THE STABILITY OF NORADRENALINE SOLUTIONS

By G. B. WEST

From the Department of Pharmacology and Therapeutics, University of St. Andrews Medical School, Dundee

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NORADRENALINE is rapidly becoming the drug of choice for the treatment of acute hypotension following splanchnicectomy and lumbar sympathectomy.[1,2] When phæochromocytoma are removed, infusions of noradrenaline have been administered over many hours to maintain the blood pressure.[3] It is important, therefore, to be sure that the activity of such infusions is maintained when they are used in medicine. The object of this investigation was to determine (*a*) the optimal conditions for stability of strong solutions of noradrenaline, and (*b*) if any deterioration occurs when dilutions of noradrenaline are stored under conditions which simulate those in the operating theatre.

METHODS

One sample of pure synthetic *l*-noradrenaline bitartrate (2 mg. = 1 mg. of base) was used for preparing solutions of noradrenaline of a strength of 1 in 1000 in freshly prepared distilled water containing 0·8 per cent. of sodium chloride (Analar). They were divided into two equal volumes and to one was added 0·1 per cent. of sodium metabisulphite (B.P.). The *p*H values of these solutions were determined with a Cambridge *p*H meter. Solutions of other *p*H values were prepared by the addition of the minimal quantity of hydrochloric acid or sodium bicarbonate. The solutions were transferred to freshly washed and dried 1-ml., 5-ml. and 10-ml. ampoules, which complied with the official tests for limit of alkalinity of glass. Some ampoules were filled with the solutions whilst others were left half full. Batches of the sealed ampoules were maintained at 115° C. for 30 minutes or 6 hours. The solutions were then assayed biologically by their effects on the blood pressure of a spinal cat and the pendular movements of an isolated strip of rabbit ileum. The standard reference solution used throughout was an unheated solution of noradrenaline bitartrate (1 in 1000 of base) containing 0·1 per cent. of sodium metabisulphite. This was stored in the refrigerator (4° C.) when not in use.

For the tests for stability of dilutions, ampoules of the standard reference solution and of noradrenaline supplied by Bayer Products Ltd. ("Levophed") were used. A known volume was first added to 100 ml. of isotonic sodium chloride solution, 5 per cent. dextrose solution in distilled water, or distilled water to give final concentrations of noradrenaline of 10^{-6}, 4×10^{-6} and 10^{-5}. The *p*H values of these solutions were determined. In some experiments, this was adjusted to *p*H 7·9 with solid sodium bicarbonate. Solutions were then stored at 37°, 18° and 4° C. for 6, 12 and 48 hours before being assayed. In the case of the

alkaline solutions, comparisons were made after storage for 6 hours at 18° C. and 30 minutes and 1 hour at 37° C. In the second series of experiments, solutions of noradrenaline of similar strengths were prepared using as diluents isotonic sodium chloride solution alone and with ascorbic acid (0·001 per cent.), 5 per cent. dextrose solution in distilled water, or rabbit, cat or human plasma and whole blood. The dilutions were stored for 6, 9, 12 and 24 hours at room temperature (18° C.) before being assayed. Control injections of the diluents into the cat were ineffective.

RESULTS

The *p*H values of solutions of noradrenaline (1 in 1000) in distilled water containing 0·8 per cent. of sodium chloride with and without 0·1 per cent. of sodium metabisulphite were 3·5 and 3·9 respectively. There was little alteration in these values following the heat treatment. The results of the assays on these heated solutions are shown in Table I.

