EFFECTS OF MORPHINE AND NALORPHINE ON VOLATILE ANAESTHETICS IN MICE

By

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Morphine as a premedicant has been claimed, besides other factors, to reduce the amount of anaesthetic required to obtain a given plane of anaesthesia (1,6,7,10,11); while other workers have denied this to be true (2,5). Ever since nalorphine was introduced as an effective antagonist of morphine, attempts have been made to use these two in combination, with the hope that the respiratory depression produced by one will be nullified by the other, during anaesthesia. Reports in this regard have also been controversial. In contrast to the general impression that nalorphine causes respiratory depression when used along with ether, May *et al.* (4) observed that neither nalorphine nor levallorphan caused a notable degree of stimulation or depression of respiration when used in narcotic premedicated patients anaesthetised with ether.

The purpose of the present study was to find out, experimentally in laboratory animals, the effects of morphine, nalorphine and their combination on the anaesthetic requirements to induce anaesthesia as well as to produce respiratory depression. This was possible because of the availability of a quantitative method for the evaluation of premedicants in mice (8).

MATERIALS AND METHODS

The volume of anaesthetic producing respiratory arrest and that producing anaesthesia (loss of righting reflex) and hence their ratio, the safety index (S.I.) were determined by the method of Ghosh *et al.* (3).

A total of 120 male mice weighing between 20-40 g. were used in the present investigation. Groups of 10 mice were used each for control, morphine (10 *mg/kg*), nalorphine (10 *mg/kg*), and morphine (10 *mg/kg*) and nalorphine (10 *mg/kg*) combined. Three anaesthetics ether, chloroform and halothane were used for such studies. The premedicant drug was injected i.p. 30 min. before the start of the experiment. The average volume of the anaesthetic producing loss of righting reflex (L.R.V.) and that producing respiratory arrest (R.A.V.) were found out for each group. S.I. was calculated, however, as before, for each animal by dividing respective R.A.V. by L.R.V. and average of the group worked out.

Significance test for small samples was ascertained according to the method described by Snedecor (9).

RESULTS

S.I. of different anaesthetics with or without pre-medicants has been presented in Table I. The S.I. of ether is significantly lowered following morphine, while following nalorphine alone or in combination with morphine the S.I. is higher than control. S.I. of chloroform is significantly lowered following morphine; unaltered following nalorphine; while raised following combination of the two. S.I. of halothane is only reduced following morphine but remains unaltered with others.

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TABLE I

Effect of premedication on the safety index of volatile anaesthetics in mice

Anaesthetics	*No. of mice*	*Premedication*	*S.I. (Mean±S.E.)*	*Significance of difference*
Ether	10	Control	2.8±0.17	
	10	Morphine	*2.0±0.25	P <0.02
	10	Nalorphine	**3.8±0.23	P <0.01
	10	Morphine+ Nalorphine	**3.8±0.13	P <0.001
Chloroform	10	Control	2.2±0.06	
	10	Morphine	*1.8±0.16	P <0.05
	10	Nalorphine	2.2±0.13	
	10	Morphine+ Nalorphine	**2.8±0.14	P <0.001
Halothane	10	Control	2.2±0.17	
	10	Morphine	*1.7±0.14	P <0.05
	10	Nalorphine	2.3±0.14	
	10	Morphine+ Nalorphine	2.4±0.19	

*Significant **Highly significant

L.R.V. and R.A.V. of different anaesthetics are presented in Table II. It will be seen that following morphine the L.R.V. of all the three anaesthetics significantly increased. With regard to R.A.V. there is significant increase in the case of ether following nalorphine alone as well as its combination with morphine, and in case of chloroform following only the combination. The rest remains unchanged.

