POTENTIATION OF PARALDEHYDE HYPNOSIS BY TOLBUTAMIDE

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The effect of tolbutamide on paraldehyde anaesthesia was studied in rats. Previous administration of tolbutamide prolongs the sleeping time. A possible mode of action is discussed.

It has been previously recorded in the New and Non Official Drugs (1958) that tolbutamide increases the barbiturate sleeping time in animals. Bhide *et al* (1963) have reported that tolbutamide increases the duration of hexobarbitone anaesthesia in rats. Consequently, the action of tolbutamide on the anaesthesia produced by other agents appeared to be worth investigating.

Beaser (1958) has recorded that prior administration of tolbutamide produces an intolerance to alcohol in the form of hot flushes. Disulfiram produces such an intolerance in a more marked way. Keplinger and Wells (1957) have reported that disulfiram prolongs the hypnotic effect of paraldehyde in mice. Hence it is possible that tolbutamide may have some action on paraldehyde anaesthesia analogous to disulfiram and the present study was undertaken to investigate it.

METHODS

Twenty four albino rats weighing between 150 and 200g were used for the experiment. The sleeping time was measured as the time from the loss of the righting reflex to its recovery. The paraldehyde was administered intraperitoneally in a dose 1.0 ml/kg as 10 per cent solution in distilled water. The onset and duration of sleep was recorded in all the twenty four rats. On the fifth day tolbutamide was administered intraperitoneally in a solution of ph 8 at a dose of 500 mg/kg in 12 rats. In the other twelve rats an inert solution of sodium bicarbonate at ph 8 was administered by the same route. The paraldehyde was administered in the above dose 1 hr after the administration of tolbutamide or the control solution. The sleeping time and the onset of sleeping were measured in all the rats. The same procedure was repeated using a tolbutamide dosage of 250 mg/kg.

RESULTS

Rats lost their righting reflex after 1.70 min with a S.D. of ± 0.05 min. The loss of righting reflex persisted for 22.1 min with a S.D, of ± 0.9 min. There was no significant difference in the sleeping times with paraldehyde alone and paraldehyde preceded by control solution. When paraldehyde was preceeded by tolbutamide at 500 mg/kg the righting reflex was lost after 1.66 min with a S D. ± 0.03 min. The loss of righting reflex persisted for 39.7 min with a S.D. of ± 0.93 min. When paraldehyde was preceded by tolbutamide (250 mg/kg), the righting reflex was lost after 1.67 min with S.D. of ± 0.05 min. The loss of righting reflex persisted for 30.1 min with a S.D. of ± 0.50 mins.

DISCUSSION

The onset of anaesthesia remains unchanged and hence tolbutamide does not change the permeability of brain cells to paraldehyde. Consequently it may be presumed that tolbutamide interferes with the metabolism of paraldehyde so that the hypnotic persists in circulation for a longer time.

Data in our laboratory (to be published) reveal that administration of insulin prior to or along with paraldehyde does not alter the sleeping time. Consequently it is unlikely that this prolongation is mediated through the release of insulin, its potentiation or by the production of hypoglycaemia.

It has previously been suggested by Keplinger and Wells (1957) that an accumulation of acetaldehyde will decrease the rate of disappearance of paraldehyde. If that be correct the disappearance of paraldehyde from the tissues would be directly regulated by systems which are concerned with the metabolism of acetaldehyde.

Hunter aad Lowry (1956) have stated that disulfiram inhibits the various enzymes which are concerned with the metabolism of acetaldehyde viz. acetaldehyde dehydrogenase, aldehyde oxidase. xanthine oxidose and glyceraldehyde-3-phosphate dehydrogenase and in the intact animal this leads to an accumulation of acetaldehyde when it is formed from ethanol.

Goodman and Gilman (1955) have stated that most of the signs and symptoms observed after the ingestion of disulfiram plus alcohol are attributable to the resultant increase in concentration of acetaldehyde in the body. Conversely it may be argued that if a drug produces a similar intolerance to alcohol it probably does so by producing an accumulation of acetaldehyde by interfering with its metabolism. Tolbutamide produces such an intolerance

possibly by interfering with the further metabolism of acetaldehyde, which in turn produces an accumulation of paraldehyde. The evidence for such an argument can be held to be complete only when the blood levels of paraldehyde and acetaldehyde are measured serially with and without tolbutamide.

TABLE

Effect of paraldehyde alone and paraldehyde preceeded by Tolbutamide on sleeping time in rats

Animals used	Drug with dose	Mean time of onset Min	Mean sleeping time Min
Rats (12)	Paraldehyde 1 ml/kg body wt.	1.70 ms. ± .05 ms.	22.1 ms. ± 0.9 ms.
Rats (12)	Paraldehyde 1 ml/kg body wt.	1.68 ms. ± .05 ms.	22.0 ms. ± 1.0 ms.
Rats (12)	Inert sol. + Paraldehyde 1 ml/kg body wt.	1.69 ms. ± .06 ms.	22.4 ms. ± 0.85 ms.
Rats (12)	Tolbutamide 500 mgs/kg + Paraldehyde 1 ml/kg.	1.66 ms. ± .03 ms.	39.7 ms. ± 0.93 ms.
Rats (12)	Tolbutamide 250 mg/kg + Paraldehyde 1 ml/kg.	1.67 ms. ± .05 ms.	30.1 ms. ± 0.50 ms.

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