responsible organ in the distribution of this drug. The slope of the integration plot was linear up to 5 min after its iv administration. The CLuptake value for IH–901 was thus calculated as 0.262 ml/min/g liver. Furthermore, we determined the CLbiliary by measuring the plasma concentration, bile concentration and liver concentration, after its iv infusion at the infusion rate of 40–400 ug/min/kg. Both the plasma and the bile concentration of IH–901 were reached at steady–state at 45 min (5 times of 1/2) after its iv infusion. The CLbiliary value for IH–901 was 0.85 ml/min/g liver. The liver concentration of IH–901 was higher by 23 times than that of plasma at steady–state. In conclusion, IH–901 was mainly distributed in the liver, followed by being excreted into the bile as an intact form. The mechanism by which IH–901 uptakes into hepatocytes requires further in vitro studies such as isolated hepatocytes and cultured hepatocytes.

[PE2–11] [ 10/18/2002 (Fri) 13:30 – 16:30 / Hall C ]

New Analytical Method of Cyclosporine A in Human Serum by High–performance Liquid Chromatography/Diode Array Detector and Its Application to Pharmacokinetics of Cyclosporine A in Human Volunteers

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A simple, specific and sensitive method for the determination of cyclosporine A (CsA) in human serum has been developed by a high performance liquid chromatography/diode array detector (DAD) and applied to pharmacokinetic study of CsA. This method involves the use of solid phase extraction procedure following rapid protein precipitation with zinc sulphate from 1 ml of human serum, using a disposable C18 extraction cartridge. Two different kinds of HPLC column (Xterra RP18 (2.1 x 150 mm, 5pm) vs. Symmetry 300 (3.9 x 150 mm, 5 pm)) and mobile phases (acetonitrile/H2O (65:35, v/v%) vs. acetonitrile–methanol:H2O (50:15:35, v/v/v%)) were used for comparison of peak areas and linearity of CsA and CsD. Effects of pressure setting of a vacuum manifold on cumulative peak areas of CsA and CsD were compared. As a result, Xterra RP18 column, low pressure (4–9 inch Hg), and acetonitrile/H2O (62/38, v/v%) as mobile phase were selected for the assay. CsA and CsD showed good resolutions in this conditions and no significant interfering peaks were observed. The detection limit is less than 50 ng/ml. A good linearity (r>0.9986) was obtained in the range of 50–500 ng/ml CsA. Intra–day accuracy and precision (CV%) were 94.3–113.3% and 4.3–10.1% and inter–day accuracy and precision were 85.8–110.8% and 6.3–15.5%, respectively. The developed method was applied on the pharmacokinetic study of CsA after oral administration of CsA (200 mg) to 8 healthy human volunteers. The principal pharmacokinetic parameters resulted in 602.5 ± 250.9 ng/hr/ml of AUC0–8hrr. 270.0 ± 82.7 ng/ml of Cmax. 1.69 ± 0.26 hr of Tmax. 0.4627 ± 0.2331 hr−1 of Ke. and 1.88 ± 0.99 hr of 1/2.

[PE2–12] [ 10/18/2002 (Fri) 13:30 – 16:30 / Hall C ]

In vivo kinetics and biodistribution of a HIV–1 DNA vaccine after administration in mice

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The present study evaluates the pharmacokinetics and tissue distribution of GX–12, a multiple plasmid DNA vaccine for the treatment of HIV–1 infection. PCR analysis after i.v. injection in mice showed that plasmid DNA was rapidly degraded in blood with a half–life of 1.34 min and was no longer detectable at 90 min post–injection. Plasmid DNA concentration also rapidly declined at the injection site after i.m. injection, with less than 1% of the initial concentration remaining at 90 min post–injection. However, sub–picogram levels (per mg tissue) were occasionally detected until 14 days post–injection. The ratios of the individual plasmids remained approximately constant at the injection site until 90 min post–injection. Plasmid DNA levels in various organs other than the injection site peaked at 90 min post–injection but was not detected after 8 h. The rapid in vivo degradation of GX–12 and low persistence in nontarget tissues suggest that the risks of potential gene–related toxicities by GX–