TABLE I

THE EFFECT OF METABISULPHITE ON THE COLOUR AND PHYSIOLOGICAL ACTIVITY OF SOLUTIONS OF NORADRENALINE BITARTRATE (1 IN 1000 OF BASE) WHEN HEATED IN AMPOULES. STANDARD REFERENCE SOLUTION IS AN UNHEATED SOLUTION CONTAINING 0·1 PER CENT. OF SODIUM METABISULPHITE

Size of ampoule (ml.)	Volume contained (ml.)	30 minutes at 115° C.				6 hours at 115° C.			
		Plain solutions		Solutions with metabisulphite		Plain solutions		Solutions with metabisulphite	
		Colour	Activity	Colour	Activity	Colour	Activity	Colour	Activity
1	1·2	Grey-brown	85	Colourless	100	Dark brown	40	Light brown	60
	0·6	Grey-brown	75	Colourless	95	Dark brown	20	Light brown	50
5	6·4	Brown	80	Colourless	100	Dark brown	20	Colourless	89
	3·2	Dark brown	75	Colourless	95	Dark brown	20	Light brown	82
10	11·0	Brown	70	Colourless	95	Dark brown	10	Colourless	70
	5·5	Dark brown	50	Colourless	91	Dark brown	5	Light brown	65

It will be noted that the presence of metabisulphite is essential for stability. In its presence, solutions of noradrenaline bitartrate may be autoclaved without a significant loss in activity. In the longer heating experiments, the colour of the solution is no longer a guide to activity. Solutions in half-filled ampoules deteriorate more than those in full ampoules.

Solutions of noradrenaline bitartrate at various *p*H values were then heated for 6 hours at 115° C. in full 5-ml. ampoules to determine the optimal *p*H value for stability. The results shown in Figure I clearly indicate that this value lies around 3·5. The reason why noradrenaline without metabisulphite should be more stable at more acid *p*H values is not clear, although a different inactivation process is suggested by the yellow-brown colour of these solutions.

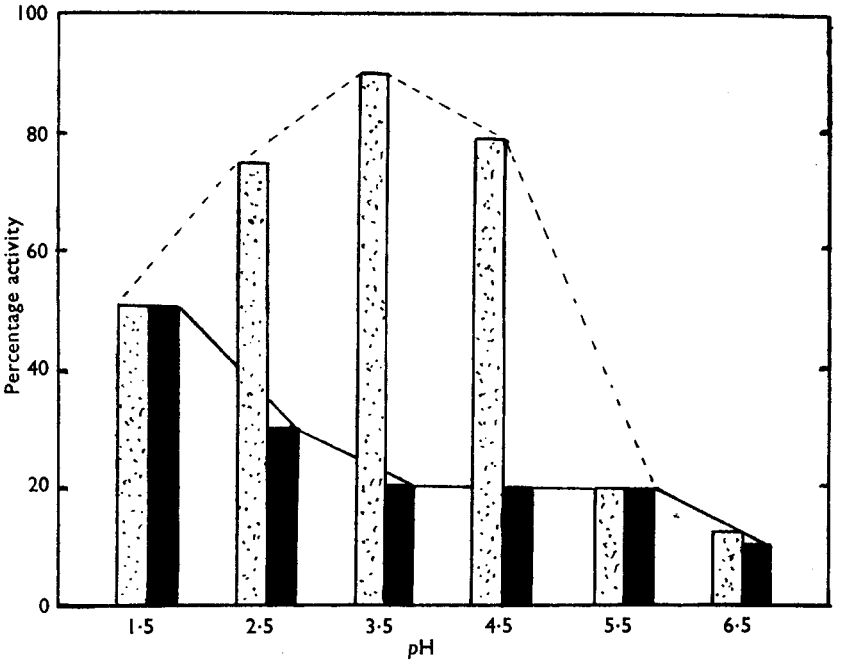

FIG. 1. The influence of metabisulphite (0·1 per cent.) on the physiological activities of solutions of noradrenaline bitartrate (1 in 1000 of base) of varying *p*H values, when heated for 6 hours at 115° C. in full 5-ml. ampoules. Black areas represent plain solutions; stippled areas are solutions with metabisulphite. Standard reference solution of noradrenaline (1 in 1000) = 100 per cent.

