SYNERGIC EFFECTS OF AMYLOBARBITONE SODIUM AND ETHANOL

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Recently, attention was drawn to the lack of information concerning the effects of ethanol and barbiturates taken together.[1] In 1934, Carriere, Huriez and Willoquet[2] reported that ethanol antagonised the hypnotic effect and reduced the toxicity of phenobarbitone. Several subsequent investigators have been unable to confirm this work. Olszycka[3,4] found that ethanol potentiated the hypnotic effect of butobarbitone in mice and rats, and Dille and Ahlquist[5], working on rabbits, showed that it produced the same effect with pentobarbitone. Jetter and McLean[6] and Ramsey and Haag[7] investigated further the synergism between ethanol and barbiturates in laboratory animals and both groups of workers reported that the toxicity of barbiturates was increased considerably by the simultaneous administration of ethanol. Some clinical evidence also exists that ethanol potentiates the toxic effects of barbiturates. Thus, there is some confusion in the literature concerning the effects of ethanol and barbiturates given together. The pharmacological effects produced by the simultaneous administration of these two substances are obviously of considerable importance clinically and, therefore, the following experiments were carried out in the hope that the results would be of more than academic interest.

Materials

Amylobarbitone Sodium.

*iso*Amylethyl barbituric acid was used. 1 g. was dissolved in 8·85 ml. of 0·5N sodium hydroxide with the aid of gentle heat (less than 80° C. for not more than 30 minutes). The solution was diluted to 10 ml. with water and filtered. It was kept for not more than one day and diluted immediately before use with water.

Ethanol. Alcohol (90 per cent.) B.P., diluted with water, was used.

Animals. The experiments were performed using male albino mice weighing 20 to 24 g.

Methods

Two types of experiments were performed. The first was designed to determine the effect of ethanol on the acute toxicity of amylobarbitone sodium, and the second to investigate the anæsthetic effects of the two substances administered together.

Results

1. *Acute Toxicity of Amylobarbitone Sodium and Ethanol.*

300 mice were used in this experiment. Amylobarbitone sodium was administered orally as a solution containing 20 mg./ml. and ethanol

(50 per cent. v/v) was given by the same route. The MLD of each of these substances, administered alone, was determined, the number of dead animals being counted 24 hours after the administration of the drugs. Subsequently the amounts of ethanol required to produce 50

TABLE I

DOSES OF AMYLOBARBITONE SODIUM AND ETHANOL NECESSARY TO PRODUCE 50 PER CENT. MORTALITY IN MICE

Amylobarbitone sodium		Ethanol
mg./kg.		ml./kg.
0	+	14·25
200	+	11·50
350	+	6·50
500	+	4·75
675	+	0

TABLE II

DOSES OF AMYLOBARBITONE SODIUM AND ETHANOL NECESSARY TO MAINTAIN ANÆSTHESIA IN 50 PER CENT. OF THE MICE FOR AT LEAST 1 HOUR

Amylobarbitone sodium		Ethanol
mg./kg.		ml./kg.
0	+	5·950
30	+	4·900
60	+	2·750
90	+	1·625
120	+	0

per cent. mortality in mice which had been given approximately one-quarter, one-half or three-quarters of the MLD of amylobarbitone sodium were determined. The results are shown in Table I and Figure 1.

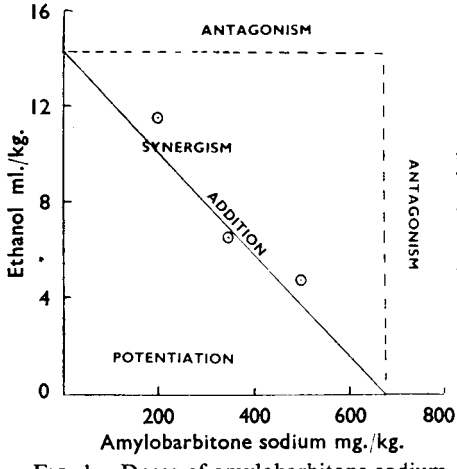

FIG. 1. Doses of amylobarbitone sodium and ethanol necessary to produce 50 per cent. mortality in mice.

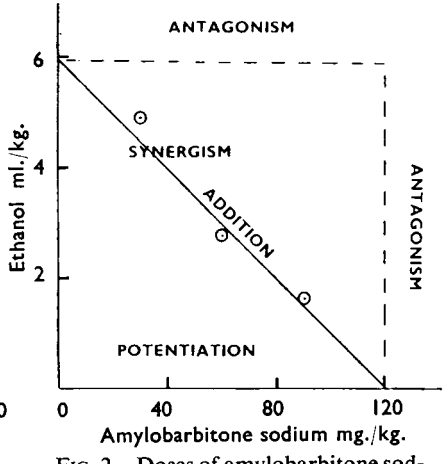

FIG. 2. Doses of amylobarbitone sodium and ethanol necessary to maintain anæsthesia in 50 per cent. of the mice for at least 1 hour.

