The effect of the concentration of plasma protein on the recovery from anaesthesia induced by equipotent doses (UD$_{95}$) of thiopentone and Althesin was studied in 48 patients. The recovery time (RT) was plotted against the concentrations of total plasma proteins (TPP) and albumin (Al). A small decrease in TPP concentration from normal range affected the recovery time minimally; a small decrease in TPP concentration from a low basal value markedly increased the recovery time with both agents. A large decrease in TPP concentration increased the recovery time from thiopentone and Althesin markedly.

Following a single i.v. administration of an anaesthetic agent recovery from anaesthesia depends on the redistribution of the agent from brain to high capacity tissues (Price et al., 1960), and on renal clearance and biodegradation. Furthermore, the activity and fate of anaesthetics are intimately linked to the degree of binding to plasma proteins, since this determines the amount of drug available to the tissues.

The quantity of the anaesthetic bound to proteins is dependent on many factors: pH of blood (Goldbaum and Smith, 1954), the age of the patient (Pruitt and Dayton, 1971), and the presence of other drugs or metabolites which may displace the anaesthetic drug from binding sites (Dundee and Richards, 1954; Odel, 1959; Anton, 1960, 1961; Lasser, Elizondo-Martel and Granke, 1963; Paghini et al., 1971; Gillette, 1973; Ghoneim et al., 1976).

In clinical practice a decrease in the concentrations of the plasma proteins is often associated with liver or kidney disease. Since these two organs are involved also in the elimination of the anaesthetic, the part played by the concentration of protein per se on the recovery time from anaesthesia is difficult to evaluate.

In this study the effect of the concentrations of the total plasma proteins (TPP) and albumin (Al) on the recovery time (RT) has been investigated in man using two anaesthetic agents: thiopentone and Althesin, which have protein-binding fractions of 0.75 (Goldbaum and Smith, 1954) and 0.4 (Jones, 1972) respectively.

PATIENTS AND METHODS

Two groups of 24 patients, (20–50 yr) of both sexes, were studied. Informed consent was obtained from each patient.

The patients were allocated in random fashion to receive thiopentone or Althesin for surgical dressings requiring very short and light anaesthesia. In all patients BUN concentration, bilirubin concentration, liver and kidney function, acid–base balance, e.g., arterial pressure and circulatory time were physiological. No patient had received any drug which interacted with protein binding or anaesthetic activity during the period before operation.

Premedication (atropine 0.007 mg kg$^{-1}$) was administered before the induction of anaesthesia. The equipotent doses required to produce unconsciousness in 95% of patients (UD$_{95}$) were used (thiopentone 2.619 mg kg$^{-1}$, Althesin 0.284 mg kg$^{-1}$) (Stella, Torri and Castiglioni, 1979) and the technique of injection standardized as proposed by Clarke and colleagues (1968). The UD$_{95}$ was injected over 30 s to an antecubital vein following active hyperaemia obtained by inflation of a sphygmomanometer cuff to 300 mm Hg for 2 min. During the injection the patient was asked to count aloud and when this stopped he was asked to respond to a simple command: "open your eyes".

If a response was not obtained the patient was stated to be asleep, and from this moment until the
The patient was able to respond to the same command—the recovery time.

The few patients that remained awake after receiving the UD were excluded from the study.

The relationship between recovery time and total plasma proteins concentration (RT/TPP) and recovery time and albumin concentration (RT/Al) were determined by the method of least squares. Both linear and exponential correlations were determined to find the best fit for the experimental data.

**RESULTS**

The two groups of patients were comparable for age and sex. In the thiopentone group the mean age was 42.08 ± 8.29 and in the Althesin group 38.42 ± 10.25 yr ($t = 1.62$; n.s.). The first group included 11 males and 13 females; the second group 10 males and 14 females ($\chi^2 = 0.08$; n.s.).

Figure 1 shows the correlations RT/TPP and RT/Al for thiopentone and Althesin. The best fits of the RT/TPP and RT/Al relationships are represented by the exponential correlations shown.

**FIG. 1.** Relationship between recovery time and total plasma protein or albumin concentrations for thiopentone and Althesin.
Using UD$_{95}$, at a normal value of TPP of 70 g litre$^{-1}$, the recovery time was shorter with Althesin (76 s) than with thiopentone (103 s).

However, it appeared that the lower the TPP concentration the longer the recovery time with both anaesthetics. Because of the particular shape of the relationships the same change in TPP concentration affected the recovery time to a different extent at normal and low values of TPP. A small change in TPP concentration within the normal range did not affect the recovery time significantly, whereas at very low values of TPP a further small decrease may increase the recovery time markedly.

