

CLINICAL SIGNIFICANCE OF THIOPENTONE BINDING TO HAEMOGLOBIN AND PLASMA PROTEIN

R. EDWARDS AND F. R. ELLIS

SUMMARY

The minimum dose of thiopentone required to induce anaesthesia was determined by giving thiopentone incrementally until verbal counting and eyelash reflexes were abolished. Males required 2.75 mg/kg (± 0.11 SE) and females 2.16 mg/kg (± 0.10 SE) to abolish verbal counting. Thiopentone requirement correlated positively with haemoglobin concentration ($P < 0.001$) but not with plasma albumin, α_1 globulin, total globulin or A/G ratio. The presence of sickle-cell haemoglobins did not influence thiopentone requirements. It is suggested that this result may have clinical importance.

From personal experiences it is commonly believed that the amount of thiopentone required for induction of anaesthesia in West Africans is higher than for Europeans. In countries where severe debilitating diseases associated with anaemia and hypoproteinaemia are common, this generalization may be dangerous. It is recognized that haemoglobin levels in West Africans are often low (ffoulkes-Crabbe, 1971) and such anaemia may result from malaria, hookworm and other intestinal parasites, bilharzia, malnutrition and sickle-cell states.

As a proportion of thiopentone is known to be protein-bound (Goldbaum and Smith, 1954) it could be anticipated that thiopentone requirements would be altered by the presence of anaemia, hypoproteinaemia and disturbed albumin/globulin ratio, all of which are interrelated. Although the greatest proportion of the bound thiopentone is with albumin, other proteins are present in the blood in greater amounts.

We have investigated the thiopentone requirements to induce anaesthesia in a Ghanaian population in which haemoglobin and other blood proteins are commonly deranged to see if there was any correlation between protein levels and thiopentone requirements.

METHODS

Adult patients of both sexes awaiting non-emergency surgery were studied; we excluded patients who were grossly obese or who were having drug therapy and any patient suffering from acute illness.

After clinical assessment, all patients were weighed and venous blood was taken for haemoglobin, haemoglobin electrophoresis and plasma protein analysis. Haemoglobin was estimated colorimetrically

using the cyan-methaemoglobin method, abnormal haemoglobins were detected using the paper and agar gel method, and plasma proteins were measured by the Biuret technique and by cellulose acetate electrophoresis.

Approximately 1 hour before induction each patient was given a standard premedication of pethidine 50 mg, promethazine 25 mg and atropine 0.6 mg intramuscularly.

In the operating theatre a needle was inserted into a vein in the antecubital fossa. After a short interval to allow venous circulation to return to normal following venous occlusion, the patient was instructed to commence counting aloud. Increments of 25 mg of 2.5% thiopentone were injected allowing 15 sec between each increment until the patient ceased verbal counting. The dose required was recorded. Thiopentone administration was continued until the eyelash reflex was abolished. The total requirement was recorded. The 15-sec time interval was chosen to approximate to one arm-brain circulation time and to enable the effect of individual increments and their cumulative effects to be assessed.

RESULTS

Eighty-two patients were investigated of which 40 were females with a mean age of 34.4 years (± 12.2 SD) and mean weight of 59.0 kg (± 12.8 SD) and

R. EDWARDS,* M.B.,B.S., F.F.A.R.C.S.; F. R. ELLIS,† PH.D., M.B.,CH.B., F.F.A.R.C.S.; Department of Anaesthesia, University of Ghana Medical School, Accra, Ghana.

Present addresses:

*Department of Anaesthesia, King's College Hospital, London.

†Department of Anaesthesia, University of Leeds.

42 were males with a mean age of 34.2 (± 11.9) and mean weight 59.4 kg (± 7.1).

The thiopentone requirement (mg/kg) to abolish verbal counting correlated positively with that required to abolish eyelash reflex ($r=0.82$; $P<0.0001$). In view of this correlation all the results which follow are assessed using the abolition of verbal counting as the criterion for induction of anaesthesia.

The frequency histograms for the dose of thiopentone for males and females are shown in figure 1.