2. *Anæsthetic Effect of Amylobarbitone Sodium and Ethanol.*

150 mice were used. The amylobarbitone sodium and ethanol were administered intraperitoneally. The median effective dose (MED) of each substance was defined as the amount necessary to maintain anæsthesia in 50 per cent. of the mice for at least 1 hour. The MED of each substance, administered alone, was determined. Groups of mice were given various doses of amylobarbitone sodium or ethanol. The animals were placed on their backs and the number in each group which failed

to right themselves within 1 hour was observed. Probits were plotted against the log-dose and the MED of amylobarbitone sodium and ethanol were estimated. Subsequent determinations were made of the amounts of ethanol to produce the median effective response when given in combination with one-quarter, one-half and three-quarters of the MED of amylobarbitone sodium. The results are shown in Table II and Figure 2.

Discussion

The results were plotted graphically to determine the nature of the combined effects of the two drugs (i.e., whether there existed synergism or antagonism) using the well-known method described by Gaddum[8]. In both figures the doses of amylobarbitone sodium were plotted as abscissæ and the doses of ethanol as ordinates. In Figure 1 a straight line was drawn to join the MLD of amylobarbitone sodium to the MLD of ethanol and in Figure 2 to join the MED of the two substances. When the results obtained with combinations of amylobarbitone sodium and ethanol were plotted on the graphs the points lay approximately on these lines. Therefore, a synergism exists between amylobarbitone sodium and ethanol. However, the combined effects are simply additive and the results of the present study provide no evidence that the toxic or anæsthetic effects of amylobarbitone sodium are potentiated by ethanol.

Several workers have investigated this problem in laboratory animals. Most investigators have reported the existence of synergic effects between barbiturates and ethanol but they have not attempted to make any quantitative studies to determine the type of this synergism. In particular, experimenters who have reported a potentiation of the effects of barbiturates by ethanol have generally not used very convincing graphical or mathematical methods to substantiate their findings.

Olszycka[3,4] measured the duration of sleep in her experiments on rats and mice. A similar method has been used in this laboratory, where an attempt was made, with mice, to determine the relationship between dose and sleeping time for amylobarbitone sodium and for combinations of the barbiturate with fixed amounts of ethanol. It was found that a linear relationship existed between the logarithm of the dose of amylobarbitone sodium and the duration of the sleep. The slope of the dose-response curve was not influenced by the presence of ethanol—a fact which provided further confirmation that the anæsthetic effect of amylobarbitone sodium is not potentiated by ethanol. However, the scatter of the observations was so wide that the method was abandoned.

In the present study, no attempt was made to follow the rates of absorption and excretion of ethanol and amylobarbitone. Since the pharmacological effects of the two drugs given together were simply additive, it was considered unlikely that the presence of one of the substances had modified the metabolism of the other. Olszycka[4] reported that the metabolism of ethanol, in rats, was not influenced by butobarbitone, and Ramsey and Haag[7] found that the distribution of ethanol and of barbiturates in body fluids was not altered when the two substances were given together.

Since the most pronounced pharmacological effect produced by both ethanol and amylobarbitone sodium is a depression of the central nervous system, it is not surprising that a synergism exists between the two substances. Jetter and McLean[6], working on rats, reported that lethal effects were produced by the administration of sublethal doses of ethanol and phenobarbitone together, and they emphasised the clinical significance of the possible effects of such a combination. Olszycka[3] found that doses of butobarbitone and ethanol, not sufficiently great to produce hypnosis when given alone, produced prolonged sleep, in mice, when administered together. The results of both these groups of workers, while indicating the existence of a synergism between these two drugs do not demonstrate that the effects of barbiturates are *potentiated* by ethanol. The present investigation showed that the type of synergism existing between amylobarbitone and ethanol is a simple additive effect. It is possible, therefore, that the administration of doses of the two drugs, not sufficient to produce toxic effects or hypnosis when administered alone, will produce very definite responses when they are given in combination. There is no doubt that the sedative effect of barbiturates would be further increased by ethanol. However, the results of experiments on laboratory animals provide no evidence that acute toxic effects would follow the ingestion of small doses of barbiturates and ethanol together.

Summary

1. Amylobarbitone and ethanol were found to act synergistically in producing toxic and anæsthetic effects in mice.

2. Graphical treatment of the results showed that the effects of the two drugs were simply additive and there was no evidence that ethanol potentiates the acute toxicity or anæsthetic effect of amylobarbitone sodium.

References

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