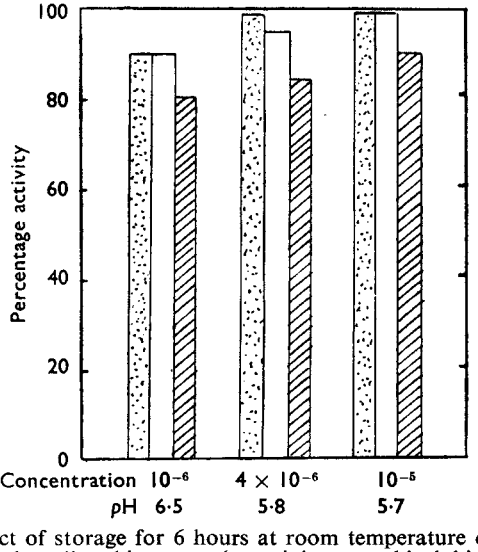

FIG. 2. The effect of storage for 6 hours at room temperature on the activities of dilutions of noradrenaline bitartrate (containing metabisulphite) in 5 per cent. dextrose solution, distilled water, and normal saline. Plain areas, distilled water; stippled areas, dextrose solution; shaded areas, saline solution.
Note that dilutions in saline solution lose activity first.

In the first series of dilution experiments, storage of solutions of noradrenaline at 3 concentrations showed that even at room temperature dilutions in saline solution tend to lose activity whilst those in dextrose solution and water do so at a much slower rate (Fig. 2). A similar picture was seen when dilutions at 10^{-5} were stored for 48 hours at 3 different temperatures (Fig. 3A). When the diluted solutions were made alkaline and stored, the results shown in Figure 3B were obtained. There was a significent loss of activity when such dilutions in saline were stored at room temperature for 6 hours.

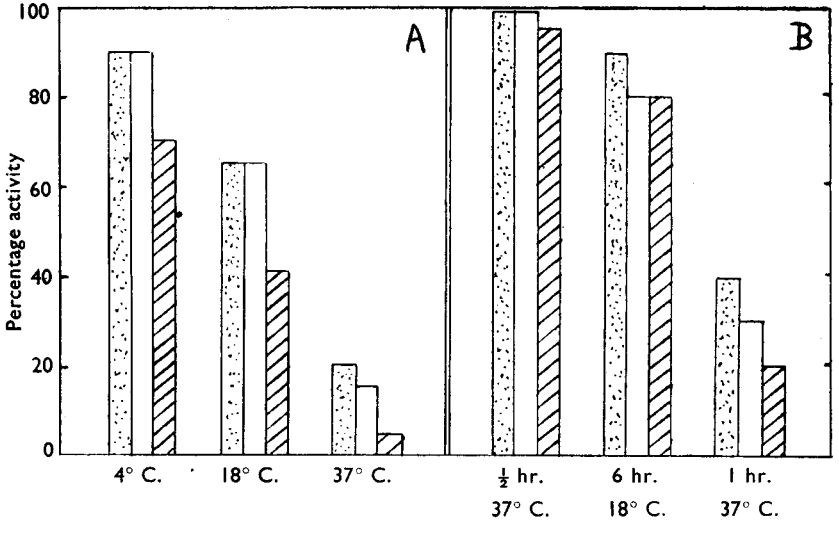

FIG. 3A. The effect of temperature on the activities of noradrenaline dilutions (10^{-6}) when stored for 48 hours. Initial *p*H 5·6. Dilutions in saline solution again show greatest loss of activity.
FIG. 3B. The effect of storage on the activities of noradrenaline dilutions (4×10^{-6}) adjusted to *p*H 7·9. Dilutions in saline solution and water show some loss when stored for 6 hours at 18° C. Plain areas, distilled water; stippled areas, dextrose solution; shaded areas, saline solution.

Similar dilutions of noradrenaline in blood, plasma and saline solution with ascorbic acid (10^{-5}) were next tested and the results of the assays are shown in Figure 4. After 6 hours storage at room temperature, some loss of activity was shown in the dilutions in saline solution and in whole blood. However, even after 12 or 24 hours, the relative activities of dilutions in plasma, dextrose solution and saline solution containing ascorbic acid were very high.

