Wellbutrin in Volunteer Studies - - Kinetics and Dose Proportionality of Bupropion and its Metabolites.

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Wellbutrin (bupropion•HCl), a novel antidepressant in current clinical use, was evaluated in two pharmacokinetic, steady-state studies. Bupropion (B), and its 3 basic metabolites, hydroxy-*t*-butyl-bupropion (HB), *erythro*-hydro-bupropion (EB), and *threo*-hydro-bupropion (TB) plasma concentrations were determined by a high pressure liquid chromatographic method at several time points on the fourteenth day of each dosing regimen. Based on mean AUC and Cmax ratios from 22 male subjects, dose proportionality was observed between 100 and 150 mg t.i.d. Mean $AUC_{0\rightarrow6}$ ratios were 1.38 for B, 1.46 for HB, 1.54 for EB, and 1.42 for TB at 150 mg compared to 100 mg. Corresponding ratios for Cmax were 1.35, 1.49, 1.69, and 1.49, respectively, for the 4 compounds while Cmin ratios were 1.41, 1.45, 1.39, and 1.38, respectively. Fluctuation index ratios averaged 0.99, 1.21, 1.46, and 1.27 for the 4 compounds, respectively. Mean Tmax values at 100 vs. 150 mg were 1.5 and 1.5 hr for B, 2.8 and 3.4 hr for HB, 2.9 and 3.8 hr for EB, and 3.1 and 3.5 hr for TB. Half- lives were found to be 21 hr for B, 20 hr for HB, 33 hr for EB, and 37 hr for TB. In a second steady-state study in 14 subjects, bioequivalence parameters were compared at 150 mg b.i.d. vs. 100 mg t.i.d. Mean $AUC_{0\rightarrow24}$ ratios for the two dosing regimens were 0.98 for B, 0.95 for HB, 0.98 for EB, and 1.00 for TB, and Cmax ratios were 1.20, 1.07, 1.02, and 1.04, respectively. Corresponding ratios for Cmin were 0.98, 0.92, 0.94, and 0.97, respectively, for these 4 entities, while fluctuation index ratios averaged 1.26, 1.42, 1.24, and 1.26, respectively. Thus, 150 mg b.i.d and 100 mg t.i.d. yield equivalent AUC values, however, the mean Cmax for bupropion was 20% greater with b.i.d. dosing.

A NOVEL COGNITIVE ENHANCING SUBSTANCE GVS-111

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Design of piracetam peptide analogues was proposed as a new approach to the creation of cognitive enchancers (Gudasheva et al, 1985). Dipeptides containing pyroglutamic acid with various natural amino acids were shown to be able to restore cognition damaged by a number of noxious influences in doses 0.001-1.0 mg/kg (Ostrovskaya et al, 1987, Gudasheva et al, 1988). Recently we showed antiamnestic effects in acyl prolyl containing dipeptides, in particular in phenylacetylprolyl derivatives . GVS-111 was chosen as one of the most active substances of this series. It was studied in the passive avoidance paradigm in rats.The substance was demonstrated to be able to facilitate acquisition per se. Administered before testing it facilitated retrieval processes as well. GVS-111 attenuated the amnestic effect of electroshock, scopolamine & proline cethylester (lypophylic prodrug of proline, designed by Skoldinov et al.). GVS-111 increased the degree of acute habituation of exploratory behavior in grouped (n= 10) mice without effect on baseline locomotion .GVS-111 showed all above listed mnemotropic effects in doses 0,1-1.0 mg/kg (i.p),LD 50 for mice is 5000 mg/kg. GVS-111 possesses much higher biological stability than TRH & AVP.GVS -111 preserved effectiveness in peroral administration.These studies demonstrate that GVS-111may encance memory under range of condition.

EFFECTS OF NOVEL SUBSTITUTED PROLYL-DIPEPTIDE, GVS-111, ON BENZODIAZEPINE WITHDRAWAL IN RATS.

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Biologically active n-acylprolyl-dipeptides were described by us recently . GVS-111 was shown to be one of the more active substances of this series.
The effects of the GVS-111 on diazepam withdrawal were studied in male Wistar rats treated for 21 days with diazepam 4 mg/kg/day (i.p.).The withdrawal syndrome was assessed 24 hours after the last diazepam injection. Withdrawal signs recorded were: anxiogenic - like behavior in the elevated plus maze (EPM), suppression of exploratory behavior in the open field and the intensification of seizures, precipitated by pentylentetrazol. Two regimes of administration of GVS-111 (0.5 mg/kg,i.p) were used: a) during withdrawal 15 minutes before testing in above mentioned paradigms, b)during last 7 days of diazepam administration and during withdrawal.GVS-111 was demonstrated to be able to attenuate the degree of anxiogenic state in EPM, dramatically increasing time spent in open arms. GVS-111 decreased the degree of pentylentetrazol precipitated seizures. There was no significant effects upon the activity in open field. All these effects of GVS-111 were more pronounced in case of long-term administration . These findings suggest that GVS-111 may have potential as a treatment for withdrawal from sedative / hypnotics.

VOLUNTARY ALCOHOL CONSUMPTION DURING PREGNANCY IN FAWN-HOODED RATS INDUCES BEHAVIORAL DEFICITS IN OFFSPRING

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Most previous studies on the effects of prenatal alcohol exposure have involved the forced intake of alcohol in rats which do not voluntarily drink alcohol. Because the Fawn-Hooded rats voluntarily drink substantial quantities of alcohol (6-8 g/kg), the present study examined the consequences of such high voluntary intake of alcohol on the offspring. Female rats were screened for alcohol intake and then mated with males. The males were removed 5 days later and two females were presented with two bottles - one containing tap water and the other alcohol (10%, v/v) throughout pregnancy and until the offspring were 10 days old. Another two females received tap water throughout the experiment. A battery of behavioral tests was conducted when the rats reached 70 days of age. The offspring of alcohol-exposed mothers tended to be hyperactive in the open field, especially for grooming. The alcohol-exposed offspring also spent less time in the open arms of an elevated plus maze, suggesting a high level of anxiety, and were more immobile in the forced swim test, suggesting a high level of depression. These findings are comparable to those found previously in Russia by Trofimov and Smolnikova following forced alcohol exposure. Further studies of prenatally alcohol-exposed Fawn-Hooded rats may be informative.