Title : EFFECTS OF AGE ON PLASMA PROTEIN BINDING OF SUFENTANIL

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Binding to plasma proteins is an important factor affecting the drug disposition as well as the duration and intensity of drug action. It was recently shown that fentanyl derivatives as sufentanil are bound to α1-acid glycoprotein (α1-AGP) (1). The plasma concentration of α1-AGP is lower in the newborn than in the adult (2) and increase with age (3). This study was undertaken to investigate the effects of age and α1-AGP concentration on the plasma protein binding of sufentanil.

METHODS : This study was approved by our human ethics committee and informed consent was obtained from the parents of the children and from the adults studied. Eighteen newborn infants at term (38-41 weeks gestation), ten infants (1 to 12 months), eleven children (3 to 10 years) and eleven adults (25 to 50 years) were studied. None of the patients were taking any medication or had disease known to modify concentration of α1-AGP or albumin. With the exception of newborn infants venous blood samples (5 ml) were drawn from a peripheral vein during the preoperative period. Neonatal blood samples (5 ml) were drawn form the maternal end of the umbilical cord immediatly after birth but before the placenta was delivered. Plasma was obtained by centrifugation and frozen at -20°C until analysis. Protein binding was determined in vitro by equilibrium dialysis by dialyzing through a Dianorm system 1.0 ml of plasma against 1.0 ml of phosphate buffer (pH : 7.4). The buffer contained 1 ng/ml of tritiated sufentanil (specific activity : 19.2 Ci/mmol). The cells were rotated for 4 hours in a bath at 37°C, previous studies having shown that equilibrium dialysis was obtained within 2-3 hours. The drug concentrations in the plasma and buffer were determined by radioactivity measurements. The free fraction was calculated as the concentration of drug in the buffer divided by the concentration in the plasma. Albumin and α1-AGP concentrations were determined in duplicate by radial-immunodiffusion (Behring, Inc.). The correlation between protein concentration and free fraction of sufentanil was tested by the significance of the r value determined by least-squares linear regression. Differences between groups were tested by analysis of variance and Newman-Keuls test. A value of $p<0.05$ was considered to be significant, all the results are expressed as mean $\pm$ S.D.

RESULTS : They are summarized in Table 1. Binding to the membrane was less than 3 % and could be neglected. The albumin plasma concentration was significantly higher in adults than in the other age groups ($p<0.05$). The free fraction of sufentanil decreased significantly with age ($p<0.001$) whereas the α1-AGP plasma concentration significantly increased with age ($p<0.001$). The free fraction of sufentanil was lower in the newborn ($p<0.01$) than in the other age groups. The free fraction was also significantly lower in infants than in children ($p<0.01$) or in adults ($p<0.01$). The free fraction of sufentanil was inversely correlated with the α1-AGP concentration ($r=-0.73$; $p<0.001$). The free fraction of sufentanil was weakly correlated with the albumin plasma concentration ($r=-0.30$; $p<0.05$).

DISCUSSION : Sufentanil is highly bound to plasma proteins, albumin accounting for a small proportion of total plasma binding whereas α1-AGP accounts for a large proportion of plasma binding (1). This could explain the strong correlation between the free fraction of sufentanil and the α1-AGP concentration. The lower level of α1-AGP in newborns and infants probably accounts for the decrease in protein binding of sufentanil in these age groups. These results are similar to the results obtained in previous studies with other basic drugs such as propranolol or lidocaine (2). The variation of the α1-AGP plasma concentration could be an important factor in determining the amount of plasma binding of basic drugs (local anesthetics or fentanyl derivatives such as sufentanil) in pediatric patients.

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TABLE 1 : Mean $\pm$ S.D.

	Sufentanil (% free)	Alb. (g/l)	α1 GPA (g/l)
Newborn	19 + 2,7	38 $\pm$ 3	0,34 $\pm$ 0,07
Infants	11,5 $\pm$ 3,2	37 $\pm$ 4	0,58 $\pm$ 0,11
Children	8,1 $\pm$ 1,4	41 $\pm$ 3	0,70 $\pm$ 0,19
Adults	7,8 $\pm$ 1,5	44 $\pm$ 3	0,74 $\pm$ 0,12