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Concentration dependency of theophylline plasma protein binding

H. TAJERZADEH, S. DADASHZADEH* AND G. ROSTAMI*

*Department of Pharmaceutics, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran, P.O. Box 14155-6451 and *Department of Pharmaceutics, School of Pharmacy, Shaheed Beheshti University of Medical Sciences, Tehran, Iran, P.O. Box 14155-6153*

The plasma protein binding of drugs has been shown to have significant effects on numerous aspects of pharmacokinetics and pharmacodynamics (Wright et al 1996). For certain drugs saturable plasma protein binding may occur at therapeutic concentrations and is a well known cause of dose dependent pharmacokinetics (Lin 1994).

Theophylline, an effective bronchodilator agent, has been reported to have dose dependent pharmacokinetics which has been attributed to nonlinear elimination kinetics of the drug (Sarrazin et al 1980). This study was carried out to explore the possible concentration dependencey of theophylline plasma protein binding by using equilibrium dialysis method

Plasma was obtained from 24 healthy nonsmoking male subjects with average age of 25 ± 5 years. The subjects were asked to abstain from food and beverages containing methyl-xanthines for 48 hr before blood sampling. An apparatus with 12 cells was designed for doing equilibrium dialysis, the method was fast and reproducible without microbial growth and pH change. Pooled plasma (1 ml) spiked with a known concentration of drug was dialyzed against an equal volume of modified Krebs - Ringer bicarbonate buffer at pH 7.4. The range of concentrations employed was from 5 μg/ml to 160 μg/ml. Since the pH of plasma samples rises on standing due to co_2 release and theophylline protein binding is pH dependent (Shaw et al 1982), the samples were adjusted to pH 7.4 just before the equilibrium dialysis separation. Dialysis cells were rotated at 10 rpm in a water bath maintained at 37 °C. The dialysis membrane was $AN_{69}S$ (Haspal, pore size = 29 A°) and the equilibrium time was 2.5 hr. Theophylline concentration in plasma was measured by high pressure liquid chromatography (HPLC).

The results showed that the percentage of protein bound drug was significantly ($p<0.001$) reduced from 42.8 to 32.8 with increasing of theophylline concentration in the range of concentration studied , but was not changed within the usual therapeutic range of concentration (10-20 μg/ml). The results indicate that theophylline plasma protein binding is concentration dependent, but this does not occur in the usual therapeutic range.

The effect of plasma pH on theophylline protein binding was also studied. The percentage of protein bound drug was lower at pH 7.4 compared to pH 8.

Table I. Effect of theophylline concentration on percent of drug bound to plasma proteins.

Concentration (μg/ml)	% Bound* (mean ± SD)
5	42.8 ± 2.80
10	41.3 ± 2.41
15	39.8 ± 2.99
25	38.8 ± 2.53
35	37.8 ± 2.97
55	37.2 ± 3.38
70	36.5 ± 3.45
80	36.1 ± 3.13
100	35.4 ± 3.78
120	34.5 ± 2.96
140	33.6 ± 2.76
160	32.4 ± 2.54

*Each is the average of determinations on each of six pools of plasma from healthy adults

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