EVALUATON OF CERTAIN TRANQUILLISERS AND SEDATIVE PREMEDICATIONS ON THE SAFETY INDEX OF VOLATILE ANAESTHETICS

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Summary: Safety index (S.I.) of ether, chloroform and halothane was determined in mice following premedication with chloral hydrate, phenobarbitone, diazepam and trifluoperazine given alone or in combination with atropine or hyoscine. The S.I. of ether was significantly raised by chloral hydrate and phenobarbitone when combined with atropine while trifluoperazine in combination with atropine or hyoscine lowered it. The S.I. of chloroform and halothane was raised by chloral hydrate, phenobarbitone and diazepam. The S.I. raising effects were augmented in chloroform anaesthesia and reduced in case of halothane (except diazepam-hyoscine) when these premedications were combined with atropine or hyoscine.

Key words : safety index, ether, chloroform, halothane, chloral hydrate, diazepam, phenobarbitone, trifluoperazine

The drugs commonly used for pre-anaesthetic medication are narcotic analgesics, tranquillizers, barbiturate and non-barbiturate sedatives administered alongwith an anticholinergic agent. Their use is chiefly aimed to decrease anxiety, provide smooth induction and maintenance of anaesthesia and emergence from it (6). Clinical studies of a number of durgs for premedication were carried out (1, 3, 5) but precise experimental studies of their influence on safety index of general anaesthetics are not available. Ghosh and Banerjee (4) and Singh and Ghosh (7-9) have reported the effects of some single and combined premedications on the safety index of volatile anaesthetics in mice and these included the anticholinergics atropine and hyoscine; narcotic analgesics morphine and pethidine and morphine - nalorphine combinations; psycho-active agents like chloropromazine, promethazine, reserpine and tetrabenazine. In the present study an attempt has been made to evaluate some of the common tranquillizers viz diazepam and trifluoperazine and sedatives such as chloral hydrate and phenobarbitone for their effects on the safety index of ether, chloroform and halothane.

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MATERIALS AND METHODS

Safety index (S.I.), which is the ratio of the amount of anaesthetic required to produce loss of respiration to the amount required to produce loss of righting reflex, was determined by the method described by Singh and Ghosh. (8.). In this method air under controlled pressure, was bubbled through the volatile anaesthetic placed in a graduated container (fabricated from a burette) and the vapour was led to an anaesthetising chamber (a wide mouth one pound bottle) into which the animal (albino mouse) under observation was placed. The bottle had a small outlet for the vapours. The animals used were albino mice (20-30 g) and the S.I. was determined individually for each animal. The mice were divided into groups of ten, and were given the test drug i p 30 min before the determination of the S.I. A group without any premedication served as control. Drugs for premedication were administered alone and also in combination with atropine (5 *mg/kg*) or hyoscine (*1 mg/kg*). The volatile anaesthetics used were anaesthetic ether (B.P.), chloroform (I.P.) and fluothane (Halothane). Chloroform was used as a prototype of halogenated hydrocarbons. The following drugs were used for premedication, diazepam (*3 mg/kg*), trifluoperazine (*10 mg/kg*), phenobarbitone (*40 mg/kg*), and chloral hydrate (100 *mg/kg*). The results were statistically analysed according to the method described by Snedecor (10).

RESULTS

Chloral hydrate alone or in combination with hyoscine did not significantly affect the S.I. of ether but in combination with atropine raised the S.I. by 29%. Phenobarbitone *per se* had no effect on the S.I. but when combined with atropine raised the S.I. by 18% (Fig. I). However, in combination with hyoscine, it failed to produce a similar rise. Diazepam alone or with atropine or hyoscine did not affect the S.I. Trifluoperazine alone or in combination with hyoscine had no effect on the S.I. but when combined with atropine, it lowered the S.I. of ether by 21%. Unlike atropine, combination of hyoscine with these premedications did not affect the S.I.

The S.I. of chloroform was significantly raised by chloral hydrate by 48%. With chloral hydrate as well as with phenobarbitone combination with atropine produced a more pronounced rise in S.I. (67 and 48% respectively) than a combination, with hyoscine which raised the S.I. by only 33% in both the cases (Fig. 1). However, diazepam hyoscine combination produced greater rise in S.I. i.e. 67% than diazepam - atropine combination which raised the S.I. by 52%. Trifluoperazine alone or in combination with atropine or hyoscine did not affect the S.I. of chloroform.

With halothane chloral hydrate, phenobarbitone and diazepam raised the S.I. but when combined with anticholinergics this beneficial effect was generally reduced

exception being diazepam. When given alone, diazepam raised the S.I. of halothane by 41% but its combination with atropine brought it down to 18% while hyoscine combination raised the S.I. by 46% (Fig. 1).