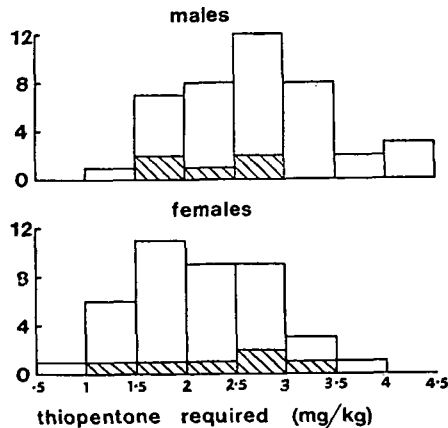


FIG. 1. Frequency histograms showing thiopentone requirements (mg/kg) to abolish verbal counting in males and females; cross-hatching indicates patients with sickle-cell haemoglobin.

TABLE I.

Correlation of thiopentone requirements against:	Correlation coefficients (r)		
	Males	Females	Males + Females
Haemoglobin concentration	0.33*	0.10	0.36**
Plasma albumin concentration	0.03	0.02	0.04
Total plasma globulin concentration	0.08	0.07	0.02
α_1 globulin concentration	0.01	0.03	0.10
A/G ratio	-0.03	-0.01	-0.02

* denotes significant correlation ($P<0.025$).

** denotes significant correlation ($P<0.001$).

The mean dose for males (2.75 mg/kg (± 0.11 SE)) was higher than that for females (2.16 mg/kg (± 0.10 SE)) and the difference was statistically significant ($P<0.001$). Eleven patients (15%) had abnormal haemoglobin of which 4 (5%) had HbAC and 7 (10%) had HbAS. These patients are indicated in figure 1 by cross-hatching. Thiopentone requirement for these patients did not differ significantly from the patients with normal haemoglobin.

Correlations between thiopentone requirements to abolish verbal counting and levels of proteins in the blood were determined using the method of least squares and the results are summarized in table I. It will be seen that the only significant correlations are with haemoglobin concentration in males and in males and females taken together. Figure 2 illustrates the correlation between haemoglobin concentration and thiopentone requirements for both males and females and shows the line of best fit ($r=0.36$, $P<0.001$).

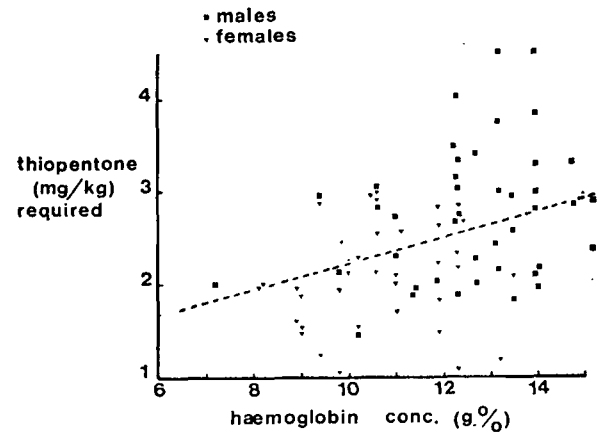


FIG. 2. Graph of thiopentone requirements (mg/kg) plotted against haemoglobin concentration (g/100 ml); males and females are indicated by different symbols; the regression line for males and females taken together is shown ($r=0.36$; $t=3.43$; $P<0.001$).

DISCUSSION

The greater thiopentone requirements in males, compared with females, although their respective mean ages and weights were indistinguishable, has been noted previously (Dundee, 1954). It is possible, however, that the marked difference in requirements found in the present study can be explained by the greater alcoholic intake of Ghanaian males compared with females.

A standard premedication was chosen for simplicity. It was fortuitous that the weights of the males and females were similar although the fat content of the females must have been greater. As there was a sex difference for thiopentone requirements, all the results were calculated separately for males and females allowing within-group correlations as well as the combined male and female results.

The results of the within-group correlations suggest that haemoglobin binds thiopentone in a clinically significant amount. It was surprising to find that the

levels of the plasma proteins, in particular albumin and α_1 globulin, did not influence thiopentone requirements for induction of anaesthesia, although in-vitro studies by others (Goldbaum and Smith, 1954) have demonstrated the contrary. It is interesting that Csögör and Kerek (1970) giving thiopentone slowly (1 ml of a 2.5% solution every 5 sec) to Europeans found that a mean dose of 4.42 mg/kg was required to abolish verbal counting. These workers demonstrated enhancement of thiopentone anaesthesia by pretreatment with sulphafurazole which they ascribed to competition for plasma binding sites.

