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One-Month Oral Toxicity Studies of A Protease Inhibitor (ABT-987) in Rats and Dogs. C. Yang, B. Gemzik, P. Ewing, M. Pratt, M. Friedman, P. Cusick, R. Krasula and R. Patterson. Drug Safety Evaluation, Abbott Laboratories, Abbott Park, IL 60064, USA

ABT-987, an orally active inhibitor of the HIV-1 protease, was developed as an antiviral agent. The purpose of the present studies was to evaluate the toxicologic and pathologic effects of ABT-987 when administered orally to rats and dogs for one month. A two to four-week recovery period was included in the study design to assess the reversibility of any adverse effects. Twice daily dosing was used to maximize exposure to the drug. The dosages were 30, 100, 300 or 1000 mg/kg bid for rats and 20, 50 or 150 mg/kg bid for dogs. Loss of body weight, decreased activity, decreased food consumption, emaciation, weakness, dehydration, emesis, excessive salivation and diarrhea were observed in dogs that received 150 mg/kg bid. One male dog at this dosage level was euthanized in moribund condition on Day 22. As a result of toxicity, the 150 mg/kg bid dosage in the dog study was lowered to 100 mg/kg bid on Day 17. Liver was identified as a target organ in both rats and dogs. The hepatic changes in rats included elevated ALT, AST, GGT and total bilirubin and histopathologic changes (multinucleated hepatocytes and single cell necrosis). The hepatic findings seen in dogs included elevated ALT, AST, ALP, GGT and total bilirubin as well as histopathologic changes (pericholangitis, fatty change, necrosis, biliary necrosis and biliary hyperplasia). Diffuse hypertrophy and cytoplasmic granularity of retinal pigment epithelium were found in the eyes of rats. Subacute gastritis with multifocal grandular necrosis were the changes found in the stomach of rats. The changes in eyes and stomach were limited to rats only. Membrane-bound inclusions were detected by electron microscopy in hepatocytes of rats and dogs, and in renal distal tubular epithelium and retinal pigment epithelium of rats. In rats, the changes in stomach were reversible, but the effects on liver and eyes were not totally reversible after a two-week recovery period. The hepatic changes seen in dogs were partially reversible after a four-week recovery period. Based on these studies, the no-toxic-effect plasma drug exposure ($AUC_{0\text{-}24\ hr}$) in rats was less than 6 mcg.hr/ml and in dogs was considered to be approximately 44 mcg.hr/ml.

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Chemoimmunotherapy(CI) by Thiophenoyl Urea(TUR) & Nonvirion antigen vaccine (NVA) for AIDS patients. A.Hollinshead, G.Wash.U.Med.Ctr., Washington D. C., USA.

TUR: Several purine and pyrimidine analogues and sulfur containing compounds affect certain host cells in such a way as to inhibit or prevent virus entry or multiplication, some by competitive inhibition; of these compounds, four showed protection in mice infected with poliovirus or influenza virus, but a later development of resistance to each of the three nucleic acid base analogues was demonstrated (1-5). The fourth compound, thiophenoyl urea (TUR), was tested against HIV in vitro and showed a good inhibitory ratio. TUR was administered orally to two late stage cancer patients, mixed as 0.03 to 0.04% of a semi liquid diet food, TID for three weeks, with no side effects. NVA:Using methods tested for other diseases (6,7) early nonstructural HIV components were extracted using the separated cell & nuclear membranes from HIV infected cells harvested four hrs after infection and stored less than one week at -75degr.C. (We discovered previously that early viral components which do not become a part of the structure of the mature virus may disappear if frozen too long) Membranes were gently sonicated over ice in neutral phosphate buffered saline, centrifuged and the supernate separated by Sephadex G 200, and the second peak eluates, which contained nonvirion antigens(NVA) were concentrated. In a specific lymphocyte(from HIV patient) stimulation assay, a titration effect was observed. Emulsification of 150 mcg protein/0.1 ml NVA with 0.1 ml incomplete Freund's adjuvant was used as vaccine, administered slowly intradermally once per month for three months to an HIV positive patient. Cell mediated immune responses but no toxicity reactions were observed during the course of six months after the first immunization. At six months the patient became HIV seronegative. CI:Two AIDS patients received TUR for three weeks, followed by NVA vaccine once per month for three months. Both were still sick at three months, with no sign of improvement. At six months, one patient showed a vast improvement and the other patient did not improve until about nine months. Both are alive and free of disease two yrs.post CI, suggesting further studies by other investigators.