PLASMA PROTEIN BINDING OF PHENOPERIDINE

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Phenoperidine is a narcotic analgesic approximately 50 times more potent than pethidine. It is sometimes used as an adjuvant during the maintenance of general anaesthesia and in the management of patients who require prolonged assisted ventilation. Previous studies on surgical patients and volunteers have shown that the drug is eliminated bi-exponentially and predominantly by metabolism (Milne et al 1980).

In the present communication, the plasma protein binding of phenoperidine and the components in plasma responsible for binding the drug are investigated. Since only free, unbound drug can diffuse from the blood stream into other compartments of the body, the interaction of a drug with plasma proteins may limit its availability to the receptor sites and to the elimination systems of the body. The binding of phenoperidine was studied in 13 subjects (aged 22 to 50 years) given 15 µg/kg phenoperidine hydrochloride i.v. Venous blood samples collected by venipuncture were spun down to yield plasma. Aliquots of plasma (1 ml) were dialysed in Teflon cells across a Visking membrane against an equal volume of pH 7.4 isotonic phosphate buffer at 37°C for 3hr., equilibrium being achieved in this time. The concentration of phenoperidine in the plasma and buffer compartments of each cell and in the original plasma samples was determined by a nitrogen-selective GLC procedure (Chan et al 1981). For the determination of the number of binding sites involved in phenoperidine attachment to plasma proteins, 1 ml aliquots of fresh plasma loaded with a range of drug concentrations (25-400 ng/ml) were dialysed against phosphate buffer at 37°C for 3hr. The binding of phenoperidine to isolated human serum fractions, albumin (HSA) and α_1-acid glycoprotein (α_1-AGP), was also determined by equilibrium dialysis. In the case of HSA, a range of albumin concentrations (1.0 - 4.5 g/100ml) spiked with 50ng/ml phenoperidine in phosphate buffer was used and for α_1-AGP, 50ng/ml phenperidine was added to a range of α_1-AGP concentrations (20-120mg/100ml) in phosphate buffer. In all experiments after equilibrium had been reached, the drug concentration in the buffer compartment was equal to the concentration of free drug, Cu, whereas the concentration in the plasma compartment was equal to the sum of the concentrations of both free and bound drug, Cu + Cb = C. Then the per cent free drug was Cu/C x 100%.

The mean percentage of phenoperidine bound to plasma proteins for the 13 subjects was 78.83 $\pm$ 0.80% (mean $\pm$ S.E.M.). Although the drug concentration in each sample varied, the average initial level of phenoperidine in the circulation was 43.7 $\pm$ 2.8 ng/ml. This correlated well with the results from the in vitro experiment on the effect of drug plasma concentration on binding to plasma proteins which showed 78.56% drug bound at a plasma concentration of 50ng/ml. A Scatchard plot r/D versus r for the range of phenoperidine concentrations (25-400ng/ml), where r is the number of moles of drug bound per mole of protein and D is the concentration of unbound drug, resulted in a curved line, an indication that two possible binding sites are responsible for the plasma protein binding of phenoperidine. It was demonstrated that phenoperidine bound to both albumin (20.5 - 28.2%) and α_1-AGP (20.2 - 54.1%) over the normal protein concentration ranges.

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Chan, K. et al (1981) J. Chromatogr. 203 (1): 213-218

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