loss) WHC (water holding capacity) WAV (water accumulation velocity) and WA (water accumulation) reflecting further understanding on the complex nature of the occurring processes. In this perspective, the authors propose the use of specifically designed descriptive models and demonstrate its applicability potential to the quantitative analysis of skin water changes.

Theoretical (Material and Methods). Epidermal capacitance (Corneometer CM820) and TEWL (Tewameter TM210) data profiles following a topical intervention on skin surface lead to the construction of a compartmental system analysis in order to obtain a mathematical characterisation of the events occurring. A 1st order mathematical model was constructed and tested on various groups of data, to confirm its applicability

Discussion and Conclusions. The authors demonstrated that the proposed mathematical models, describing the whole cutaneous structure involved in water balance, are suitable to be applied to the obtained experimental data, providing more accurate and precise indicators on the occurring events. These can be applied to each variable involved in water dynamic behaviour characterisation, namely TEWL and epidermal capacitance. This way, kinetic description of each variables allows a precise evaluation of the mass of water involved in the process, or to characterise individual "barrier" integrity, while regarding epidermal capacitance maximal hydration capacity or maximal "embedding" capacity can also be precisely evaluated and compared.

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Study on the effects of short-time hydration induced by topical polimeric gels on in vivo skin biomechanics

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Introducion O/W emulsions containing humectants and moisturising agents are normally incorporated to re-establish, or, to help to maintain SC emoliency and its global rheological properties. This study investigates the influence of three different polymeric gels (Merquat -cream 1, Gafquat-cream 2 and Acacia-cream 4) on the biological effects of creams prepared with a non-ionic surfactant (cetyl steraryl alcohol-12 mol EO and cetyl alcohol). A placebo containing no polymer (cream 3) was also investigated.

Material and Methods. Biological effects of the present formulations were assessed in human forearm skin (n=10, young healthy females,18-25 years old) through non-invasive technology (TEWL, epidermal "Capacitance", skin surface pH and skin biomechanics). Short-time experimental studies were made: *(a)* to obtain global information on the biological effects of the tested creams during 300 minutes; *(b)* to approach differences among formulations regarding water kinetics during 30 minutes. Glycerine (97% sol.) was employed as reference standard; *(c)* to prevent interference from skin lipids. *(d)* to disclose water balance changes under occlusive stress (POST-test : plastic occlusion stress test) *(e)* to assess the eventual changes involving skin biomechanical characteristics. Results were compared with a respective control area (anatomically equivalent). Descriptive statistics, ANOVA and paired t-student test was performed and a 95% confidence level adopted.

Results and Conclusion: Analysis on the overall biological effects of the in vivo tested formulations were discrete. Nevertheless the methodological procedures chosen allowed to identify positive results regarding skin water dynamics expressed in terms of capacitance and TEWL changes, and also regarding the biomechanical indicators used to assess these properties. Nevertheless this preliminary results may find other expression following the repetitive (long term) use of these substances, which is currently being investigated.