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DISTRIBUTION TO THE BRAIN, PROTEIN BINDING AND LOG(P) OF 3'-FLUOROTHYMIDINE DERIVATIVES, A MICRODIALYSIS STUDY

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The aim of this study was to correlate hydrophobic parameters of a series of 3'-fluorothymidine derivatives (FTD) to plasma protein binding, and distribution over the blood-brain barrier in the rat. The hydrophobic property was determined as the partition coefficient (log P) in octanol-water, which was calculated from log P = log C_{oct} - log C_{aq} where C_{oct} is the concentration in the octanol phase and C_{aq} is the concentration in the aqueous phase. The microdialysis technique was used to study protein binding in human plasma (in vitro) and to sample the extracellular space of rats with microdialysis implanted into the striatum of the brain and the gastrocnemic muscle (in vivo) which we have previously shown reflects free plasma levels. The compounds were analyzed by high-performance liquid chromatography with UV-detection. The partition coefficients of the FTD varied from 0.22 to 0.84 while the partition coefficient of thymidine was 0.06. The protein binding of the FTD varied from 0 to 90 %. After s.c. administration (25 or 50 mg/kg) brain and muscle extracellular levels were not equal. Brain levels were 1/2 to 1/7 of peripheral (muscle) concentrations. Thus, the FTD are able to penetrate the blood-brain barrier in the rat and their concentrations in the brain can be monitored continuously by microdialysis. However, we were not able to demonstrate a linear relation between log P, protein binding and penetration to the brain.

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TOXICOLOGICAL RESEARCH ON MOPYRIDONE A NEW DRUG WITH ANTIVIRAL ACTIVITY.L.Tantcheva,A.S.Galabov,M.Behar,D.Sidzhakova,N.Runevski Institute of Physiology,Institute of Microbiology,Bulgarian Academy of Sciences (Sofia),Higher Medical School (Sofia and Plovdiv)

Mopyridone is a new chemotherapeutic with a strong antiviral effect and certain advantages over the chemotherapeutics known so far.The toxicological studies reveal its low oral and intraperitoneal toxicity in mice and rats.The 5 and 14 day administration of mopyridone(37.5 mg/kg p.o.)to male rats established a growing tendency to shortening of hexobarbital sleeping time,associated with moderate changes in the hepatic monooxygenase activity on the 15^{th} day,most pronounced for amidopyrin N-demethylase (by 37%) and less for benzphetamine N-demethylase(by 17%).Anilin hydroxylase activity was slightly diminished (by 18 and 16%resp.) No significant changes in the components of the cytochrome P-450 system were established- the content of cytochrome P-450 and b-5 and cytochrome C-reductase, both after 5 and 14 day mopyridone administration.