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Pharmacokinetics of MEN-11420, a new tachykinin NK-2 receptor antagonist, in the rat after intravenous administration.

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MEN 11420 (c{[Asn(2-desoxy-2-AcNH-β-D-Glc)-Asp-Trp-Phe-Dap-Leu](2β-5β)}) is a tachykinin NK-2 receptor antagonist which is presently under clinical development. The pharmacokinetics of MEN 11420 was investigated in the rat after a single i.v. administration of 14C-MEN 11420 (0.3 mg/kg; 44.1 μCi/kg). The levels of cold compounds were determined in plasma using a specific HPLC method whith fluorimetric detector, while total radioactivity levels wee measured in plasma and blood by beta counter. The total radioactivity excretion was also measured in urine and faeces. Levels of radioactivity in plasma and in blood lasted for 96 hours after administration with terminal half-lives of 35.4 and 41.7 for plasma and blood respectively. The concentrations of total radioactivity in plasma were higher than in blood (the blood to plasma ratio was in the range 0.48-0.99). The half-life of cold MEN 11420 was 0.6 hours, the volume of distribution was 812 ml/kg and the plasma clearance was 923 ml/h*1/Kg. After 96 hours the total radioactivity recovery in the urine and faeces was approximately 71 % and 23 % of the administered radioactivity respectively. Most of the excretion of total radioactivity in urine and faeces had occurred in the first 24 hours of collection.

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ISOLATION AND IDENTIFICATION OF THE MAJOR URINARY METABOLITE OF N-VINYL-2-PYRROLIDINONE FROM THE CONSCIOUS RAT

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N-vinyl-2-pyrrolidinone (NVP) is an exocyclic vinyl lactam compound which is present in small amounts as a contaminant in the polymeric materials it is used to produce. Resent studies in our laboratories have shown that when NVP was administered as an i.v. infusion to conscious rats, the pharmacokinetic profile of NVP showed evidence of an induction process for the elimination of this compound. The isolation and identification of the major urinary metabolite of NVP was then undertaken in order to provide some information on the enzyme system(s) involved in this elimination. Male Sprague-Dawley rats were administered an i.v. infusion of NVP (1.7 mg/hr for 6 hr) containing either [^{14}C]-NVP (1.0 μCi) or non-radiolabeled NVP. Urine was collected for 6 hours post infusion and was lyophilized, extracted, and injected onto a reverse-phase HPLC. Using the radioactive urine as a marker, the major metabolite was collected from the HPLC, lyophilized, and concentrated. Preliminary ^{13}C-NMR and GC/MS data, showed a compound with a molecular wt. of 145 and the lactam ring of NVP unchanged. Thus, a synthetic procedure, using 2-pyrrolidinone and glycoaldehyde dimer, was able to produce the target molecule, N-(1,2-ethanediol)-2-pyrrolidinone. Both the synthetic compound and the metabolite showed the same retention time and fragmentation pattern from a GC/MS system. Thus showing that the major urinary metabolite of NVP was N-(1,2-ethanediol)-2-pyrrolidinone.

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AN OPEN TWO-WAY CROSS-OVER STUDY TO COMPARE THE BIOAVAILABILITY OF TWO FLUOXETINE FORMULATIONS AFTER SINGLE ORAL DOSE ADMINISTRATION IN 24 HEALTHY VOLUNTEERS

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Fluoxetine is a bicyclic derivate of phenylpropylamine. It is the most widely used selective serotonin (5-hydroxytryptamine ; 5-HT) reuptake inhibitor (SSRI). It is prescribed for a variety of psychopathological conditions including mood and eating disorders, obsessive-compulsive disorders, depression in the elderly and dysthemia. The aim of the study was to compare the relative bioavailability of fluoxetine and norfluoxetine from a new 20 mg fluoxetine capsule, the test formulation developed by EURO-LABOR SA, versus a reference caspule from Lilly Portugal, after a single oral administration of 40 mg fluoxetine.

The study was designed as an open two-way cross-over study. Each subject received both treatments in two different periods separated by a 90-day wash-out period. Plasma samples were collected from predose up to 1008 hours after dosing. Fluoxetine and its metabolite norfluoxetine were measured by LC-MS. The limit of quantification was 0.25 ng.ml^{-1} for both compound. Twenty-two subjects completed the study (10 males and 12 females)

Under the conditions of the study, the clinical and biological tolerability was good and similar for both formulations. It is concluded from this study that after single oral administration of 40 mg fluoxetine, the new capsule developed by EURO-LABOR SA and the reference capsule are bioequivalent in terms of rate and extent of absorption for fluoxetine and its main metabolite norfluoxetine.

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PHARMACOKINETIC STUDY OF A CONTINUOUS-COMBINED ESTRADIOL VALERATE(2MG) /DIENOGEST (2MG) 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 of a new continuous-combined hormone replacement drug containing estradiol valerate 2 mg and dienogest 2 mg after single and repeated oral administrations in 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 with negative chemical ionization mode.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, the clinical was good and no relevant changes in laboratory parameters were observed. It can also be concluded that the pharmacokinetic of dienogest are linear and not time dependant. There is a significant accumulation of estradiol and free estrone higher than that expected whereas for total estrone the accumulation is in the range of the theoretical accumulation calculated from the single dose results. The discrepancy between the results may be explained by the high variability observed with estradiol and estrone.