SAFETY INDEX OF ULTRA-SHORT ACTING INTRAVENOUS ANAESTHETICS

R.K. SRIVASTAVA*, A.K. GHOSH, O.P. SRIVASTAVA

AND P.R. PABRAI*

Defence Research Laboratory (Materials), Kanpur-4, India

Received for publication April 10, 1967

The selection of a potent anaesthetic agent is mainly guided by its margin of safety. "Safety index" or therapeutic coefficient of intravenously administered barbiturates has been determined in the past by employing various methods in different laboratory animals. Consequently results obtained are neither uniform nor comparable. The ratio of minimal lethal dose/minimal head drop dose in 50% of rabbits has been considered as the therapeutic coefficient by Werner, Pratt and Tatum (1). Swanson and Chen (2) determined the median anaesthetic dose (AD_{50}) and median lethal dose (LD_{50}) in rabbits, rats, cats and dogs for predicting safety of intravenous barbiturates. While some believe that toxicity of these agents runs parallel to their hypnotic potency others feel that doses of the various barbiturates required to produce sedative, hypnotic and anaesthetic grades of depression bear a rather fixed relationship to the median fatal dose. This is believed to be because of lack of a suitable method for accurate measurement of various grades of central depression in laboratory animals [Goodman and Gilman (3)]. Recently Ghosh, Srivastava and Ghosh (4, 5) and Srivastava and Ghosh (6) described a method for determining the margin of safety of volatile anaesthetics. Herein individual anaesthetic and fatal doses have been measured accurately in mice, rats and guinea-pigs. In the present study margin of safety of seven ultra-short acting intravenous barbiturates has been determined in rabbits by a method which permits accurate measurement of different stages of central depression in individual animals.

METHODS AND MATERIALS

Male albino rabbits (1.3 to 2.1 kg) were fasted for 18 hours prior to experiment, water being allowed *ad lib*. Five animals were used for each drug, the difference in weight of animals in any one group being not more than 0.4 kg. Animals were partially restrained in a rabbit box with the head left free (Fig. 1A). A freshly prepared 5% aqueous solution of the drug was injected intravenously into the marginal ear vein by means of a slow injector at a constant rate of 0.5 ml per minute. The rate of injection permitted accurate recording of time and dose for (i) head drop (loss of righting reflex) (Fig. 1B); (ii) anaesthesia (loss of corneal reflex) (Fig. 1C); and (iii) death (respiratory arrest). The terms thiopentone, hexobarbitone, etc. used hereafter refer to their sodium salts.

* Present address: Detachment Defence Research Laboratory (Materials), Gwalior-2, India.

FIG. 1. Showing different grades of central depression produced by intravenously administered barbiturates in rabbits ; (A) Before drug, (B) Head drop, (C) Anaesthesia.

The safety index (S.I.) values for each agent were calculated as ratios of individual fatal dose/individual head drop dose (IFD/IHD) and of individual fatal dose/individual anaesthetic dose (IFD/IAD). Corresponding standard errors and 95% confidence limits were also worked out.

RESULTS

The results obtained with different barbiturates are summarized in Table 1. Thio-butone or buthalitone (Baytenal and Transithal) and thialbarbitone (Kemithal) have higher S.I. (IFD/IHD) values than others. There is close agreement between the mean S.I. values for two brands of hexobarbital (Evipan and Cyclonal). Similarly the three thiopentone preparations (Pentothal, Intraval and Nesdonal) show almost equal mean S.I. values. The mean safety indices for methitural (Thiogenal or Neraval), thiamylal (Surital) and methohexital (Brietal or Brevital) are the lowest of the series.

S.I. (IFD/IAD) value, like the IFD/IHD index, for buthalitone is again the highest. Thialbarbitone has a somewhat lower index. With methohexital, anaesthesia occurs almost simultaneously with respiratory failure.

Consideration of onset times of head drop (see Table 1) indicates that methitural has

TABLE I. Chemical structure and safety indices (S.I.) of ultra-short acting barbiturates in rabbits.

