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ALTHESIN, KETAMINE AND METHOHEXITONE AT PRESSURE—DURATION OF ACTION OF A SINGLE I.V. DOSE

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SUMMARY

General anaesthesia for emergency surgery in a pressurized habitat is likely to involve the use of i.v. agents. The anaesthetic property of such agents is known to be antagonized by pressure, but the effect on their duration of action is not easily predicted. The recovery of mice from a single i.v. dose of Althesin, ketamine or methohexitone was estimated by their ability to remain upright in a rotating drum. At 35 atm abs. duration of action was significantly reduced: $P<0.05$ for Althesin; $P<0.01$ for ketamine and methohexitone. A number of animals in each group, however, displayed recovery times that were comparable to control. The convulsion rate with methohexitone was 60% at 35 atm abs., whereas at 1 atm abs. it was 20%. The clinical implications of these findings are discussed.

Since pressure reversal of anaesthesia was first demonstrated (Johnson, Brown and Marsland, 1942) much research has been carried out, primarily with the aim of explaining the phenomenon and using it as a tool to elucidate the mechanism of action of anaesthetic agents. The most recent hypothesis of anaesthetic action has been formulated using this technique (Halsey, Wardley-Smith and Green, 1978). Research into the pressure–anaesthetic interaction, however, has another and perhaps more practical application.

The past 10 years have seen a move towards the use of saturation diving for industrial purposes. With this technique a team of divers live for periods of about 3 weeks in a pressurized habitat. Decompression takes several days. Thus it is possible that emergency surgery for intercurrent illness or trauma may have to be carried out under pressure. To date there has been only one documented case of major surgery in a saturation system (Carter and Goldsmith, 1970), but with as many as 1000 divers working in the North Sea alone, one may expect the problem at any time, and an appropriate anaesthetic would have to be administered. Because of the special problems of such an environment, i.v. anaesthesia would seem to be the method of choice (Ross et al., 1979).

At present it is believed that pressure will reverse the narcotic effect of both gaseous and i.v. agents. There is an approximately linear relationship within the pressure range presently experienced by man although at higher pressure the effect is less predictable. The degree of reversal obtained at any one pressure depends on the agent used. As regards the i.v. agents, we know, from work in animals (Halsey, Wardley-Smith and Green, 1978) and in man (Dundas, 1979), that a greater dose is required to maintain a given level of anaesthesia at pressure. From this it could be assumed that awakening would occur at a higher plasma concentration of the agent used and that, if all other factors are equal, the effect of a single dose would last for a shorter time at pressure. However, pressure may affect the circulation (Matsuda et al., 1975) and protien binding (Miller and Wilson, 1978) and pharmacokinetics may be altered. If the plasma half-life of a drug is increased, the duration of action of an anaesthetic may also be increased even though the effective plasma concentration is greater (fig. 1, point C). We have studied the duration of action of three commonly used i.v. anaesthetic agents at pressure.

METHODS

Althesin, ketamine and methohexitone were studied using groups of adult female mice (table I).

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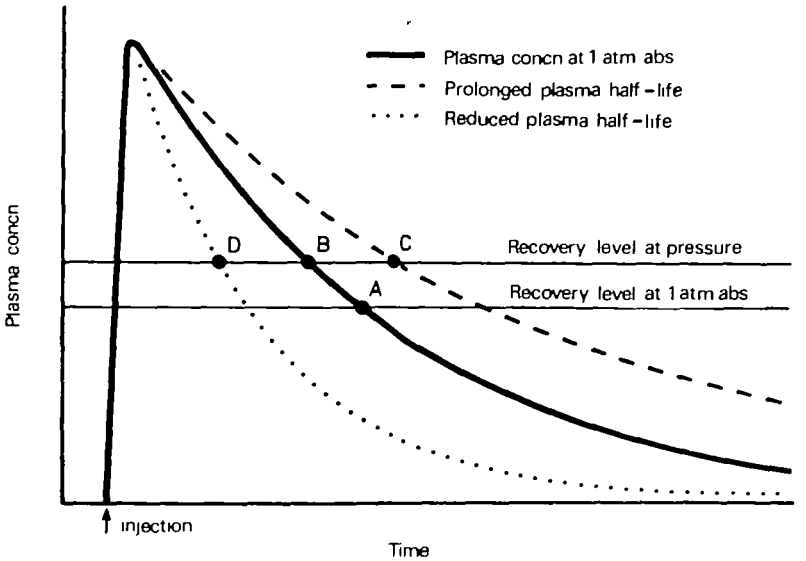

FIG. 1. Hypothetical plasma concentrations after a single injection of i.v. anaesthetic agent. Point A = recovery at 1 atm abs. Points B, C and D = recovery at pressure if plasma half-life unchanged (B), prolonged (C) or reduced (D).

