Abstract

Tacrine (1,2,3,4-tetrahydro-9-amino acridine) is clinically used in the treatment of Alzheimer’s disease. We have previously demonstrated that the drug penetrates into the brain via a saturable process in brain microdialysis and MBEC4 culture study, and then choline transport system was partially involved in that process. However, brain level of a drug is dependent on both influx (e.g., blood brain barrier penetration) and efflux [e.g., elimination from the cerebrospinal fluid (CSF) via choroids plexus] processes. However, efflux process for this drug from the brain has not been adequately studied previously. In this study, therefore, we have examined in vivo kinetics of elimination of tacrine from the cerebrospinal fluid to understand better the kinetics of tacrine in the brain. Sprague-Dawley rats (male, body weight 270-300g) were undergone a surgery involving catheterization of lateral ventricle (LV, drug administration) and cisterna magna (CM, CSF collection). Tacrine was administered via LV cannulae at the doses of 5, 25 or 125 µg (in 5 µl). CSF (15 µl/sample) was collected at pre-determined times via the CM cannulae. Tacrine level in the CSF sample was assessed by an HPLC assay for tacrine. Clearance and volume of distribution of tacrine was estimated from the temporal profiles by the standard moment analysis. In some cases, phenol red was included in the injection mixture (dose; 3.75 µg/rat) as a CSF volume marker. In all experimental condition, temporal profiles of tacrine concentration in the CSF were declined in a multi-exponential manner. Tacrine clearance from the CSF was 1.968 ± 0.257 ml/min for 5 µg dose. Since the reported bulk flow clearance ranges from 2-5 µl/min for the rat, tacrine appears to be eliminated from the CSF via mechanism(s) in addition to the bulk flow. Interestingly, apparent clearance for tacrine in CSF was decreased with dose (0.564 ± 0.269 ml/min for 25 µg dose, 0.210 ± 0.108...
ml/min for 125 µg dose), indicating that the elimination pathway, probably through the choroid plexus, the blood-CSF barrier, is saturable. Also choline inhibition study showed that tacrine apparent clearance decreased in 1.305 ± 0.108 ml/min when tacrine 5 µg dose administrated with choline. Tacrine is not likely to be metabolized in the brain and, thus, a saturable elimination from the CSF may represent a saturable efflux process for tacrine via choroid plexus.

Key words: Tacrine (1,2,3,4-tetrahydro-9-amino acridine), blood-brain barrier (BBB), choroid plexus (CP), cerebrospinal fluid (CSF), lateral ventricle, cisterna magna, HPLC