[S1-3] [10/17/2002 (Thurs) 11:30-11:50/Hall A]

High Throughput Screening System for Kinetics of Brain Influx

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Traditionally, kinetics of brain influx of drugs has been evaluated by a number of experimental techniques. Brain uptake index and in situ brain perfusion study have been used for the determination of the kinetics; However, these methods generally focus on the accuracy of the uptake rate into the brain rather than the speed of the determination. In addition, application of radiolabelled substrates (e.g., ^{14}C-labelled sucrose) further impedes the wide spread acceptance of these techniques for the application of high throughput screening system. Other experimental techniques, such as microdialysis study, have also been used for a more accurate determination of kinetics into and out of the brain. However, it is generally recognized that the technique requires much more rigorous surgical techniques and longer recovery time on the experimental animals than other previous techiques; Therefore, these techniques may not be directly applicable for the high throughput determination of brain influx of drugs. We have studied the possibility for the use of "integration plot analysis" in the high throughput determination of pharmacokinetics of brain uptake. Uptake kinetic scheme states that drug amount in the tissue at time t is directly proportional to the area under the plasma concentration vs. time curve up to time t assuming the efflux of drug from the brain is minimal (e.g., at early times). Therefore, by dividing the amount of drug in the brain at time t and the area under the curve upto the time t, one can obtain the estimation of brain uptake clearance.

We have noted that the throughput of the determination of brain uptake clearance may be increased based on in vivo high throughput estimation of area under the curve. As a result, two-point determination of brain uptake, rather than multiple determinations of drug concentration in the brain and the plasma. In addition, use of cassette dosing may further increase the throughput. We have applied this method for a number of model drugs (e.g.,

propranolol, ambroxol, theophylline, caffeine and KR-31378). When compared with the traditional integration plot analysis, we could enhance the productivity by 5 fold with the application of estimation of area by sample-pooling method. In addition, 20 fold increase in throughput was realized by the application of sampling pooling and cassette dosing technique.

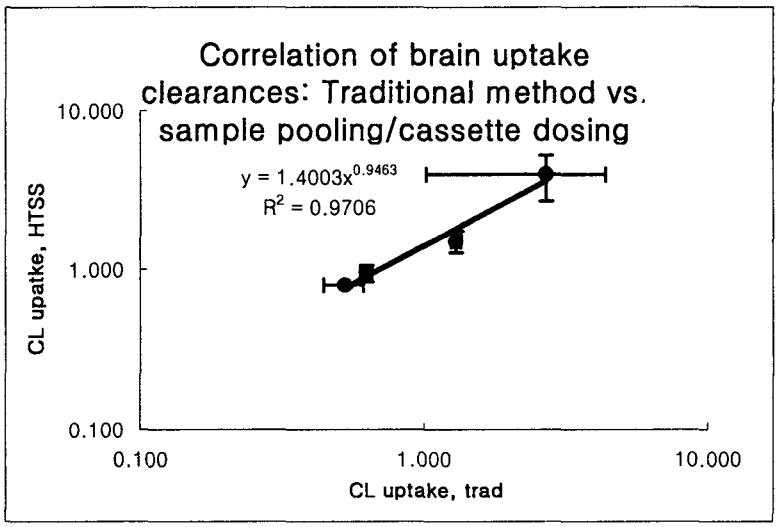

Figure 1. Correlation of brain uptake clearances: Traditional method vs. sample pooling/cassette dosing technique

The correlation of the conventional analysis vs. the high throughput method appear reasonable (i.e., correlation coefficient greater than 0.97), indicating that the high throughput method may be applicable in the fast and accurate determination of brain uptake clearance. Theoretical consideration indicates that CLuptake larger than approximately 0.0151 ml/min/rat may be evaluated in this increased throughput method.