RESEARCH PAPERS

POLYVINYLPYRROLIDONE AS A DRUG RETARDANT

PART I. EFFECT ON BARBITURATES

BY W. DONALD GRAHAM, R. SLINGER and H. TEED

From the Food and Drug Laboratories, Department of National Health and Welfare, Ottawa, Canada.

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A CONSIDERABLE body of evidence[1] has accumulated concerning the efficacy of polyvinylpyrrolidone in prolonging, and in some cases increasing, the action of various drugs. Among the drugs thus affected, it is claimed, are the barbiturates. Quevauviller[2] has demonstrated that in the presence of a hypertonic solution of polyvinylpyrrolidone, the duration of anæsthesia induced by hexobarbitone, when injected intravenously into mice, is nearly doubled. Roux *et al.*[3] showed that in humans, for a given dose of thiopentone, the presence of polyvinylpyrrolidone appreciably prolonged the duration of anæsthesia. On the other hand Moss *et al.*[4] have found that the presence of polyvinylpyrrolidone decreased the toxicity of pentobarbitone for mice and at the same time decreased the effectiveness of the drug as measured by duration of anæsthesia. According to Schubert[5] polyvinylpyrrolidone had a similar effect on phenobarbitone but not on barbitone. Moss *et al.*[4] concluded that the effect of polyvinylpyrrolidone as an adjuvant in therapy was not predictable and that its use with each drug must be tested.

In view of the present interest in this use of polyvinylpyrrolidone and of the confusion which appears to exist, some of the barbiturates have been studied to determine whether or not prolongation of drug action occurred when polyvinylpyrrolidone solution was used as the drug vehicle.

EXPERIMENTAL METHODS AND RESULTS

Thiopentone was prepared just before use as a 10 mg./ml. solution in water containing 0, 1·0, 2·0, or 4·0 per cent. w/v of polyvinylpyrrolidone*. (Anhydrous sodium carbonate was added at the rate of 60 mg./g. of thiopentone sodium.) These solutions were each injected into the tail vein of 10 female albino mice weighing 18 to 31 g. at the rate of 4·0 ml./kg. of body weight. The time from injection to return of the righting reflex was recorded. The results of this experiment were rather variable so that a trend toward increased duration of anæsthesia with increasing amounts of polyvinylpyrrolidone proved to have no statistical significance. The experiment was repeated using a group of female mice of narrower weight range (22 to 28 g.) and extending the polyvinylpyrrolidone concentrations to cover 0, 2·5, 5·0, 10·0, 20·0 and 40·0 per cent. w/v. The

* The polyvinylpyrrolidone used in these experiments was Plasdone, supplied by General Aniline and Film Corporation. A 1 per cent. aqueous solution has a K (Fikentscher) value of 30 ± 2.

results of this experiment are shown in Table I. From these results it would appear that the intravenous injection in mice of polyvinylpyrrolidone with thiopentone failed to influence the duration of the anæsthesia induced by the barbiturate.

These experiments were extended to include similar studies on albino

TABLE I

EFFECT OF POLYVINYLPYRROLIDONE ON THE DURATION OF THIOPENTONE ANÆSTHESIA IN FEMALE MICE

Polyvinylpyrrolidone per cent. w/v	Time to return of righting reflex in minutes		Survivors of 10
	Mean	Standard deviation	
0	7·0	2·9	10
2·5	7·6	1·3	9
5·0	7·5	2·7	10
10·0	7·5	3·0	10
20·0	7·0	2·0	10
40·0	7·2	1·9	10

rats. The 10 mg./ml. solutions of thiopentone in buffered water containing 0, 5·0, 10·0, 20·0, or 40·0 per cent w/v of polyvinylpyrrolidone were administered to groups of 10 male rats at the rate of 2·0 ml./kg. of body weight. The injections were made *via* the saphenous vein. The results of one of two such experiments are presented in Table II. Analysis of

TABLE II

EFFECT OF POLYVINYLPYRROLIDONE ON THE DURATION OF THIOPENTONE ANÆSTHESIA IN MALE RATS

Polyvinylpyrrolidone per cent. w/v	Time to return of righting reflex in minutes		Survivors of 10
	Mean	Standard deviation	
0	46·4	14·3	10
5·0	34·6	21·3	10
10·0	50·1	20·3	10
20·0	39·6	30·3	10
40·0	22·6*	16·2	10

* 22·6 by the "t" test is the only mean differing significantly (P = 0·05) from 46·4, the mean for the control group.

variance indicated that there was a "between groups" effect (just significant at P = 0·05), largely attributable to the shortened duration of anæsthesia at the 40 per cent. level of the carrier. When the experiment was repeated this effect was not observed. It may be concluded that polyvinylpyrrolidone did not prolong or potentiate the effect of thiopentone in male rats.

