of occipital areas, increase of coherence in alpha rhythm and decrease of coherence in delta rhythm was found, and for EEG of frontal areas decrease of coherence in a wide range of frequencies (tetha, alpha, beta 1 bands). This type of EEG changes was more characteristic for a test dose of noopept than for a course therapy in both groups of patients. During course therapy group 1 was characterized by significant decrease of coherence in delta rhythm between occipital areas and tetha rhythm between frontal areas. In group 2, changes of interhemispheric coherence at the end of treatment were statistically nonsignificant.

Thus, noopept caused EEG changes typical for that induced by nootropic drugs which were more pronounced in the right hemisphere. EEG effects of noopept depended on the character of brain pathology and were more typical for those of nootropic drugs in vascular pathology than in posttraumatic disorders.

P.5.038 Clinical pharmacological study of the novel peptide nootropic drug noopept

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Noopept (N-phenylacetyl-L-prolylglycine ethyl ester), a novel original peptide drug with nootropic and neuroprotective activity, was developed at Zakusov Institute of Pharmacology. A standard clinical pharmacological study of noopept (with previous placebo control, using psychological, psychophysiological methods and EEG) was carried out on 40 patients with psychoorganic syndrome. All patients had organic asthenic disorders (emotional lability) of vascular and posttraumatic genesis (F06.60, F06.61). The test dose of noopept was 5 and 10 mg, and during the course treatment – 15 and 30 mg per day. Clinical trials lasted 28 days. It was shown that noopept doses of 15 and 30 mg per day relieved the main symptoms of organic disease: cerebroasthenic, hyperesthetic and sleep disturbances, vegetative dysfunctions as well as cognitive and dismnestic problems (attention, memory, efficacy of activity). Therapeutic effects of noopept were connected with mild stimulatory, anxiolytic, nootropic effects and vegetostabilization. The stimulatory effect differed from that of psychostimulators: it was not accompanied by anxiety, aggressiveness, sleep and vegetative disturbances. The medicine did not demonstrate real hypnotic effect, but clear positive normalizing influence on nocturnal sleep was revealed. The specific nootropic effect of noopept developed after a latent period, starting from the 3–4th week of therapy, which agrees with traditional dynamic characteristic of medicines with nootropic action. A positive effect in cognitive disorders was also observed (improvement of memory, attention, minimization of mistakes with interference, improvement of short memory). The most marked improvement was in attention (distribution, stability and volume), increase of complex sensomotor reactions, volume of short visual memory. The analysis of EEG showed general improvement in alpha-rhythm frequencies, decrease in delta-rhythm frequencies and increase in beta-rhythm in frontal and central parts of the brain.

It was established that noopept is an effective drug for the treatment of psychoorganic disorders with cerebroasthenic and cognitive disturbances. Equal therapeutic response was observed in patients of young and medium age with the course of 30 mg daily. With the course of 15 mg daily younger patients with psychoorganic syndrome of posttraumatic origin showed better results. The present study of noopept demonstrated that during therapy of asthenic disorders of organic nature the effect of the medicine is characterized by non-specific "fast" antiasthenic and anxiolytic effect, as well as by specific nootropic effect. The results obtained suggest that noopept could be employed in clinical practice as effective nootropic drug.

P.5.039 Experimental and clinical pharmacokinetics of noopept

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The present study was conducted with the purpose to examine experimental and clinical pharmacokinetics of a new dipeptide drug noopept (N-phenylacetyl-L-prolylglycine ethyl ester) possessing nootropic, anxiolytic and neuroprotective activities [1]. The experiments have been performed using high performance liquid chromatography technique. The results obtained from experimental pharmacokinetic studies showed noopept to be more resistant to the action of metabolizing enzyme systems as compared to naturally occurring neuropeptides. Noopept was determined in rat blood plasma independently of the route of administration for 25 min. Noopept was subjected to an intense biotransformation thus demonstrating rather low bioavailability. Pharmacokinetic investigation was carried out with two formulations for peroral usage: tablets (Technological Department of Zakusov State Institute of Pharmacology RAMS) and capsules (DVD Pharma Inc.,

