# INFLUENCE OF LIPOPHILICITY ON THE RENAL CLEARANCE OF A SERIES OF 5-ETHYL-5-ALKYLBARBITURIC ACIDS IN THE ISOLATED PERFUSED RAT KIDNEY PREPARATION

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Most structure-activity studies relate the dose administered to the response produced at a predetermined time. Although Hansch and Fujita (1964) acknowledged the importance of the movement of externally applied 'drug' substance on its concentration at the receptor and the ensuing biological response, the pharmacokinetic events were not considered separately. Yet, the pharmacokinetics of a drug can markedly influence the temporal changes in biological response.

Few attempts have been made at defining the overall relationship between molecular structure and pharmacokinetics (Seydel et al 1980). Renal excretion is an important determinant of elimination for many drugs. While an increase of lipophilicity is generally associated with a lower renal clearance, precise quantitative information is lacking within a molecular series of compounds. The present study was designed to gain such information.

The renal clearance of a series of 5-ethyl-5-alkylbarbituric acids was studied in an isolated perfused rat kidney preparation. The compounds were analysed using post-column derivatization h.p.l.c. (Toon & Rowland 1981). The compounds were administered as a multicomponent mixture,no effect of one on the renal clearance of the other was observed,implying linearity of their renal excretion.Functional characteristics of the isolated kidney were not influenced by the mixture.

As shown in Fig.1, the renal clearance decreased progressively, from 0.51±0.11 (mean±SD) of the glomerular filtration rate, with increasing molecular weight and lipophilicity, as measured by the hplc index, $R_Q$ (Toon and Rowland 1980).

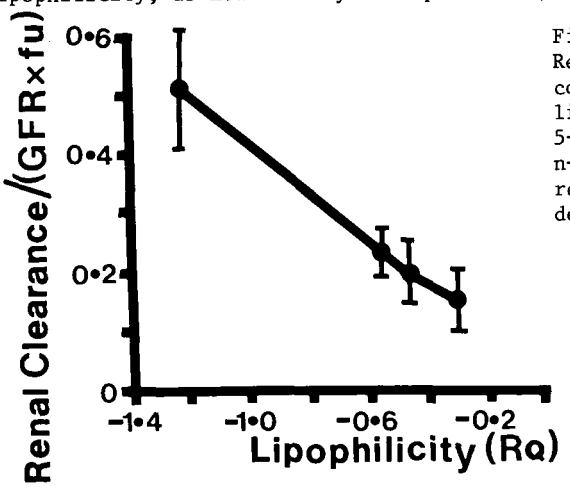


Fig.1
Relationship between the corrected renal clearance and lipophilicity of four 5-ethyl-5-alkylbarbituric acids. (H to n-butyl analogue). Each point represents the mean (± standard deviation) of eight preparations.

All the compounds are filtered and reabsorbed,including 5-ethylbarbituric acid, the lowest and most popular homologue of the series. The degree of reabsorption increases with lipophilicity and by the n-butyl homologue equilibrium is achieved between the compound in urine and that in perfusate. Variability in urine flow (0.02 - 0.27 ml $min^{-1}$ ) and urine pH (6.8 - 7.3) was observed,and in the range encountered,the former was found to be an important determinant of renal clearance.

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