TABLE I. *Drug dosage and the weight, strain and number of mice for each group studied*

Drug	Dose	Body weight (g)	Strain	No. of mice
Althesin	1.5 ml kg^{-1}	34.0–36.0	MF1	20
Ketamine	50 mg kg^{-1}	34.0–36.0	TO	20
Metho-hexitone	30 mg kg^{-1}	30.0–33.0	TO	21

No attempt was made to use equianaesthetic doses of the different agents. Ten animals in each group were randomly selected to be pressurized while the remainder were prepared in the same way using the pressure chamber, but not pressurized. The experiments were run for one animal at a time. The mouse was placed in a Perspex drum, its tail pulled out through a hole in the end of the drum and lightly restrained (fig. 2). A tail vein was cannulated percutaneously using a 26-gauge needle which was attached through a disconnect mechanism to tubing containing the measured dose of drug.

The dose was measured using a length of Portex PP25 tubing (i.d. 0.4 mm) which had been calibrated for volume using mercury. The drug to be injected was placed in the tube and separated from normal saline before and after it by two small air bubbles. The length of the column was measured and its volume calculated. The dose was thus measured with an accuracy of ± 0.22 µlitre (1 SD) for Althesin, ± 11 µg for ketamine and ± 4.4 µg for methohexitone. One end of the tubing was then connected to a motorized syringe charged with normal saline and operated from outside the chamber and the other to the i.v. line.

The disconnect mechanism consisted of a 2-ml syringe which was filled, through its nozzle, from a second motorized 1-ml syringe. The movement of the syringe barrel in relation to its plunger, which was fixed, was used to pull a connector out of the tubing leaving only a short piece attached to the i.v. needle. The restraining thread was looped over the same connector so that, after disconnection, the mouse was free to move within the drum.

A calibrated temperature probe (Yellow Springs Instruments thermistor) was inserted rectally so that its tip was located 30 mm cephalad to the anus. Using this measurement the animal's core temperature was maintained at the initial value (the value obtained after placement in the chamber but before pressurization and before injection) ± 1.0 °C by adjusting ambient temperature. This was done using a water jacket encasing the chamber and a small fan heater which also served to circulate the chamber atmosphere. A second similar thermistor measured ambient temperature in the chamber. Both devices were accurate to

