TITLE : EFFECTS OF INCREASED ALPHA-1-ACID GLYCOPROTEIN IN CANCER PATIENTS ON PHARMACOKINETICS OF ALFENTANIL

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The concentration of alpha-1-acid glycoprotein (AAG) is an important determinant in the protein binding of fentanyl derivatives such as sufentanil and alfentanil **(1,2)**. Previous reports have shown a close relationship between the plasma levels of AAG and the free fraction of these drugs **(1,2)**. Elevation of AAG in cancer patients has been reported **(3)**, therefore we compared alfentanil pharmacokinetics in a reference group of cancer patients and in a group of cancer patients with an increased plasma level of AAG.

METHODS

Nineteen patients (26 to 60 years old) with colorectal cancer scheduled for intra abdominal surgery were studied. The plasma level of AAG was less than 1.2 g/l in group A (n=10) whereas it was above 1.2 g/l in group B (n=9). The protocol was approved by the local ethical committee and informed consent was obtained from the patients. None had significant impairment of renal or hepatic function. They were premedicated with oral flunitrazepam (1 mg). Anesthesia was induced with thiopental (7 mg/kg) and pancuronium (0,1 mg/kg). After intubation anesthesia was maintained with nitrous oxide (60 % in oxygen) and enflurane administered at a concentration of 1.5 %. A bolus of alfentanil (50 ug/kg) was slowly injected intravenously over 2 min. Venous blood samples were drawn a few minutes before administration and 3, 5, 7, 10, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360 and 480 min. after injection of alfentanil. After centrifugation plasma was stored at -20°C until assay. Plasma albumin was measured from the electrophoretic pattern and AAG was determined with a laser nephelometry technique (BEHRING, INC.). Alfentanil concentrations were determined in duplicate by a radioimmunoassay with a sensitivity of 0.1 ng/ml and a coefficient of variation of 3.7 % over the concentrations studied. Data were fitted to a biexponential equation interpreted as a two-compartment open model using a nonlinear least-squares regression. Plasma protein binding was determined by equilibrium dialysis between plasma and buffer containing tritiated alfentanil. The following parameters were calculated : the half-lives of distribution ($T_{\frac{1}{2}}\alpha$) and elimination ($T_{\frac{1}{2}}\beta$), the apparent volume of distribution at steady state (Vdss) and the plasma clearance (Cl). A two tailed Mann-Whitney U test was used to evaluate the differences between the two groups, All the results are expressed as mean $\pm$ S.D.

RESULTS

Age and weight of the patients did not differ between the two groups. The plasma albumin concentration was within the normal range in all the patients. The mean plasma AAP concentration was 0.8 $\pm$ 0.3 g/l in group A and 2.0 $\pm$ 0.6 in group B. The pharmacokinetic parameters are summarized in table 1. The Vdss was significantly lower in patients with an increased level of AAG (281 $\pm$ 45 ml/kg) than in patients with a normal level of AAG (372 $\pm$ 57 ml/kg, $p < 0.01$). AAG. The Vdss of alfentanil correlated negatively with AAG plasma concentration ($r = -0.58$; $p < 0.01$).

DISCUSSION

Cancer patients with increased plasma level of AAG show a 24 % reduction of the Vdss of alfentanil. This could be due to the increased protein binding in these patients since it has been previously shown that the free fraction of fentanyl derivatives was inversely correlated with the plasma level of AAG (1,2). Furthermore there is a significant correlation between the plasma level of AAG and the Vdss of alfentanil. The alfentanil hepatic extraction ratio being intermediate and close to 0.3-0.4 (4), the slightly decreased alfentanil clearance in group B could be partly due to an increased plasma protein binding because less drug is available for elimination. However the elimination half-life was slightly but not significantly increased which is usual for a drug with a low to intermediate extraction ratio because changes in Vdss and Cl tend to cancel one another out.

In conclusion changes in AAG plasma level modify pharmacokinetic parameters, and contribute to individual variations in alfentanil pharmacokinetics.

REFERENCES

1. MEULDERMANS WE, HURKMANS RM, HEYKANTS JJ : Arch Int Pharmacodyn Ther **257** : 4-19, 1982.
2. MEISTELMAN C, BENHAMOU D et al : Anesthesiology **67** : A158, 1987.
3. CHU CY, LAI LT, POKALA HP : JNCI **68** : 75-79, 1982.
4. BOWER S, HULL CJ : Br J Anaesth **54** : 871-877, 1982.

TABLE 1 : Pharmacokinetics paramaters, mean $\pm$ S.D.

	Group A (AAG < 1.2 g/l)	Group B (AAG > 1.2 g/l)	P
$T_{\frac{1}{2}}\alpha$(min.)	5.9 $\pm$ 2.4	4.8 $\pm$ 1.7	N.S
$T_{\frac{1}{2}}\beta$(min.)	104 $\pm$ 14	120 $\pm$ 39	N.S.
Vdss (ml/kg)	372 $\pm$ 57	281 $\pm$ 45	< 0.01
Cl (ml/min/kg)	3.15 $\pm$ 0.63	2.21 $\pm$ 1.37	< 0.05
Alfentanil free fraction (%)	7.2 $\pm$ 2.3	4.2 $\pm$ 1.2	< 0.01