Generic or approved name	Trade name and (Manufacturer*)	X	R ¹	R ⁵	R ^{5'}	Mean onset time for head drop in seconds	IFD/IHD** S.I. ± S.E.M.	IFD/IAD** S.I. ± S.E.M.
Hexobarbitone ; Hexobarbital	Evipan (Bayer)	O	-CH ₃	-CH ₃		55	4.6 ± 0.49 (3.87-5.33)	1.5 ± 0.38 (1.0 -2.24)
	Cyclonal (May & Baker)	"	"	"	"	60	4.7 ± 0.36 (4.00-5.40)	1.8 ± 0.48 (1.0 -2.74)
Thiopentone ; Thiopental ; Penthiobarbitone	Pentothal (Abbott)	S	H	-CH ₂ CH ₃	-CHCH ₂ CH ₂ CH ₃ CH ₃	44	3.5 ± 0.38 (2.70-4.24)	1.7 ± 0.21 (1.29-2.11)
	Intraval (May & Baker)	"	"	"	"	46	3.5 ± 0.28 (3.05-3.95)	1.8 ± 0.47 (1.0 -2.72)
	Nesdonal (Specia)	"	"	"	"	37	3.4 ± 0.34 (2.84-3.96)	1.6 ± 0.27 (1.07-2.13)
Buthalitone ; Thiobutone	Transithal (May & Baker)	S	H	-CH ₂ CH=CH ₂	-CH ₂ CH(CH ₃) ₂	72	6.4 ± 0.80 (5.42-7.38)	3.3 ± 0.33 (2.73-3.86)
	Baytenal (Bayer)	"	"	"	"	69	7.3 ± 1.02 (5.32-9.30)	3.2 ± 0.31 (2.59-3.81)
Thialbarbitone	Kemithal (I.C.I.)	S	H	-CH ₂ CH=CH ₂		68	6.9 ± 1.33 (4.30-9.50)	2.4 ± 0.73 (1.0 -3.83)
Methitural	Thiogenal (E. Merck)	S	H	-CH ₂ CH ₂ SCH ₃	-CHCH ₂ CH ₂ CH ₃ CH ₃	86	3.1 ± 0.49 (2.14-4.06)	1.5 ± 0.27 (1.0 -2.03)
Thiamylal	Surital (Parke Davis)	S	H	-CH ₂ CH=CH ₂	-CHCH ₂ CH ₂ CH ₃ CH ₃	43	2.9 ± 0.45 (2.02-3.78)	1.7 ± 0.30 (1.12-2.28)
Methohexital	Brietal (Eli Lilly)	O	-CH ₃	-CH ₂ CH=CH ₂	-CHC≡CCCH ₂ CH ₃ CH ₃	24	2.8 ± 0.30 (2.28-3.40)	— ***

* Receipt of free samples from the respective manufacturers is gratefully acknowledged.

** Figures within parentheses are the 95% confidence limits.

*** Anaesthesia and respiratory arrest occurred almost simultaneously.

the longest induction time. Buthalitone and thialbarbitone can be grouped together on this basis. Similarly thiopentone and thiamylal have almost equal onset times. The consistency of results is thus emphasized by the fact that the time required for the onset of head drop in rabbits, like their safety indices, is almost identical for different brands of the same barbiturate.

DISCUSSION

The most significant feature of the present method is that the different stages of central depression are distinct and that the head drop, anaesthetic and fatal doses in individual animals can be measured accurately. Thus a relatively small number of animals gives fairly reproducible results. Werner, Pratt and Tatum (1), on the other hand, used 14 to 18 rabbits for each dose of drug to determine its therapeutic coefficient.

The consistency of the ratio IFD/IHD for a group of chemically similar drugs is noteworthy. Thus Evipan and Cyclonal (see Table 1) have almost the same mean S.I. values (4.6 and 4.7). Similarly the S.I. figures of Pentothal, Intraval and Nesdonal are around 3.5. Transithal and Baytenal have their S.I. values 6.4 and 7.3 respectively; this difference, though difficult to explain, is however statistically not significant.

S.I. values of Surital, Pentothal and Evipan obtained by other workers and by us are available for comparison. Werner, Pratt and Tatum (1) assigned a slightly higher therapeutic coefficient for Evipan (5.3) than for Pentothal (5.0). This is in general agreement with our findings (4.6 and 3.5 respectively). The difference in numerical values could be due to different techniques employed; the aforesaid workers used divided doses and assessed therapeutic ratio, MLD/MHD. The lower margin of safety assigned to Surital by Tabern and Volwiler (7) is confirmed by the present study.