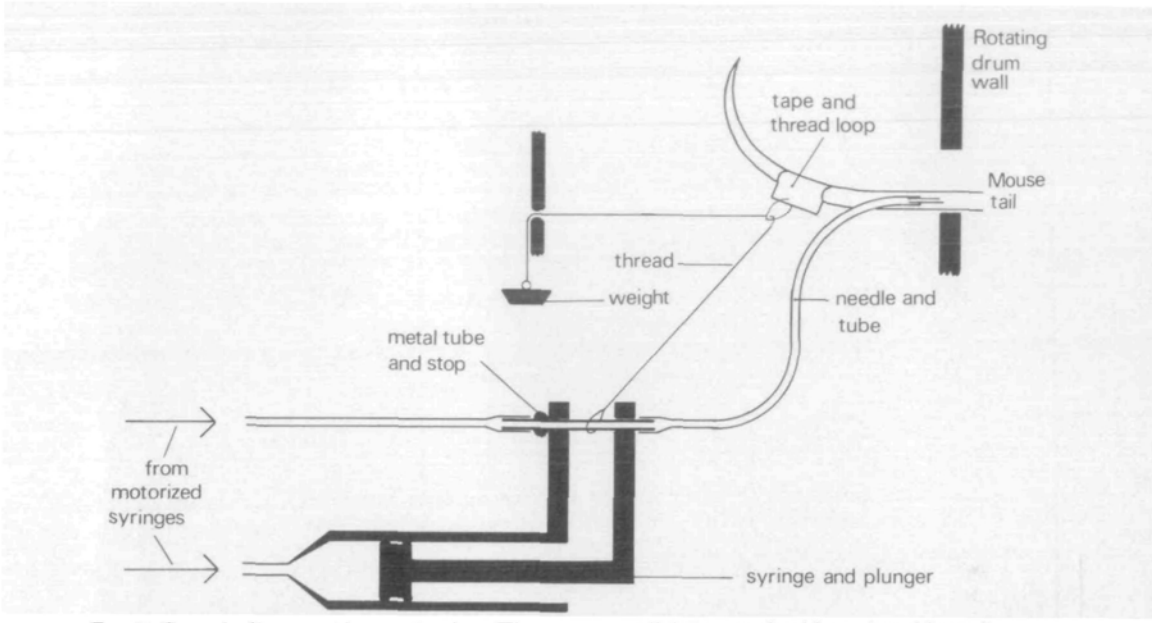

FIG. 2. Cannula disconnecting mechanism. The mouse was lightly restrained by a thread looped over a connector in the i.v. line at one end, running through a loop of thread attached to the tail by tape and held under slight tension by a small weight at the other end. After injection of the drug, the syringe was filled hydraulically and movement of the barrel in relation to the plunger pulled the connector out of the i.v. line and released the restraining thread.

± 0.04 °C (root mean squared residual deviation from regression line) and previous work (DeBoer, Stetzner and O'Brien, 1975) has shown that the accuracy of this type of thermistor is maintained at pressures up to 41 atm abs.

The Perspex drum was mounted on a mechanism by which it could be rotated intermittently at 32 rev min^{-1} and the entire rig placed in the pressure chamber which had an internal volume of 12.3 litre and was equipped with observation ports at each end. For the experiments under pressure a mixture of helium and oxygen was introduced through a silencer so that pressure increased by 9 atm abs. min^{-1} to give a final pressure of 35 atm abs. and a partial pressure of oxygen of 0.5 atm abs. The control experiments were conducted in air. Because of the size of the chamber and the short duration of the experiment, the calculated oxygen consumption (Sheehan and Brauer, 1975) and carbon dioxide production were not regarded as being significant and no provision was made for either oxygen make up or carbon dioxide absorption. On achieving full pressure or, in the case of the controls, on closure of the chamber, a short time was allowed before injection for temperature to stabilize.

After injection the disconnect mechanism was activated and rotation of the drum withdrew the rectal probe. Chamber temperature was then kept at a steady value, pilot studies having indicated that the mouse's temperature would thus be maintained during recovery. The time of injection and the pressure of the experiment were unknown to the observer who rotated the drum every 10 s as the animal showed signs of wakening and recorded recovery time as the start of the first 10-s period over which the mouse remained upright with all four paws coordinating, with the drum rotating. The animal was then killed by introduction of nitrous oxide into the chamber.

RESULTS

Figures 3–5 show the results plotted graphically. Because of the method of drug delivery there was a small scatter of doses. Assuming that, over such a narrow range, the dose–response line was linear, the results have been adjusted to a standard dose as shown in figure 6 and these are the doses referred to in the rest of the paper. On comparison with the control groups, using Student's t test, we found that, at 35 atm abs., the duration of action of all agents tested was significantly reduced (table II) at

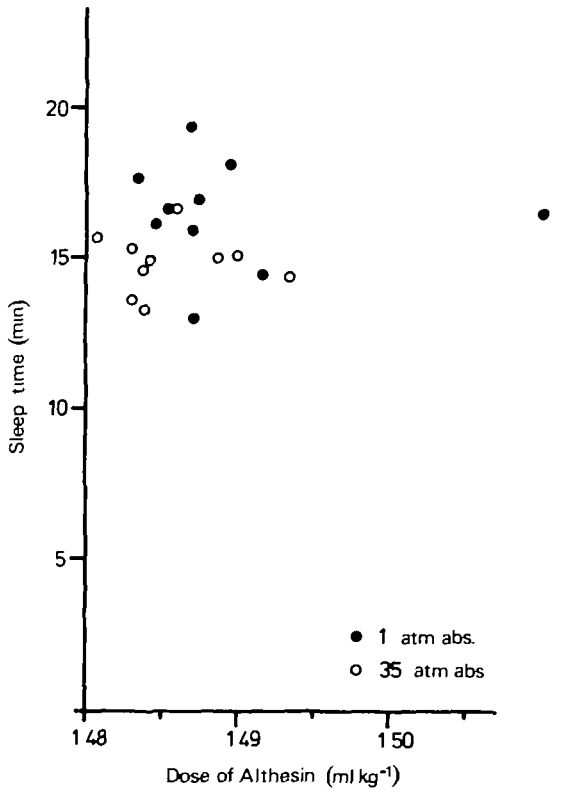

FIG. 3. Sleep times after single i.v. injection of Althesin at 1 and 35 atm abs. against measured dose.