USA). This study showed that capsules have no advantage over tablets neither in rate nor in extent of absorption. Pharmacokinetics studies in animals of different species and humans revealed significant interspecies differences: half-life time of noopept increased in the following order: rat < rabbit < human. These peculiarities could be attributed to different activity of biotransformation by enzymic systems. In view of obtained data, for the clinical trials the noopept dose of 10 mg was selected as the test dose, while the dose for course therapy was scheduled as 15 mg per day (5 mg × 3 times daily) throughout 28 days. The results of clinical pharmacokinetic investigation in patients with cognitive disorders of traumatic and vascular genesis showed that noopept was rapidly absorbed from the gastrointestinal tract, its concentration reached maximal level in the majority of patients 15 min after the test dose. Noopept was detected in patients' blood plasma throughout 45 min. Half elimination time was 22.05±14.37 min. In patients with vascular disorders this period was longer than that in subjects with craniocerebral trauma, and this should be taken into account in case of course therapy. Our previous experiments demonstrated that the metabolism of noopept has as a consequence the formation of cyclo-L-prolylglycine – cPG [2]. This cyclic dipeptide, possessing pronounced antiamnestic activity, was determined in blood plasma of rats up to 5–6 hours after noopept administration. It possible to suppose that not only the parent molecule of noopept, but its metabolite also contribute to clinical effects of this systemically active dipeptide.

References

[1] R.U. Ostrovskaya et al., 1999. Memory restoring and neuroprotective effects of the prolin-containing dipeptide, GVS-111, in a photochemical stroke model. Behav. Pharmacol. 5: 549–553.

[2] T.A. Gudasheva et al., 1997. The major metabolite of dipeptide piracetam analogue GVS-111 in rat brain and its similarity to endogenous neuropeptide cyclo-L-prolylglycine.Eur. J. Drug Metabol. Pharmacokinetics 3: 245–252.

P.5.040 Individualizing dosage regimens of antiepileptic drugs: Multiple Model (MM) adaptive control

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"Old" antiepileptic drugs (AEDs) have narrow therapeutic ranges of serum concentrations. Individual patient pharmacokinetic (PK) parameter values vary widely. General therapeutic ranges of AEDs cannot guarantee freedom from seizures, especially in special patient subpopulations (newborns, pregnancy, elderly, abnormal protein binding, renal or hepatic dysfunction). Individualized dosage can be done with therapeutic drug monitoring (TDM). However, serum concentrations alone, without software for modeling and adaptive dosage individualization is often ineffective. Selection of a specific individualized therapeutic goal, based on each individual patient's need for the AEDs, his/her previous response, and on clinical judgment of the acceptable risk of toxicity is most important for individualized dosing. We have used nonparametric (NP) population PK modeling, which permits MM design of individual regimens to achieve the selected patient-specific therapeutic goal with maximum precision (minimum weighted squared error), in the new MM-USCPACK software. We used a linear 1-compartment PK model to describe absorption, disposition, and elimination of old AEDs (postinduction behavior of carbamazepine, valproate, phenobarbital) and nonlinear PK models to describe the dose-dependent pharmacokinetics of phenytoin and the time-dependent autoinduction of carbamazepine. Probability densities of the NP population PK parameter distributions were estimated by the nonparametric NPEM method from routine TDM data (more than 800 patient files). Because MM regimens make optimal use of all information present in the nonparametric population distribution and are specificAlly designed to achieve target goals most precisely, they maximize efficacy and safety, and minimize toxicity. After beginning therapy, 47 AED patients were monitored both clinically and by TDM. MM-USCPACK helps plan initial regimens. It makes multiple predictions, instead of only one, of the future serum concentrations resulting from any candidate dosage regimen which is "given" to all the models (support points) in the NP population model discrete joint distribution. Further, the measured serum concentrations were used especially to make the Bayesian posterior individualized PK model. This model permitted optimal prediction of the time