The indices obtained as a ratio of IFD/IAD are also generally the same for a chemically identical group of drugs. A drug which has a higher IFD/IHD index has also a relatively higher IFD/IAD ratio. However significant differences were observed in the case of methohexital and thiamylal. Both these agents have almost equal IFD/IHD indices but widely separated indices for IFD/IAD. With the former loss of corneal reflex occurred almost simultaneously with respiratory arrest. This is evidently due to pronounced respiratory depression produced by methohexital [Wood-Smith and Stewart (8)]. On the whole it appears that the S.I. values, as determined by the ratio IFD/IHD, are more consistent than the indices obtained by the ratio of IFD/IAD; the head drop end point is sharper than the disappearance of corneal reflex so that large S.E.M. values for IFD/IAD indices were obtained.

The assumption that the safety of barbiturate anaesthetics may be related to their hypnotic activity or that a fixed relationship exists between the sedative, hypnotic and anaesthetic doses and their median fatal dose is not borne out, at least in rabbits, by this report. For example, methitural which is said to be less potent than thiopentone [Grollman (9)] has S.I. value close to that of the latter. Further hexobarbital and thiamylal exhibit unequal S.I. values though their minimal head drop doses are close to one another

as has been the observation of Werner, Pratt and Tatum (1).

No structural correlation with safety indices of barbiturates is apparent from this study. The S.I. values of the different thiobarbiturates range from 2.8 to 7.3. The presence of H and CH₃ substituents at R¹ (see Table 1) does not affect safety indices uniformly. Similarly compounds with allyl group at R⁵ have a wide distribution of safety indices; for example, S.I. of buthalitone and thialbarbitone lies between 6.4 and 7.3 whereas that of thiamylal is 2.9 only. Likewise, the substituents at R^{5'} seem to have little effect on the safety of the preparation. It would thus appear that structure of the molecule as a whole is important in this respect.

SUMMARY

1. Margin of safety of ultra-short acting intravenous barbiturates has been determined in rabbits by continuous infusion. The method is simple and accurate giving reproducible results with five animals only.

2. Safety indices calculated as the ratio of the individual fatal dose/individual head drop dose (IFD/IHD) show that buthalitone and thialbarbitone are the safest, hexobarbitone and thiopentone possess intermediate S.I. values whereas methitural, thiamylal and methohexital exhibited the lowest values. Similarly indices have been obtained as the ratio of individual fatal dose/individual anaesthetic dose (IFD/IAD) but the former are more dependable.

3. The assumption that safety of barbiturates is related to their hypnotic doses or that their fatal dose bears a fixed relationship with doses required to produce sedative, hypnotic and anaesthetic effects is not supported by this study.

4. Structural correlation with safety indices of barbiturates is not apparent.

REFERENCES

- 1) WERNER, H.W., PRATT, T.W. AND TATUM, A.L.: *J. Pharmac. exp. Ther.* **60**, 189 (1937)
- 2) SWANSON, E.E. AND CHEN, K.K.: *Proc. Soc. exp. Biol. Med.* **82**, 212 (1953)
- 3) GOODMAN, L.S. AND GILMAN, A.: *The Pharmacological Basis of Therapeutics*, Ed. 2, p. 137, Macmillan Company, New York (1955)
- 4) GHOSH, M.N., SRIVASTAVA, R.K. AND GHOSH, A.K.: *Archs int. Pharmacodyn. Thér.* **138**, 548 (1962)
- 5) GHOSH, M.N., SRIVASTAVA, R.K. AND GHOSH, A.K.: *Ibid.* **150**, 96 (1964)
- 6) SRIVASTAVA, R.K. AND GHOSH, A.K.: *Ibid.* **163**, 296 (1966)
- 7) TABERN, D.L. AND VOLWILER, E.H.: *J. Am. chem. Soc.* **57**, 1961 (1935)
- 8) WOOD-SMITH, F.G. AND STEWART, H.C.: *Drugs in Anaesthetic Practice*, p. 153, Butterworths, London (1962)
- 9) GROLLMAN, A.: *Pharmacology and Therapeutics*, Ed. 5, p. 90, Lea & Febiger, Philadelphia (1962)