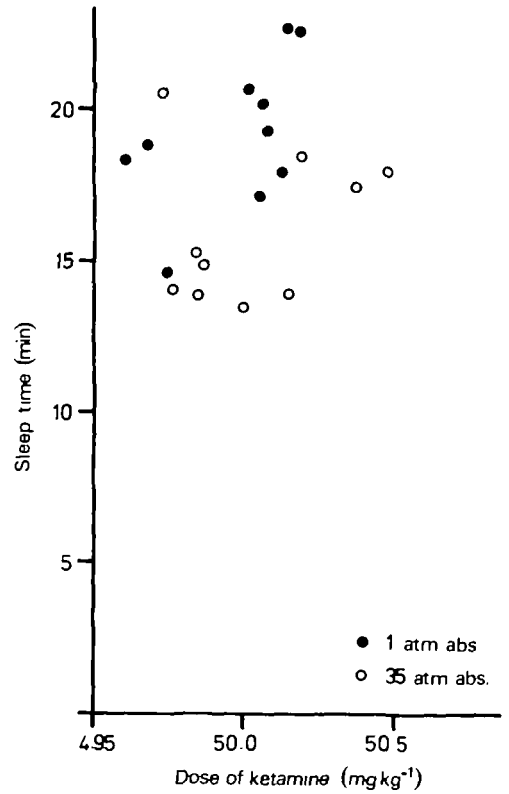

FIG.4. Sleep times after single i.v. injection of ketamine at 1 and 35 atm abs. against measured dose.

TABLE II. *Single i.v. injection of anaesthetic agents at 1 and 35 atm abs.—mean sleep times, differences and significance (Student's t test)*

Agent	Sleep time 1 atm abs. (min)	Sleep time 35 atm abs. (min)	95% confidence limits of difference (min)	Significance
Althesin 1.5 ml kg^{-1}	16.50	14.89	0.16–3.06	$0.05 > P > 0.02$
Ketamine 50 mg kg^{-1}	19.23	16.00	0.94–5.51	$0.01 > P > 0.001$
Methohexitone 30 mg kg^{-1}	15.45	10.05	2.02–8.79	$0.01 > P > 0.001$

$P < 0.05$ for Althesin and $P < 0.01$ for ketamine and methohexitone.

Of the mice that received methohexitone (table III) six of 10 at pressure convulsed compared with two of 11 controls. Another two control animals died, but without convulsing.

TABLE III. *Convulsions and deaths after injection of methohexitone 30 mg kg^{-1}*

	Total	Convulsions	Deaths
1 atm abs.	11	2	2
35 atm abs.	10	6	0

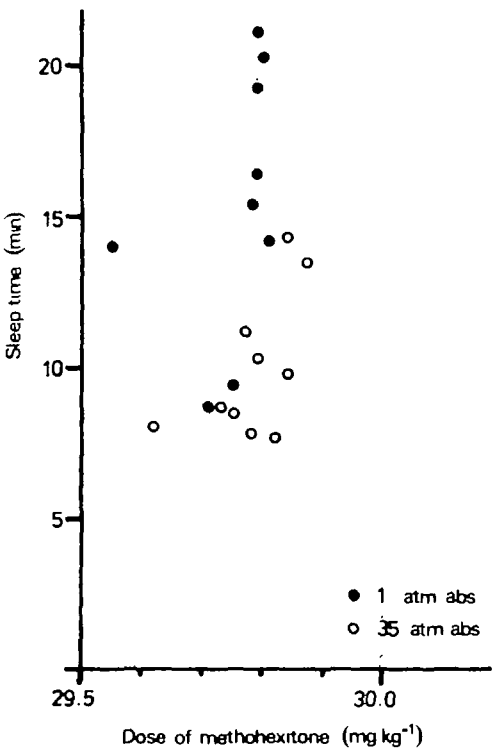

FIG. 5. Sleep times after single i.v. injection of methohexitone at 1 and 35 atm abs. against measured dose.