If the thiopentone had not been given slowly and incrementally, thus allowing time for recirculation, the correlation of the thiopentone requirements could have been explained by a greater cardiac output and therefore more rapid equilibration in the brain of the anaemic patient. It is felt that the results cannot be explained by the changes in pH described by Waddell and Butler (1957). With a fall in pH, induced by respiratory depression, protein binding increases but to offset this, thiopentone is less dissociated and a given dose would be more effective.

In conclusion we feel that haemoglobin concentration has a greater influence than plasma protein levels on thiopentone requirements. The dose of thiopentone for anaesthesia in Ghanaians seems to fall within the expected range for Europeans but it would be interesting to make a direct comparison with a similar study conducted in a European country.

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SIGNIFICACION CLINIQUE DE LA FIXATION DU THIOPENTONE SUR L'HEMOGLOBINE ET LES PROTEINES PLASMATIQUES

SOMMAIRE

La dose minimale de thiopentone requise en vue d'induire une anesthésie, a été déterminée en administrant progressivement cet agent anesthésique jusqu'à ce que les malades interrompent une énumération de chiffres et que les réflexes oculo-palpébraux soient supprimés. Les individus du sexe masculin ont eu besoin d'une dose de 2,75 mg/kg ($\pm 0,11$ ES) de thiopentone et les sujets du sexe féminin, de 2,16 mg/kg ($\pm 0,10$ ES) pour que l'énumération de chiffres soit interrompue. Les quantités nécessaires en thiopentone ont présenté une corrélation positive avec la concentration en hémoglobine ($P < 0,001$), mais pas avec l'albumine, la α -globuline, la globuline totale plasmatique ou le rapport albumine/globuline. La présence d'hémoglobine provenant d'hématies falciformes n'a pas rendu nécessaire une modification des quantités de thiopentone administré. Il est suggéré que ces résultats puissent revêtir une certaine importance sur le plan clinique.

ÜBER DIE KLINISCHE BEDEUTUNG DER BINDUNG VON THIOPENTONE AN HAEMOGLOBIN UND PLASMAPROTEIN

ZUSAMMENFASSUNG

Die Minimaldosis von Thiopentone, welche zur Einleitung der Anaesthesia erforderlich ist, wurde bestimmt, indem solange Thiopentone verabreicht wurde, bis die Patienten aufhörten zu zählen und bis die Augenwimpernreflexe aufhörten. Männliche Patienten benötigten 2,75 mg/kg ($\pm 0,11$ SE), weibliche Patienten 2,16 mg/kg ($\pm 0,10$ SE), ehe sie zu zählen aufhörten. Die erforderliche Menge an Thiopentone korrelierte positiv mit der Haemoglobinkonzentration ($P < 0,001$), jedoch nicht mit dem Plasmaalbumin, alpha 1 globulin, Gesamtglobulin oder dem Albumin/Globulin Quotienten. Das Vorliegen von Sichelzellhaemoglobin hatte keinen Einfluß auf den Bedarf an Thiopentone. Es wird darauf hingewiesen, daß diese Untersuchungsergebnisse klinische Bedeutung haben könnten.

SIGNIFICACION CLINICA DE LA TIOPENTONA LIGADA A LA HEMOGLOBINA Y PROTEINAS PLASMATICAS

RESUMEN

Administrando tiopentona progresivamente, contando verbalmente y hasta que se producía la abolición de los reflejos palpebrales, se determinó la mínima dosis de tiopentona necesaria para inducir la anestesia. Los hombres requerían 2,75 mg/kg ($\pm 0,11$ SE) y las mujeres 2,16 mg/kg ($\pm 0,10$ SE) para abolir el recuento verbal. Las cantidades requeridas de tiopentona estaban en correlación positiva con la concentración de hemoglobina ($P < 0,001$), pero no con la albúmina plasmática, globulina α_1 , globulina total o relación de A/G. La presencia de células falciformes no tenía influencia sobre la cantidad de tiopentona requerida. Se cree que este resultado puede tener importancia clínica.