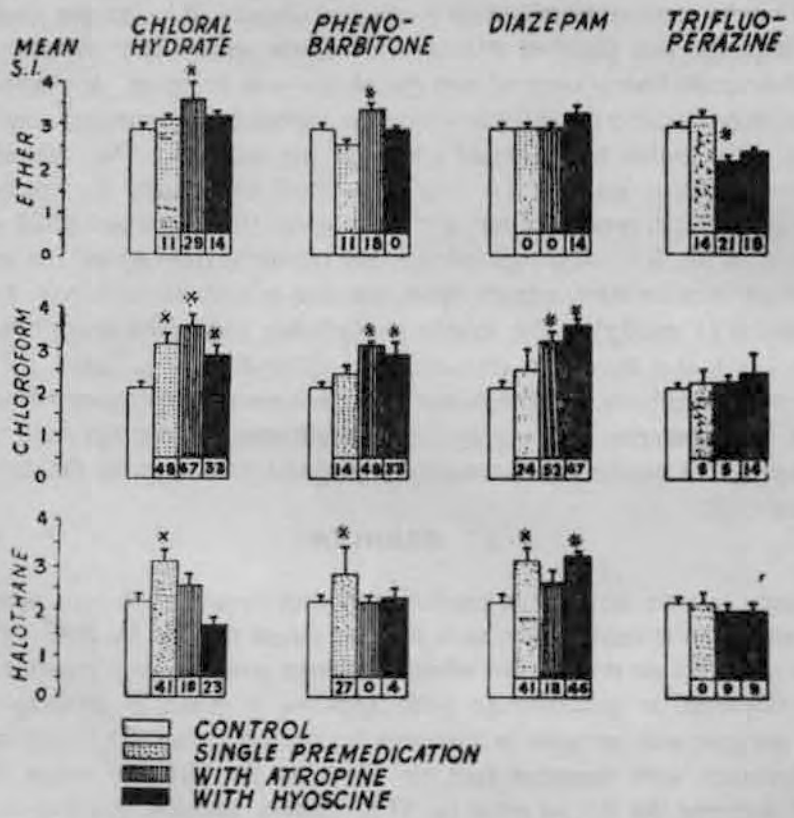

Fig. 1: Effects of single and combined premedications on the safety index (S.I.) of ether, chloroform and halothane in mice. The vertical bars represent mean S.I. (n=10 in each case) and vertical lines denote the standard errors. Figures in the boxes (at the base) indicate the percent rise/fall in the S.I. as compared to the control. Asterisks denote statistically significant results ($P<0.05$).

DISCUSSION

The results with ether anaesthesia indicate that atropine increased the S.I. when premedication was with chloral hydrate or phenobarbitone but not with diazepam or trifluoperazine. Atropine may have produced this effect in two ways: by antagonizing the central respiratory depressant effects of the anaesthetic or by reducing the airway resistance caused by the irritant action of ether vapours. The inability of hyoscine to produce a similar rise in the S.I. of ether when combined with chloral hydrate or phenobarbitone could possibly be due to the lesser potency of this drug for the

bronchodilatory effect. It is interesting to observe that while combination of atropine with the sedative group provided a protective effect on respiration, it rather produced a significant reduction of S.I. with trifluoperazine. It is difficult to offer any satisfactory explanation for this disparity of effects of combination of atropine with these two groups of premedications since both these groups produce central nervous system depression. However, these results suggest that it is beneficial to administer chloral hydrate or phenobarbitone along with atropine and not alone. Since with ether anaesthesia an anticholinergic is indispensable, it is better to substitute trifluoperazine with some other premedication.

S.I. of chloroform was significantly raised by atropine as well as hyoscine when combined with chloral hydrate, phenobarbitone or diazepam. Since chloroform does not irritate the respiratory passages the rise in S.I. produced by these premedications in combination with anticholinergics could be mainly a result of the central action of atropine and hyoscine providing a protective effect on the respiratory centre. It is again difficult to explain the lack of effect of trifluoperazine. These results suggest that if chloral hydrate, phenobarbitone or diazepam are to be used as premedication in chloroform anaesthesia, they should be given in combination with atropine or hyoscine rather than given alone.

The S.I. of halothane was raised by all the premedications investigated except trifuoperazine but combination of atropine with these agents produced an entirely different pattern of effects when compared with chloroform i.e. atropine instead of producing any further rise lowered the S.I. of halothane when combined with these agents. A possible explanation for this disparity with halothane anaesthesia could be that halothane in itself possesses a bronchiolar dilating effect (2) and it is likely that no further benefit could be provided by adding atropine as far as this peripheral action is concerned. The inability of hyoscine to raise the S.I. of halothane when combined with chloral hydrate or phenobarbitone could also be explained on the same basis. However, the part played by this peripheral component does not appear to be significant in the case of hyoscine diazepam combination which produced a rise in the S.I. probably due to a central effect. As is evidenced by these results perhaps atropinization is not necessary with halothane. Further experimental and biochemical studies would be required for a more detailed explanation of these findings.

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