RESEARCH PAPERS

POLYVINYLPYRROLIDONE AS A DRUG RETARDANT

PART II. EFFECT ON ANALGESICS

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IN 1948, Siguier *et al.*[1] reported that polyvinylpyrrolidone prolonged the clinical analgesic effect of morphine and opium, thus permitting an appreciable reduction in the number of injections needed daily to produce satisfactory analgesia. In addition, the total daily dose of morphine could be reduced to 67 per cent. of that required when polyvinylpyrrolidone was not used. Animal experiments were inconclusive. Physical measurements of the influence of polyvinylpyrrolidone on morphine dialysis rates indicated that the polymer had no retardant action unless its concentration was 15 per cent. or greater. Schubert[2] found that polyvinylpyrrolidone had no influence on morphine toxicity in guinea-pigs. Wide interest exists in the use of polyvinylpyrrolidone as a drug retardant and, as part of a continuing study[3], the following investigations were conducted in an effort to establish whether or not polyvinylpyrrolidone extended the effective duration of analgesia or influenced the potency of the more common analgesic drugs.

EXPERIMENTAL METHODS AND RESULTS

By random selection, 60 Wistar strain rats of one sex were divided into 5 equal groups and placed in individual cages. No rats smaller than 100 g. or larger than 200 g. were used and, within any one group of 60, the weight range was kept to 60 g. Each rat was tested for its sensitivity to a painful stimulus by placing it in a specially constructed holder and exposing an area about 1 inch from the tip of the blackened tail to a high intensity light beam from the Hardy–Wolff–Goodell apparatus. The time required for the rat to respond to this stimulus, by flicking its tail, was recorded. After several trial runs to accustom the animals to the procedure, the final set of readings was used to calculate a "cut off" time for the exposure. With this duration of exposure, usually 5 to 7 seconds, 95 per cent. of the rats might be expected to respond to the stimulus in 95 per cent. of trials.

Immediately upon completion of this calculation, the animals were dosed on a timed schedule. At 30 and 60 minutes and at hourly intervals thereafter up to 4 to 6 hours the rats' tails were exposed to the standard stimulus. The number of rats in each group failing to respond to the stimulus was recorded. In this manner a measure of the rapidity of onset, the degree, and the duration of analgesia was obtained.

The solutions of analgesics to be injected were prepared in 5 times

the required concentration and diluted to the final volume with appropriate amounts of a 50 per cent. aqueous solution of polyvinylpyrrolidone and of distilled water. Polyvinylpyrrolidone* concentrations in the final solutions were 0, 5·0, 10·0, 20·0, or 40·0 g./100 ml. of solution. The concentration of analgesic drug was such that the stated dose in mg./kg. was administered subcutaneously in 2·0 ml./kg. or intramuscularly in 1·0 ml./kg. Subcutaneous injections were made below the skin of the ventral surface while intramuscular injections were made through the inner aspect of the right thigh.

When morphine sulphate (4·0 mg./kg.), pethidine hydrochloride (32 mg./kg.), or methadone hydrochloride (2·5 mg./kg.) was given intramuscularly the only observable effect of the polyvinylpyrrolidone was, at the high concentrations, a delay in the onset of analgesia. Analgesic potency and duration of action were virtually unaffected. A typical protocol for pethidine, with which the effect was most obvious, is presented in Table I.

TABLE I

EFFECT OF POLYVINYLPYRROLIDONE ON THE ACTION OF PETHIDINE IN FEMALE RATS. EXPERIMENTS MADE ON DIFFERENT DAYS

Polyvinyl-pyrrolidone per cent.	Number of rats of 12 failing to respond to a standard stimulus						
	Minutes after intramuscular injection of 32 mg. of pethidine/kg.						
	30	60	120	180	240	300	360
Experiment I							
0	10	11	9	6	5	4	3
5·0	9	8	9	7	3	3	2
10·0	11	8	7	5	3	3	2
20·0	7	9	6	6	5	2	2
40·0	2	3	7	10	8	4	2
Experiment II							
0	11	12	11	9	7	1	0
5·0	12	12	12	10	8	6	2
10·0	12	12	11	10	9	3	2
20·0	11	12	10	9	8	5	1
40·0	5	6	9	12	12	9	2