As an example of a barbiturate with more prolonged action than thiopentone, hexobarbitone was selected for investigation. 3 concentrations of the drug were prepared as aqueous solutions containing 0, 5·0, 10·0, 20·0 or 40·0 per cent. w/v of polyvinylpyrrolidone. All doses were administered intraperitoneally at the rate of 4·0 ml./kg. of body weight to female albino rats in randomly selected groups of 10 animals. The results of one of these experiments are presented in Table III. When the results were summed by polyvinylpyrrolidone level, the application of the

"t" test failed to indicate that polyvinylpyrrolidone had any significant influence on the activity of the barbiturate.

With quinalbarbitone, in addition to a series where the polyvinylpyrrolidone was mixed directly with the barbiturate, a second series of tests was run where the polyvinylpyrrolidone (saline controls) was adminis-

TABLE III

EFFECT OF POLYVINYLPYRROLIDONE ON THE DURATION OF HEXOBARBITONE ANÆSTHESIA IN FEMALE RATS

Polyvinylpyrrolidone per cent. w/v	Hexobarbitone mg./kg. intraperitoneally		
	60	75	94
	Time to return of righting reflex in minutes Mean ± standard deviation		
0	30·8 ± 5·7	46·4 ± 14·4	72·6 ± 15·3
5·0	37·0 ± 4·1	43·1 ± 15·2	72·6 ± 17·7
10·0	32·0 ± 7·0	56·9 ± 16·8a	68·8 ± 25·8
20·0	38·4 ± 5·7b	52·2 ± 19·9b	67·3 ± 5·1a
40·0	42·7 ± 12·7	52·6 ± 18·9	78·3 ± 18·4ab

a — 1 dead.
b — 1 failed to lose righting reflex.

tered as a separate injection 30 minutes before the injection of the quinalbarbitone. All injections were made intraperitoneally into groups of 10 female albino rats. The polyvinylpyrrolidone was administered at the rate of 10·0 ml. of a 25·0 per cent. solution per kg. of body weight. The quinalbarbitone was given at the rate of 3·0 ml/kg. in such concentrations that the rats received 15·4, 19·2, 24·0, or 30·0 mg. of quinalbarbitone per kg. The combined quinalbarbitone-polyvinylpyrrolidone was injected at the rate of 13·0 ml./kg. The results of this experiment are presented in Table IV.

TABLE IV

EFFECT OF POLYVINYLPYRROLIDONE ON THE DURATION OF QUINALBARBITONE NARCOSIS IN FEMALE RATS

Quinalbarbitone mg./kg.	Polyvinylpyrrolidone		Saline	
	Given early	With quinalbarbitone	Given early	With Quinalbarbitone
	Time to return of righting reflex in minutes Mean ± standard deviation			
15·4	23·9 ± 9·6	28·5 ± 12·5	33·1 ± 5·7	——a
19·2	65·8 ± 23·6	72·7 ± 28·4b	59·0 ± 21·4	60·2 ± 20·5
24·0	97·7 ± 39·0	105·1 ± 33·4	120·0 ± 14·9	98·4 ± 39·7
30·0	134·0 ± 39·8	153·4 ± 28·6	148·2 ± 36·0	144·0 ± 42·6c

a — This group was omitted because of lack of space.
b — 1 dead.
c — 2 dead.

It is apparent from these results that only in a few instances was the return of the righting reflex delayed by the presence of polyvinylpyrrolidone as compared with the respective saline control groups. Where a delay did occur, application of the "t" test indicated that the values were not significantly different at $P = 0.05$.

