Date :

Title : PLASMA BINDING OF PANCURONIUM - EFFECT OF AGE, SEX AND DISEASE

Authors : Margaret Wood, M.B.Ch.B., F.F.A.R.C.S., William J. Stone, M.D. and Alastair J.J. Wood, M.B.Ch.B., M.R.C.P.

Affiliation: Departments of Anesthesiology, Pharmacology and Nephrology, Vanderbilt University, Nashville, Tennessee 37232

Introduction. It is well recognized that plasma drug binding has a profound effect on drug disposition and elimination. In addition, it is the unbound or free fraction of total drug in plasma that is available for binding to receptor sites and thus for exerting pharmacological effect. Although early workers have suggested that pancuronium does not bind to any great extent to plasma proteins, Thompson[1] reported high in vitro binding to isolated protein preparations and calculated that at clinical concentrations 87% would be bound, leaving less than 13% of the serum concentration unbound or free. However binding in isolated protein solutions does not reflect physiological changes in human plasma binding. The binding of pancuronium in human plasma has not previously been defined, and controversy exists as to the extent of plasma binding. The purpose of the present study was therefore to determine the extent of pancuronium binding in human plasma and, in addition, to investigate the effects ofage, sex and renal disease on pancuronium binding. The determination of the binding of pancuronium in the newborn is of particular interest since differences in the protein binding of other drugs in the neonate have been observed[2] and reduced binding might explain, at least in part, the altered sensitivity of the neonate to the non-depolarizing relaxants. In addition the use of oral contraceptives has been shown to effect plasma binding of some drugs. Informed consent and institutional approval for the study were obtained.

Methods. Pancuronium binding was measured by equilibrium dialysis in a dialysis cell, 1 ml of plasma being dialyzed against 1 ml of phosphate buffer pH 7.4 containing 55 ng/ml ^{3}H pancuronium (Specific Activity 3.6 mci/mg). The cells were rotated at 15 rpm at 37°C for 4 hours. Samples from the plasma and buffer were added to scintillation fluid and counted. The free fraction of pancuronium was then calculated as the concentration of radioactive pancuronium in the buffer (dialysate) divided by the concentration in plasma. Blood samples were obtained from 9 mothers (aged 19-35 years; 39-41 weeks of gestation) and their newborns at delivery. Umbilical cord blood was collected at delivery and a simultaneous venous sample was obtained from the mother. In addition, binding studies were also performed on plasma samples obained from 10 males (aged 20-32 years) and 10 non-pregnant female subjects (20-31 years), and 10 females (aged 20-26 years) receiving oral contraceptives. Binding studies were also carried out on blood samples obtained from 8 (mean age 50.7 ± 3.4) patients with severe renal impairment, not on hemodialysis, with creatinine clearances less than 15 mls/minute.

Results. The results are shown in the table. The free fraction of pancuronium was 93.2% (±1.6) in male subjects and 88.9% (±2.5) in adult non-pregnant female subjects, indicating that pancuronium is not extensively bound in plasma. There was no significant difference between the plasma binding of pancuronium in male, female whether on oral contraceptives or not, pregnant or newborn subjects studied.

TABLE: The binding of pancuronium in mother, newborn, male and non-pregnant female subjects, and in patients with renal disease.

Subject	N	% Free Pancuronium
Newborn	9	91.0 (±1.8)
Mother	9	89.0 (±1.3)
Adult Male	10	93.2 (±1.6)
Adult Nonpregnant Female	10	88.9 (±2.5)
Adult Female - Oral Contraceptive	10	87.1 (±0.6)
Renal Disease	8	90.7 (±2.1)

N = number of subjects. Results are expressed as mean ± standard error of the mean.

Conclusions. We have thus defined the extent of pancuronium plasma binding, and conclude that the plasma binding of pancuronium is very low, the free fraction being 93.2 (±1.6) and 88.9 (±2.5) in adult male and female subjects, respectively. There was also no significant difference between the plasma binding of pancuronium in any of the groups studied indicating that age, sex, oral contraceptive use and renal disease do not influence the plasma binding of pancuronium.

References.

[1]Thompson JM: Pancuronium binding by serum proteins. Anaesthesia 31:219-227, 1976.

[2]Krasner J, Giacoia GP, Yaffe S: Drug-protein binding in the newborn infant. Ann N Y Acad Sci 226:101-114, 1973.