An analysis of variance of these data indicated that the main effects due to "time" and to "experiments" were significant at $P = 0{\cdot}05$. The effect of polyvinylpyrrolidone was not significant. Of the first order interactions, that between "polyvinylpyrrolidone" and "time" closely approached significance as might be expected from the observed tendency for high levels of the carrier to delay response to the analgesic. The significant effect due to "experiments" indicates that one lot of rats was more susceptible to pethidine. Part of this may have been caused by considerable variations in room temperature between the days on which the experiments were conducted and part by the fact that the rats in experiment II were heavier than those in experiment I.

A consideration of the data in Table I will reveal how an apparently increased potency for pethidine in 40 per cent. polyvinylpyrrolidone

* 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.

might be demonstrated if potency measurements were made 3 to 4 hours after injection of the drug. If potency measurements were made only 1 hour after the injection the reverse would be true. This effect appears to be one of delayed absorption and occasionally was observed with 20 per cent. of polyvinylpyrrolidone but never with the lower concentrations. In several experiments 40 per cent. of polyvinylpyrrolidone appeared to prolong analgesic activity; in others the analgesia wore off more rapidly. In general, the duration of action of the analgesics was virtually unchanged regardless of the concentration of the drug carrier over the range 0 to 40 per cent.

These comments apply almost equally well to the experiments where the analgesics were injected subcutaneously. The dosages used were for morphine sulphate 5 mg./kg., for pethidine hydrochloride 40 mg./kg., and for methadone hydrochloride 4 mg./kg. A typical protocol, that for methadone, is presented in Table II. Here the peak response to methadone in 40 per cent. polyvinylpyrrolidone was not sufficiently delayed that any increase or decrease in potency of the methadone might erroneously be attributed to the presence of the carrier.

TABLE II

EFFECT OF POLYVINYLPYRROLIDONE ON THE ACTION OF METHADONE IN MALE RATS

Polyvinyl-pyrrolidone per cent.	Number of rats of 12 failing to respond to a standard stimulus					
	Minutes after subcutaneous injection of 4 mg. of methadone/kg.					
	30	60	120	180	240	300
Experiment I						
0	12	12	11	9	7	3
5·0	11	11	10	4	2	1
10·0	11	11	11	6	6	2
20·0	10	12	11	5	4	2
40·0	9	12	11	7	4	2
Experiment II						
0	12	12	12	5	2	3
5·0	12	12	11	6	4	2
10·0	11	12	11	6	2	1
20·0	12	12	12	10	4	4
40·0	9	11	10	7	4	3

An analysis of variance of these results indicated that the effect due to "time" was significant as would be expected. None of the other main effects or first order interactions were significant.

From the results of these experiments involving 720 rats it would appear that the use of polyvinylpyrrolidone as a retardant for morphine, pethidine, or methadone is of little practical significance in so far as its effects can be measured in rats by the techniques used. A 40 per cent. solution of polyvinylpyrrolidone is much too viscous to be handled easily and concentrations lower than this have little or no influence on the duration, potency, or onset of the analgesia produced by the drugs studied.

CONCLUSION

Under the conditions described, polyvinylpyrrolidone in concentrations up to 40 per cent. had no marked influence on the duration of action, or potency of morphine, pethidine, or methadone in rats. The onset of

analgesia was somewhat delayed by the presence of the highest concentration of polyvinylpyrrolidone, particularly when the drugs were injected intramuscularly.

REFERENCES

1. Siguier, Giudicelli and Walter, *Progrès méd.*, 1948, No. 9, 223.
2. Schubert, *Ärztl. Forschg.*, 1950, **4**, 42.
3. Graham, Slinger and Teed, *J. Pharm. Pharmacol.*, 1954, **6**, 27.