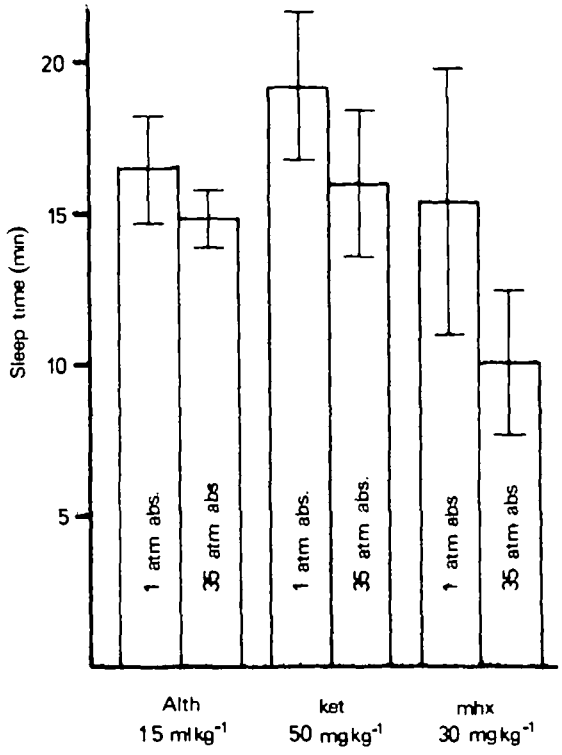

FIG. 6. Mean and standard deviation of sleep times after single i.v. injection of each agent at 1 and 35 atm abs. Alth = Althesin; ket = ketamine; mhx = methohexitone.

DISCUSSION

The results show a reduction in the duration of action of Althesin, ketamine and methohexitone in mice after a single i.v. injection at pressure. Similar results in guineapigs have now been published for ketamine (McCracken et al., 1979) and thiopentone (Tobey et al., 1978). The order of magnitude of the reduction in sleep time, when viewed in relation to the increased dosage of these agents required to maintain a given level of anaesthesia in rats at pressure (Halsey, Wardley-Smith and Green, 1978), is in keeping with the pressure reversal of anaesthesia causing the animals to waken at a higher plasma concentration of the drugs (fig. 1, point B). A relatively minor part played by any factors which may affect the plasma half-life of the agents is suggested by the above work with rats which showed that the waking times from similar levels of steady-state anaesthesia, produced by continuous infusion, were the same at pressure and in control.

The percentage reduction of sleep time was not the same for the three agents: Althesin 10%, ketamine 17% and methohexitone 35%. This order, however, differs from that reported for the percentage increase in dosage required to produce a given level of anaesthesia in rats with the same agents at 35 atm abs. (Halsey, Wardley-Smith and Green, 1978). As equianaesthetic doses were not used and as recovery time from a single dose of drug is also dependent on the rate of plasma clearance and the peak plasma concentration attained, importance cannot be attached to the relative reductions in sleep time between agents. Similarly, the data do not necessarily contradict earlier, steady-state experiments.

For all three agents a decrease in the standard deviation of the sleep times with pressure was noted. The reason for this is not clear, but a decreased scatter of response with increasing pressure was also observed in a study of the pressure reversal of anaesthetic agents, including Althesin and ketamine, administered i.p. to mice (Miller and Wilson, 1978) and it was suggested that this was a result of stricter control of body temperature

at pressure. In the current study, however, both pressurized and non-pressurized animals experienced a similar degree of temperature control.

An increased frequency of convulsions occurred after injection of methohexitone at pressure. This may be caused by the high pressure neurological syndrome (HPNS) by the combination of a relatively fast compression rate and a drug which decreases the convulsion threshold at pressure. Previous work has demonstrated that the pressure at which convulsions are manifest in mice is decreased by faster compression rates (Brauer et al., 1975) and that both methohexitone and propanidid decrease the convulsion pressure threshold in rats (Green, Halsey and Wardley-Smith, 1977). It would seem, therefore, that methohexitone and perhaps other induction agents with similar properties are best avoided in this context. The two deaths in the methohexitone control group were probably a result of over-dosage, indicating that the dose used was around LD_{20}. At pressure the inspired Po_2 was greater and the action of methohexitone was reduced, both factors tending to reduce the mortality.

