

Title: THE EFFECTS OF pH ON THE OXIDATION RATE OF EPINEPHRINE

Authors: S.M. Parnass, M.D., V.L. Baughman, M.D., D.J. Miletich, Ph.D., R.F. Albrecht, M.D.

Affiliation: Department of Anesthesiology, Michael Reese Hospital and Medical Center
Chicago, Illinois 60616

Introduction Local anesthetics containing epinephrine are frequently alkalinized with sodium bicarbonate to shorten the onset and enhance the quality of block during regional anesthesia.^{1,2} It has been reported that alkalinization of epinephrine markedly reduces its effectiveness through rapid oxidation.³ This may invalidate the use of alkalinized epinephrine containing solutions as test doses for intravascular injection. There are similar warnings during ACLS training that sodium bicarbonate will inactivate epinephrine and care must be taken⁴ not to administer these drugs through the same line. Our clinical experience suggested that the oxidation of epinephrine in alkaline solutions was a slow reaction that would not be relevant over the time periods necessary for most clinical situations. The purpose of this study was to determine the rate of oxidation of epinephrine in an alkaline solution. We followed pressor responses in rats to aged alkalinized solutions of epinephrine and assessed epinephrine oxidation at different pH solutions via high performance liquid chromatography (HPLC).

Methods In the first series of experiments male Sprague-Dawley rats weighing 250-350 g were anesthetized with halothane and paralyzed with d-tubocurarine. Femoral arterial and venous lines were placed for blood pressure monitoring and drug administration. Rectal temperature was maintained at 37°C. A stable baseline blood pressure was obtained using hexamethonium, a ganglionic blocker. Commercial epinephrine hydrochloride was diluted in pH adjusted (4.0-5.0) normal saline (.2 ug epi/.01 ml) and injected intravenously to determine the dose of epinephrine needed to obtain a reproducible 10-20 mmHg rise in systolic blood pressure. Similar concentrations of epinephrine were then prepared in standard resuscitation 8.4% sodium bicarbonate (pH 8.0-8.2) and injected in the rat intravenously. The various aged solution (5, 10, 30, 60, 120, 180 and 300 minutes) were injected in a randomized manner in each rat. The pressor responses to each solution was determined by the change in systolic blood pressure compared to control value. Injections of a control epinephrine solution (pH 4.0-5.0 in normal saline) were randomly performed during the test sequence to determine if sensitization to epinephrine had occurred and to verify that the control solution elicited the original pressor response.

In the second series of experiments, HPLC was performed with different aged solutions of epinephrine in alkalinized saline with pH 4, 6 and 8. Samples of each pH adjusted solution were removed at time intervals of 10 and 30 minutes, 1 and 2 hours, and 24 hours to determine epinephrine oxidation.

Results Results of this study as measured by both the pressor response in the rat (Table 1) and HPLC (Table 2) show that oxidation of epinephrine is a slow process requiring many hours before significant inactivation of epinephrine occurs. At pH 8 significant oxidation of epinephrine is not seen by HPLC until 2 hours. Similarly, no clinically significant decrement in pressor response is evident over the same time period. However, after 180 min, a significant decrease was seen in pressor response.

Discussion The pH of alkalinized local anesthetic solutions is usually 7.0-7.2 (raised from the pH of 4.5-5.0 at which these solutions are manufactured in order to prevent oxidation). We studied the rate of epinephrine oxidation to see whether it was clinically relevant over short periods of time. We also used standard resuscitation 8.4% NaHCO₃ (pH 8.0) as our medium for diluting epinephrine in the rat to address the question of whether epinephrine could safely be given through the same IV line as NaHCO₃ during ACLS.

The results show that even when epinephrine is mixed in 8.4% NaHCO₃ (pH 8.0) there is no significant oxidation by either HPLC, or pressor response in rats for at least 2 hours thus supporting the validity of epinephrine in an alkaline solution as a marker for intravascular injection. The data also support the use of NaHCO₃ and epinephrine through the same IV line during ACLS. We conclude that there is no measurable oxidation of epinephrine in an alkaline solution (pH = 7.0-8.0) over short, clinically relevant periods of time.

Table 1
Pressor Response to Alkalinized Epinephrine
Time (min)

	5	10	30	60	180
%					
Control Response	99±2	93±9	99±11	87±8	73±15*

*Significantly lower than 5 min response; P<0.05, n=4

TABLE 2 HPLC DETERMINATIONS OF THE EFFECTS OF TIME AND pH ON THE OXIDATION RATE OF EPINEPHRINE (MEAN UGS ± SE)

	0	10 min	30 min	1 hour	2 hours	24 hours
pH 4	41±1.8	38±0.6	40±1.4	39±1.7	39±1.5	38.5±0.8
pH 6	41±1.6	39±1.1	39±1.0	40±1.4	39±1.4	32.6±1.4*
pH 8	40±1.1	37±0.2	37±1.7	37±1.7	33±0.7*	10.1±0.8*

* Significantly lower than time zero value; p<0.05 n=6

References

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