Since concentrated solutions of polyvinylpyrrolidone are very viscous it was considered that when such solutions bearing a pharmacologically active drug were given by subcutaneous injection, some delay in absorption of the latter might occur. To test this possibility hexabarbitone solutions of 3 different concentrations were prepared in 0, 5·0, 10·0, 20·0, or 40·0 per cent. w/v of polyvinylpyrrolidone in water. All solutions were injected subcutaneously into groups of 10 female albino rats at the rate of 4·0 ml/kg. of body weight. The time from injection to return of the righting reflex was recorded with the results shown in Table V.

TABLE V

EFFECT OF POLYVINYLPYRROLIDONE ON THE DURATION OF ANÆSTHESIA CAUSED BY HEXOBARBITONE IN FEMALE RATS

Polyvinylpyrrolidone per cent. w/v	Hexabarbitone mg./kg. subcutanously		
	70	87	109
	Time to return of righting reflex in minutes Mean ± standard deviation		
0	56·7 ± 10·8	75·5 ± 24·4	115·1 ± 23·1
5·0	51·9 ± 10·4	72·4 ± 14·6	95·9 ± 13·5
10·0	60·6 ± 12·6	73·2 ± 19·5	101·7 ± 26·1d
20·0	56·6 ± 1·7a	44·8 ± 17·9	109·5 ± 24·6
40·0	———b	———b	87·6 ± 19·8c

a — 5 failed to lose righting reflex.
b — 10 failed to lose righting reflex.
c — 3 failed to lose righting reflex. Mean difference between 87·6 and 115·1 significant at P = 0·05.
d — 1 dead.

The results with the 40 per cent. level of polyvinylpyrrolidone indicate that the potency of the hexobarbitone was decreased by the presence of the viscous carrier. These results may readily be explained on the basis that absorption of the hexobarbitone in these instances was slowed to such a degree that only at the high barbiturate level was the blood level of hexobarbitone sufficient to produce loss of the righting reflex and then only in 7 of 10 rats. Even with 20 per cent. polyvinylpyrrolidone as the carrier only 5 of 10 rats receiving 70 mg. of hexobarbitone per kg. lost their righting ability; at the 87 mg./kg. level of hexobarbitone the time to return of the righting reflex was significantly shortened. This would appear to be a mechanical effect which might be expected from any highly viscous carrier.

In an effort to duplicate the work of Moss *et al.*[4] on the influence of polyvinylpyrrolidone on the toxicity of pentobarbitone, 120 mice were distributed at random into 10 groups. 5 of these groups received 0·5 ml. of 20 per cent. w/v polyvinylpyrrolidone solution and 5 received 0·5 ml. of 0·9 per cent. saline solution by intraperitoneal injection. Immediately after this injection pentobarbitone was administered by the same route at the rate of 10 ml. of solution per kg. of body weight. The concentrations of pentobarbitone were such that 132·0, 145·2, 159·7, 175·7, or 193·3 mg. of drug were administered per kg. of mouse. Mortality was recorded with the results shown in Table VI.

Probit analysis failed to reveal any significant difference in toxicity of the pentobarbitone whether or not polyvinylpyrrolidone was also

administered. From observation of the time of recovery of the surviving mice in this experiment there was no reason to believe that the potency of the pentobarbitone was influenced by the treatment.

TABLE VI

EFFECT OF POLYVINYLPYRROLIDONE ON THE TOXICITY OF PENTOBARBITONE TO FEMALE MICE

Pentobarbitone mg./kg.	Per cent. mortality	
	With polyvinylpyrrolidone	With saline solution
132·0	0	16·2
145·2	33·4	16·2
159·7	58·4	66·7
175·7	91·8	83·4
193·3	100·0	100·0

CONCLUSION

It has been demonstrated that polyvinylpyrrolidone solutions up to 40 per cent. w/v in concentration, when used as carrier vehicles for barbiturates, had little or no influence on the potency or on the duration of action of the drugs administered by the intraperitoneal quinalbarbitone, hexobarbitone, pentobarbitone) or intravenous (thiopentone) routes. By the subcutaneous route (hexobarbitone) the polyvinylpyrrolidone, in the highest concentration used, served to delay absorption of the drug. In this instance a higher drug dosage level was required for a given effect. Polyvinylpyrrolidone did not influence the toxicity of intraperitoneally-administered pentobarbitone.

No explanation for the discrepancies between these results and those in the literature demonstrating a drug retarding action of polyvinylpyrrolidone has been found.

REFERENCES

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