When the changes in TPP concentration were large, it was observed that, despite their different protein binding fraction, the two anaesthetics had similar effects. In fact, when the concentration of TPP was decreased to 50 g litre$^{-1}$ recovery time was three times greater than that observed at TPP value of 70 g litre$^{-1}$ for both agents.

The statistical analysis of the correlation coefficients ($r$) of the RT/TPP and RT/AI relationships indicates that the best correlation was found for RT/AI both for thiopentone ($t = 5.58$; $P < 0.001$) and Althesin ($t = 4.64$; $P < 0.001$).

**DISCUSSION**

Many previous studies have investigated the displacement of i.v. anaesthetics from their binding sites by other drugs and the consequent increase in anaesthetic activity. In the present study an increase in anaesthetic activity was observed as a result of a decrease in the concentration of TPP and of the subsequent increase in the amount of free drug.

Since we used two anaesthetics which differ in their protein binding fractions, different effects were expected. The results indicate that the changes in recovery time were similar with both anaesthetics when identical decreases in TPP concentration were considered. Since thiopentone is bound extensively to plasma proteins, and Althesin to a lesser extent, a similar decrease in TPP concentration results in a larger amount of free drug with thiopentone than with Althesin. Nevertheless, since Althesin has an anaesthetic potency 10 times greater than thiopentone (Stella, Torri and Castiglioni, 1979) this increases the clinical effect of the smaller increase in unbound drug. Thus, although in theory the action of an anaesthetic with a low protein-binding fraction should be affected little by changes in the concentration of TPP, in practice, this advantage may be counteracted by the high potency of the drug.

The best correlations pertained to the RT/AI relationship, a result which seems to confirm that albumin plays the most important role in binding anaesthetic agents. In spite of this we have stressed the correlation between RT/TPP because (1) albumin is not the only binding site for anaesthetics, as Althesin may be bound to other proteins such as lipoproteins or immunoglobulins (Jones, 1972); (2) usually every change in albumin concentration is associated with a proportional change in the concentration of TPP.

The use of the equipotent dose UD$_{95}$ allowed us to obtain comparable results from the two anaesthetics, to avoid total saturation of the protein binding sites, and to avoid large decreases in ventilation with consequent changes in arterial pH.

Significant changes in the concentrations of TPP or albumin must be considered important factors which affect the recovery time from anaesthesia. In clinical practice this effect must be considered following acute blood loss, in undernourished patients and when haemodilution techniques are used.

**REFERENCES**


CONCENTRATIONS DE PROTEINES DANS LE PLASMA ET REPRISE DE CONSCIENCE APRES UNE ANESTHESIE CHEZ L'HOMME

RESUME
Nous avons fait une etude couvrant 48 patients et portant sur l'effet qu'ont les concentrations de proteines dans le plasma sur la reprise de conscience, aprés une anesthesie induite par des doses a efficacite egale (UD_{95}) de thiopentone et d'Althesine. Le temps necessaire a la reprise de conscience (RT) a ete porte sur un graphique de meme que les concentrations totales de proteines dans le plasma (TPP) et l'albumine (Al). Une petite diminution dans les concentrations de TPP par rapport a la plage normale n'a affecte que d'une maniere minimale le temps necessaire a la reprise de conscience; alors que toute faible diminution dans les concentrations de TPP par rapport a une faible valeur de base a fait augmenter tres sensiblement le temps necessaire a la recuperation, dans le cas de ces deux agents. Toute importante diminution dans les concentrations de TPP a fait tres nettement augmenter le temps necessaire a la reprise de conscience aprés le thiopentone et l'Althesine.

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PLASMAEIWEISSKONZENTRATION UND ERHOLUNG VON DER ANÄSTHESIE BEIM MENSCHEN

ZUSAMMENFASSUNG

CONCENTRACION PROTEINICA EN EL PLASMA Y RECUPERACION DE LA ANESTESIA POR PARTE DEL HOMBRE

SUMARIO
Se estudió el efecto que en 48 pacientes ejerció la concentración proteínica del plasma en lo tocante a la recuperación de la anestesia inducida por dosis equipotentes (UD_{95}) de tiopentona y de Althesina. El tiempo de recuperación (RT) se trazó contra las concentraciones totales de proteína (TPP) y de albúmina (Al) en el plasma. Una pequeña disminución de la TPP con relación a la gama normal afectó minimamente al tiempo de recuperación; una pequeña disminución de la concentración de TPP a partir de un valor basal bajo aumentó notablemente el tiempo de recuperación con ambos agentes. Una gran disminución en la concentración de TPP aumentó notablemente el tiempo de la recuperación para la tiopentona y la Althesina.