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PHARMACOKINETIC STUDY OF A CONTINUOUS-COMBINED ESTRADIOL VALERATE(2MG) /DIENOGEST (3MG) PRODUCT AFTER SINGLE AND REPEATED ORAL ADMINISTRATIONS IN SIXTEEN POST-MENOPAUSAL HEALTHY WOMEN

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The aim of the study is to compare the pharmacokinetic parameters after single and repeated oral administrations of a new continuous-combined hormone replacement drug containing estradiol valerate 2 mg and dienogest 3 mg in sixteen post-menopausal women.

It was an open study composed of one single oral administration period, followed by a seven day wash-out period, then a three 28-day cycle multiple dose administration period. Plasma samples were collected from 0 (pre-dose) until 72 hours after single dose and on day 28 of cycle 3. Estradiol, free and total estrone were measured by GC/MS. The limit of quantification was 10 $pg.ml^{-1}$ for estradiol and free estrone, and 0.10 $ng.ml^{-1}$ for total estrone. Dienogest was measured by RIA. The limit of quantification was $1ng.ml^{-1}$. Fifteen post-menopausal women completed the study.

This study has shown that under the conditions of the study, single and repeated administration by oral route of new combination preparation of estradiol valerate 2 mg and dienogest 3 mg, the clinical tolerability was good and no relevant changes in laboratory parameters were observed. It can also be concluded that after multiple oral dosing of the new combination preparation of estradiol valerate 2 mg and dienogest 3 mg there is a significant accumulation of dienogest, estradiol, free and total estrone, based on C_{max} and $AUC_{0\text{-}24h}$. This accumulation is in the range of the theoretical accumulation calculated from the single dose results.

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EFFECTS OF H2-RECEPTOR ANTAGONISTS CIMITIDINE, RANITIDINE AND FAMOTIDINE ON PSYCHOMOTOR PERFORMANCE IN HUMANS

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The H2-receptor antagonists are commonly used drugs in the treatment of peptic ulcer disease. In a double-blind, balanced and randomised study, the effects of oral cimitidine 400 mg, ranitidine 150 mg, famotidine 20 mg and identical placebo on psychomotor performance were investigated in 32 healthy young volunteers. Volunteers were randomly divided into 4 groups each of 8 subjects. Parameters of psychomotor performance (choice reaction time CRT, recognition reaction time RRT, Movement reaction time MRT and critical flicker-fusion frequency CFF) were measured before therapy and hourly afterward for 3 hours. Results were analysed using ANOVA test which showed that all treatments produced no significant change in all tested parameters. In conclusion, single oral doses of cimitidine (400 mg), ranitidine (150 mg) and famotidine (20 mg) did not alter significantly the sensorimotor performance as indicated by CRT, RRT & MRT nor the arousal state as indicated by CFF in young healthy volunteers.

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EVALUATION OF BINDING CAPACITY OF CISPLATIN AND ALBUMIN USING ANALBUMINEMIC RATS

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Cisplatin (CDDP) has been believed to have a strong and irreversible protein-binding capacity. We evaluated the binding capacity of CDDP and albumin using analbuminemic rats (NAR rats) and normal rats (Wister rats).

(1) Two, 5, and 10 μg/ml of CDDP serum, extracted from NAR or Wister rats, were made, and their non-protein-binding platinum (free platinum: F-Pt) was measured by atomic absorption spectrophotometry. The protein-binding ratios of CDDP in the serum of which contained 2, 5, and 10 μg/ml of CDDP were 69, 56, and 64 %, respectively, for the NAR rats, and 52, 52, and 56 %, respectively, for the Wister rats.

(2) Five, 10, and 20 mg/kg of CDDP was administered intravenously to NAR and Wister rats (male, Ca 300 g of weight), and total platinum (T-Pt) in the serum was measured at 2, 5, 10, 20, 30 min and 1, 2, 3, 4, 5, and 6 hr, while F-Pt was measured at 6 hr. The disappearance profiles of T-Pt in serum after CDDP administration to both NAR and Wister rats were similar; for example, after 20 mg/kg of CDDP administration, the maximal T-Pt in the serum of NAR and Wister rats was 67.3 (NAR rats) and 56.6 μg/ml (Wister rats) at 2 min, and the minimal T-Pt in serum was 4.8 (NAR rats) and 5.8 μg/ml (Wister rats) at 6 hr, while F-Pt in serum at 6 hs was 0.86 (NAR rats) and 1.54 μg/ml(Wister rats).

The results indicated that CDDP seemed to bind not only to albumin in serum.

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EXPERIMENTS FOR THE POSSIBILITY OF RELEASING CISPLATIN FROM PROTEIN *IN VITRO*

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Cisplatin (CDDP) has been believed to bind to protein strongly and irreversibly. We examined a possibility of releasing protein-bound cisplatin *in vitro*.

(1) The binding ratio of CDDP to α_1-acid glycoprotein (α_1-GP) or albumin was calculated. CDDP solutions at the concentration of 5 and 10 μg/ml were made containing 75 mg/dl of α_1-GP or 4.5 g/dl of albumin. Non-protein-binding platinum (free platinum: F-Pt) in the solutions was measured by atomic absorption spectrophotometry, and it was calculated that 34% (CDDP: 5.0 μg/ml) and 27% (CDDP: 10 μg/ml) of CDDP bound to α_1-GP, and 57% (CDDP: 5.0 μg/ml) and 66% (CDDP: 10.0 μg/ml) of CDDP bound to albumin.

(2) An equiliburium dialysis experiment was done with cells (10 ml for each) separated by a dialysis membrane. One cell was filled with CDDP (10 μg/ml) serum (extracted from Wister rats) and another cell was diluted with deionized water at 2 ml/min. Total platinum (T-Pt) in the CDDP serum was measured at 0, 0.5, 1, 3, 5, and 8 hr after the dilution, and F-Pt was measured at 24 hr. All the diluted deionized water was stored between each serum sampling points, and F-Pt was measured. The maximal concentration of T-Pt in serum was 9.5 μg/ml at 0 h, and the T-Pt decreased to 5.2, 2.4, and 2.2 μg/ml at 1, 8, and 24 hs, respectively. The maximal concentration of F-Pt in deionized water was 7.7 μg/ml during 0.5 to 1hr and decreased to 0.5 and 0.6 μg/ml from 3-5 and 8-24 hs, respectively. Ninety-eight percent of CDDP was removed from the CDDP serum to diluted deionized water until 24 hr.

These results indicated the co-existence of CDDP with α_1-GP or albumin, and that both protein-binding CDDP and non-protein-binding CDDP existed in the solutions; i.e. not all the CDDP bound to albumin or α_1-GP, and protein-binding CDDP released CDDP *in vitro*.