DISCUSSION

The effect of *p*H on the stability of noradrenaline in solution (1 in 1000) has been studied at a high temperature (115° C.) for short periods since it would be necessary to keep the solutions for many months or even years to obtain any considerable destruction at low temperatures. It is

possible, however, to use the results to form an opinion of the effects of low temperatures and long periods, i.e. the stability during storage. The optimum conditions for stability have been found to be possessed by solutions of noradrenaline bitartrate (1 in 1000 of base) containing 0·1 per cent. of sodium metabisulphite. Such solutions (*p*H 3·5 to 3·9) may be autoclaved (115° C. for 30 minutes) without loss of activity, provided the ampoules are more than half-full. These conditions are very similar to those found in corresponding experiments carried out to test the stability of adrenaline tartrate in solution.[4]

In the dilution experiments carried out under conditions similar to those used in clinical practice, saline solution appears to be the diluent allowing greatest loss of activity. No significant loss of activity, however, was found

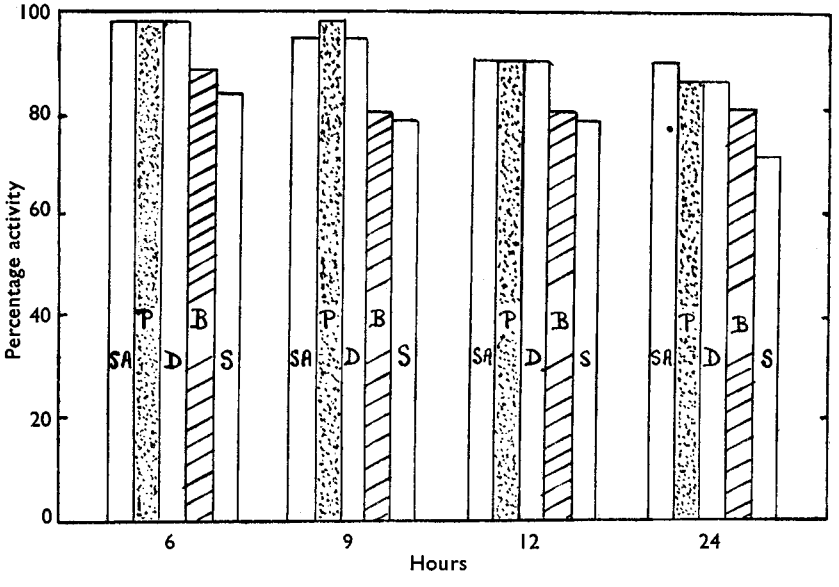

FIG. 4. The effect of storage at room temperature on the activities of dilutions of noradrenaline bitartrate (10^{-6} to 10^{-5}) in saline solution with 10^{-5} ascorbic acid (SA), plasma (P), dextrose 5 per cent: in water (D), whole blood (B), and saline solution (S). Initial *p*H values 5·9 to 6·7. Dilutions in dextrose solution or plasma are fairly stable.

when dilutions in plasma, dextrose solution or saline solution containing ascorbic acid (10^{-5}) were stored for up to 9 hours at room temperature. Corresponding experiments using adrenaline acid tartrate also showed a similar pattern of results. Dilutions of adrenaline or noradrenaline in a mixture of equal volumes of normal saline solution and dextrose solution again showed loss of activity but it was not as great as that found in dilution experiments in saline solution alone. Further work showed that dilutions of noradrenaline in an isotonic mixture of 4 per cent. dextrose solution and 0·18 per cent. sodium chloride solution in distilled water are as stable as those in 5 per cent. dextrose solution in distilled water.

SUMMARY

(1) It is suggested that the optimum conditions for stability and storage of solutions of noradrenaline when enclosed in well-filled ampoules are (*a*) an initial *p*H of approximately 3·6, and (*b*) the presence of 0·1 per cent. of sodium metabisulphite.

(2) A solution of noradrenaline bitartrate with metabisulphite satisfies these conditions and can be sterilised by autoclaving (115° C. for 30 minutes), for the loss of activity would be negligible.

(3) Dilutions of noradrenaline bitartrate solutions with metabisulphite are more stable in 5 per cent. dextrose solution, in distilled water, and in plasma than in saline solution and whole blood.

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