THE EFFECT OF TWO CHEMOTHERAPEUTIC AGENTS ON PARALDEHYDE AND BARBITURATE HYPNOSIS

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The effects of prior administration of nitrofurantoin and griseofulvin on hypnosis produced by paraldehyde and hexobarbitone are studied. Both the chemotherapeutic agents significantly prolong the sleeping time produced by the two anaesthetics. Possible modes of action are postulated. It is suggested that this phenomenon may have a clinical significance.

Simon and Rantz (1961) have reported the occurance of intolerance to alcohol in the form of tachycardia and flushing when alcohol was preceded by griseofulvin. Beckman (1961) has recorded that nitrofurantion produces a peculiar flushing and dyspneic reaction to alcohol.

Tetraethyl thiuram disulphide is well known for its production of intolerance to alcohol. It was reported that disulfiram prolongs the hypnotic effect of paraldehyde in mice. Goodman and Gilman (1955) have recorded that TETD markedly prolongs the duration of barbiturate-sleeping in several species of laboratory animals. Tolbutamide is also known to produce an intolerance to alcohol. It has been recorded in the New and Non official Drugs (1958) that tolbutamide prolongs the barbiturate sleeping time in rats. It was also reported that tolbutamide prolongs the paraldehyde sleeping time in rats.

Consequently, it was thought likely that griseofulvin and nitrofurantoin may have some effect in barbiturate and paraldehyde anaesthesia and the present study was undertaken to investigate it.

METHODS

Paraldehyde.—Twelve albino rats weighing between 150 and 200g were used for the experiment. The sleeping time was measured as the time from the loss of righting reflex to its recovery. The onset and duration of sleep was recorded. Six were fed with griseofulvin 500 mg/kg. Four hrs after-all the twelve rats were injected paraldehyde (1 ml/kg as a 10 per cent solution in distilled water' intraperitoneally. After a week the experiment

was repeated, crossing over the control and drug-treated animals. The procedure was repeated using griseofulvin at 250 mg/kg.

Hexobarbitone.—Only male albino rats were used for the experiment. The procedure was identical to the above excepting that instead of paraldehyde. hexobarbitone (100 mg/kg) was employed.

DISCUSSION

Keplinger and Wells have presented evidence that an accumulation of acetaldehyde will decrease the rate of disappearance of paraldehyde in the intact animal. Gaddum (1959) has stated that in a TETD—alcohol reaction acetaldehyde accumulates and produces the unpleasant effects. Hunter and Lowry (1956) have reported that TETD depresses the liver enzymes like acetaldehyde dehydrogenase, aldehyde oxidase, xanthine oxidase and glyceraldehyde-3-phosphate dehydrogenase, which are involved in the metabolism of alcohol, and produces an accumulation of acetaldehyde. Tunbridge (1959) and others have reported the occurance of intolerance to alcohol after prior administration of tolbutamide. In the case of tolbutamide also it has been reported by Fasset (1963) that the intolerance to alcohol is due to the depression of liver enzymes, alcohol dehydrogenase and acetaldehyde dehydrogenase and the consequent accumulation of acetaldehyde. Both griseofulvin and hitrofurantoin produce an intolerance to alcohol. They are also found to prolong the action of paraldehyde. Hence it is likely that the intolerance to alcohol is produced by the accumulation of acetaldehyde and that the accumulation of acetaldehyde is responsible for the prolonged sojourn of paraldehyde in the body.

Only male rats were used for the experiment, since it is known that the sleeping times between male and female rats with hexobarbitone vary enormously. Bhide *et al.*, (1963) have stated that hexobarbitone is destroyed by microsomal enzymic systems in the liver and it appears that there are a series of substances which can either activate these enzymes or inhibit them. Brodie (1962) has stated that phenobarbitone, chlorcycline and phenylbutazone produce an enhancement of the enzymes which metabolise hexobarbitone. SK F525 and tolbutamide inhibit this enzyme (Rummer, 1962). Pretreatment with the former group of drugs shortens the hexobarbitone sleeping time, where as pretreatment with the latter group increases the hexobarbitone sleeping time. It it quite possible that these two chemotherapeutic agents inhibit enzymes concerned with the metabolism of hexobarbitone.

TABLE I

Showing the mean sleeping time with and without the previous administration of drugs.

(Figures in parenthesis denote the number of animals used)

Species	Drug with dose	Mean time for onset in minutes	Mean sleeping time in minutes.
Rats (12)	Hexobarbitone 100 mg/kg I.L.	2.60 ± 0.03	24.5 ± 0.4
Rats (12)	Griesofulvin 500 mg/kg oral	2.58 ± 0.02	38 2 ± 0.5
	Hexobarbitone 100 mg/kg I.L.		
Rats	Griesofulvin 250 mg/kg		
(12)	Hexobarbitone 100 mg/kg I.P.	2.61 ± 0.04	31.1 ± 0.50
Rats	Hexobarbitone 100 mg/kg I.L.	2.61 ± 0.05	23.5 ± 0.5
(12)	Nitrofurantoin 200 mg/kg oral	2.62 ± 0.04	35.2 ± 0.4
	+		
	Hexobarbitone 100 mg/kg I.L.		
Rats	Nitrofurantoin 100 mg/kg		
(12)	Hexobarbitone 100 mg/kg	2.61 ± 0.02	27.1 ± 0.5
Rats (12)	Paraldehyde 1 mg/kg I.L.	1.61 ± 0.03	22.4 ± 0.4
	Griseofulvin		
	500 mg/kg oral	1.62 ± 0.04	39.6 ± 0.5
	+		
	Paraldehyde 1 ml/kg I.L.		
Rats	Griseofulvin 250 mg/kg oral		
(12)	+		
	Paraldehyde 1 ml/kg	1.60 ± 0.0	31.2 ± 0.3
Rats (12)	Paraldehyde 1 ml/kg I.L.	1.62 ± 0.03	22.1 ± 0.3
	Nitrofurantoin		
	200 mg/kg oral		
	+		
	Paraldehyde 1 ml/kg I.L.	1.61 ± 0.04	35.6 ± 0.5
Rats			
(12)	Nitrofurantoin		
	100 mg/kg oral		
	+		
	Paraldehyde	1.59 ± 0.01	29.1 ± 0.2.
	1 ml/kg. I.L.		

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