TABLE II

Effect of premedication on the anaesthetic volumes in mice

Anaesthetic	*No. of mice*	*Premedication*	*L.R.V. (Mean±S.E.)*	*Significance*	*R.A.V. (Mean±S.E.)*	*Significance*
Ether	10	Control	1.0±0.03		2.7±0.15	
	10	Morphine	*1.3±0.14	P <0.05	2.6±0.32	
	10	Nalorphine	1.0±0.08		**4.0±0.35	P <0.01
	10	Morphine+ Nalorphine	1.1±0.08		**4.1±0.31	P <0.001
Chloroform	10	Control	0.24±0.02		0.48±0.04	
	10	Morphine	*0.35±0.04	P <0.02	0.60±0.05	P> 0.05
	10	Nalorphine	0.20±0.01		0.50±0.03	
	10	Morphine+ Nalorphine	0.20±0.02		*0.68±0.06	P <0.05
Halothane	10	Control	0.30±0.02		0.69±0.04	
	10	Morphine	*0.42±0.04	P <0.05	0.68±0.04	
	10	Nalorphine	0.30±0.01		0.70±0.06	
	10	Morphine+ Nalorphine	0.30±0.06		0.70±0.12	

L.R.V. = Volume producing loss of righting reflex
R.A.V. = Volume producing respiratory arrest
*Significant **Highly significant

DISCUSSION

Although the estimation of the anaesthetics consumed during anaesthesia by the present method cannot be as reliable as the methods of estimation of blood and alveolar concentration of anaesthetics in surgical patients, yet a number of points are revealed by the present study. For instance, morphine significantly lowers the S.I. of ether, chloroform as well as halothane. It is rather tempting to ascribe this to the respiratory depressant action of morphine. But a study of the Table II reveals that it is not so. The volume which produces respiratory arrest (R.A.V.) is not reduced in any of the three cases. On the other hand, L.R.V. which is indicative of the onset of anaesthesia (loss of righting reflex) is significantly increased in all the three cases thereby contributing towards the lowering of S.I. A number of workers observed a reduction in the amount of anaesthetic required following morphine (1,6,7,10,11). Potter *et al.*, (5) and Cohen and Beecher (2), on the other hand, failed to observe any such reduction. Our results in mice not only fail to support the observations of the former group but actually give an indication towards the opposite direction. We have no explanation to offer in this regard excepting to allege the species for this peculiarity.

Nalorphine produces no change in the S.I. of chloroform and halothane, while that of ether is significantly raised. The rise in S.I. is due to the significant increase in R.A.V. indicating some protection afforded by the drug to the respiratory centre against ether.

Combination of morphine and nalorphine shows no change in the S.I. of halothane which means that nalorphine has counteracted the S.I. lowering effect of morphine. A careful look in Table II reveals that this has been achieved not by any protective action on respiratory centre but by counteracting the L.R.V. raising value of morphine. This is an interesting observation but difficult to explain in the absence of any further information.

The S.I. of ether is increased to the same extent and by the similar mechanism (*i.e.* rise in R.A.V.) by combination of the two drugs as with nalorphine alone. The S.I. lowering effect of morphine has been counteracted by nalorphine also at the L.R.V. level. Impression that nalorphine causes respiratory depression during ether anaesthesia has also been refuted by May *et al.* (4) who failed to demonstrate any difference in the minute volume exchange in surgical patients premedicated with nalorphine and morphine during and after ether anaesthesia compared to the series without nalorphine premedication.

Combination of nalorphine and morphine has raised the S.I. of chloroform significantly and this again by raising the R.A.V. It is interesting to note that nalorphine alone does not alter the S.I.; morphine alone lowers the S.I.; whilst their combination shifts the S.I. towards the opposite direction. This is not surprising as a number of similar reversals have been reported with different combinations of premedicants in the mice (8).

SUMMARY

Quantitative studies of the anaesthetic volumes of ether, chloroform and halothane in mice following morphine, nalorphine and their combination reveal the following.

S.I. of all the three anaesthetics is significantly lowered following morphine. T lowering is due to increase in the volume needed to produce loss of righting reflex and not to reduction in the volume producing respiratory arrest.

Nalorphine alone increases the S.I. of ether only without affecting the other two anaest tics. This rise, however, is due to increase in the volume necessary to produce respirat arrest.

Combination of morphine and nalorphine raised the S.I. of ether and chloroform not of halothane which remains unaltered. These rises are due to the increase in the volu needed to produce respiratory arrest.

Probable mechanisms by which these changes are brought about have been discussed the light of the controversial reports available in the literature on human subjects.

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