Shorter sleep times at pressure have been demonstrated. Several cautionary points must be made, however, in extrapolating this observation to clinical practice. Individual variation of sleep times within the various subgroups was quite marked. This meant that for any drug a number of the pressurized animals slept for a time comparable to the control. We could not be sure, therefore, that an individual animal would require a very much larger dose of anaesthetic for a given duration of effect at pressure. Large variations in the human response to anaesthetics are often experienced and, from these results, the assumption that a larger dose of anaesthetic is always required at pressure may be false. Second, by the very nature of the emergency requiring anaesthesia at depth one might expect a debilitated patient who might only require a small dose of anaesthetic if encountered under normal circumstances and, even taking into consideration the decreased action of anaesthetics at pressure, a relatively small dose may still be required. In addition to this, it must be pointed out that most saturation work is carried out at pressures much less than 35 atm abs. and any reversal of anaesthetic effect will be correspondingly less. The conclusion is, therefore, that in conducting anaesthesia at pressure traditional caution is necessary, and the dose of the drug should be closely titrated to its effect.

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ALTHESINE, KETAMINE ET METHOHEXITONE SOUS PRESSION: DUREE D'ACTION D'UNE SEULE DOSE ADMINISTREE PAR VOIE INTRAVEINEUSE

RESUME

L'anesthésie générale pour chirurgie d'urgence dans un environnement pressurisé peut mettre en cause l'usage d'agents administrés par voie intraveineuse. La propriété anaesthésiante des agents de ce genre est connue pour être contrariée par la pression, mais l'effet de leur durée d'action n'est pas facilement prévisible. La reprise de conscience des souris, après une seule dose intraveineuse d'Althésine, de kétamine ou de méthohexitone a été estimée par la capacité de ces animaux à rester debout dans un tambour rotatif. A 35 atmosphères absolues, la durée d'action s'est trouvée considérablement réduite: $P < 0,05$ pour l'Althésine, $P < 0,01$ pour la kétamine et le méthohexitone. Certains animaux de chaque groupe ont cependant affiché des temps de récupération similaires à ceux des animaux témoins. Le taux de convulsion avec le méthohexitone a été de 60% à 35 atmosphères absolues, alors qu'à 1 atmosphère absolue, celui-ci n'a été que de 20%. Dans cet article, les implications cliniques de ces découvertes font l'objet de débats.

ALTHESIN, KETAMIN UND METHOHEXITON UNTER DRUCK—WIRKUNGSDAUER EINER INTRAVENÖSEN EINZELDOSIS

ZUSAMMENFASSUNG

Allgemeine Narkose für Notchirurgie in einer unter Druck stehenden Umgebung dürfte die Verwendung intravenöser Mittel erforderlich machen. Die narkotische Wirkung dieser Mittel kann durch Druck aufgehoben werden, doch ist die diesbezügliche Wirkung auf die Wirkungsdauer nicht leicht vorherzusagen. Die Erholung von Mäusen nach intravenösen Einzeldosen von Althesin, Ketamin oder Methohexiton wurde nach Fähigkeit der Mäuse beurteilt, sich in einer rotierenden Trommel aufrecht zu halten. Bei 35 atm abs. war die Wirkungsdauer deutlich reduziert: $P < 0,05$ für Althesin; $P < 0,01$ für Ketamin und Methohexiton. Mehrere Tiere in jeder Gruppe zeigten jedoch Erholungszeiten, die mit der der Kontrolltiere vergleichbar waren. Die Krampfrate bei Methohexiton betrug 60% bei 35 atm abs., bei 1 atm abs. hingegen 20%. Die klinischen Konsequenzen dieser Ergebnisse werden diskutiert.

ALTESIN, KETAMINE Y METOHEXITONA BAJOR PRESION: DURACION DEL EFECTO DE UNA DOSIS INTRAVENOSA SENCILLA

SUMARIO

La anestesia general a utilizar en operaciones de emergencia, en un ambiente presionizado, involucrará probablemente el uso de agentes intravenosos. Se sabe que la propiedad anestésica de tales agentes queda antagonizada por la presión, pero su efecto no es fácilmente predecible. El grado de recuperación de los efectos de una dosis intravenosa sencilla de Altesin, ketamina o metohexitona en ratones, se estimó mediante la habilidad de estos para permanecer de pie dentro de un tambor giratorio. A una presión de 35 atmósferas absolutas, la duración de los efectos se redujo significativamente: $P < 0,05$ para el Altesin; $P < 0,01$ para le ketamina y la metohexitona. Sin embargo, un cierto número de animales de cada grupo presentaron tiempos de recuperación comparables a los del grupo de control. El régimen de contracción con la metohexitona fue del 60% a una presión de 35 atmósferas absolutas, mientras que a 1 atmósfera absoluta fue del 20%. Se discuten las repercusiones clínicas de estos resultados.