Treatment of Shock and Prevention of Ischemic Necrosis with Levarterenol-Phentolamine Mixtures

By GARY ZUCKER, M.D., ROBERT P. EISINGER, M.D., MARTIN H. FLOCH, M.D., AND MARK M. SINGER, M.D.

ISCHEMIC NECROSIS resulting from accidental extravasation of levarterenol (Levophed) in patients in shock can be prevented by local injection of 5 or 10 mg. of the anti-adrenergic drug phentolamine (Regitine). This method is not effective when vasoconstriction has existed for several hours and irreversible tissue damage has occurred.

Preliminary observations suggest that immediate protection can be secured by adding phentolamine to the flask of levarterenol. In rabbits, as little as 2.5 mg./L. of phentolamine antagonizes the necrotizing effect of solutions containing 8, 16, and 32 mg./L. of levarterenol. In 5 normotensive patients, 5 to 40 mg./L. of phentolamine did not diminish the pressor effect of levarterenol. Similar observations were made in 5 patients in shock.

The purpose of this paper is to evaluate the routine use of levarterenol-phentolamine mixtures in treatment of 68 cases of shock.

Material and Methods

Of the 68 cases, shock was due to coronary thrombosis in 25, terminal malignancy in 12, operative procedure in 9, sepsis in 6, pulmonary embolism in 4, cerebral hemorrhage or thrombosis in 4, hepatic coma in 2, aortic rupture in 1, and arrhythmia in 1. The patients had a systolic pressure of 80 mm. Hg or less and clinical signs of shock, such as pallor, sweating, cyanosis, restlessness, torpor, and oliguria.

Mixtures were prepared in 1,000 ml. of 5 per cent glucose in water and administered by needle or polyethylene catheter into a vein of the forearm, antecubital fossa, hand, or leg.

Vasopressor treatment was started with a mixture containing 4 or 8 mg./L. of levarterenol. Rate of administration was at or below 20 drops per minute. Increments of 4 mg. of levarterenol were added when needed to maintain elevation of blood pressure.

The concentration of phentolamine varied at different stages. At first, 5 to 10 mg. were added for each 4 mg. of levarterenol. Subsequently, regardless of levarterenol dosage, 10 mg. and later only 5 mg. of phentolamine were added to each liter.

Extravasations were observed but no local therapy was administered.

Results

Continuous vasopressor therapy was administered for 1 hour to 11 days. The dosage of levarterenol was 4 to 48 mg./L. and of phentolamine 5 to 60 mg./L. or a range of 0.08 to 0.96 mg./Kg./minute for levarterenol and 0.1 to 1.2 mg./Kg./minute for phentolamine. Good pressor responses were obtained in 51 cases (75 per cent), as evidenced by a systolic blood pressure of 90 to 120 mm. Hg. Twenty patients survived shock and maintained normal blood pressure after vasopressor therapy was discontinued: 9 cases of coronary thrombosis (36 per cent), 7 cases of postoperative shock (78 per cent), 1 case of sepsis, (16 per cent), 1 case of pulmonary embolus (25 per cent), 1 case of cerebral thrombosis (25 per cent), and in the only case of cardiac arrhythmia. No recovery was observed in any case requiring more than 20 mg./L. of levarterenol. Survivals from shock were observed with mixtures containing 5 to 50 mg./L. of phentolamine.

Thirty-four extravasations occurred in 22 patients (fig. 1). None of the mixtures produced any necrosis. The only patient who developed a slough was of crucial interest, since he served as his own control. He had two large extravasations of mixtures involving both arms and antecubital fossae, which did not produce any necrosis. One contained 8 mg./L. and the other 12 mg./L. of levarterenol; both contained 10 mg./L. of phentolamine. He also had a smaller extravasation of 8 mg./L. of levarterenol on the leg, from which phentolamine had inadvertently been...
OUTCOME OF
34 EXTRAVASATIONS IN 22 PATIENTS

+ ISCHEMIC NECROSIS
○ NO ISCHEMIA OR NECROSIS

LEVOPHED, mg./L.

36
16
12
8
4
0 5 10 20 30 40
REGITINE, mg./L.

Figure 1
Absence of necrosis in extravasations of levarterenol-phenolamine mixtures.

omitted; a large slough developed within 72 hours. All infiltrations occurred in spite of cut-downs and polyethylene catheters.

Discussion
Phentolamine can be given together with levarterenol by slow intravenous drip to patients in shock without reducing pressor response. This fact is attributable to the low rate of administration. For the average adult receiving 5 or 10 ml./L. of phentolamine this would be equivalent to 0.1 to 0.2 mg./Kg./minute. This is much less than that previously used for antihypertensive effect; Moyer and Caplovitz gave 1 to 3 mg./Kg. as a single intravenous injection. The local tissue concentration of phentolamine, however, is high enough in areas of extravasation to prevent vasoconstriction and necrosis. Despite slight dilution by extracellular fluid it approximates the concentration in the flask. No necrosis ensued in 22 instances in which 10 mg./L. of phentolamine were used and in 5 extravasations in which 5 mg./L. of phentolamine were used (fig. 1). It is our current practice to administer mixtures containing only 5 mg./L. of phentolamine. Only in this manner can enough experience be accumulated to determine whether this is the smallest effective dose.

The heterogeneous nature of the group, which included different types of shock and many patients with terminal diseases precludes a definitive evaluation of the effect of the mixtures upon prognosis. On the other hand the 25 cases of coronary thrombosis are a homogeneous group and represent a prime indication for vasopressor therapy. Nine cases (36 per cent) recovered from shock, a result comparable to those obtained with levarterenol alone.

Levarterenol has certain advantages over other pressor amines. These include the rapid onset and offset of action, the ease with which dosage can be varied, and its efficacy in some cases in which other vasopressor drugs have failed. Its tendency to produce ischemic necrosis at sites of extravasation has discouraged its use. Routine addition of 5 or 10 mg. of phentolamine may eliminate this one serious disadvantage. The method is simple, pressor response is not diminished, and protection against local ischemia is automatic.

Summary
Good pressor responses were obtained in 51 of 68 cases of shock treated with levarterenol-phenolamine mixtures. No necrosis developed in 33 extravasations of mixtures. One slough resulted from an extravasation of 8 mg./L. of levarterenol alone. Our present practice is to add 5 mg. of phentolamine to each liter of levarterenol solution.

Sumario in Interlingua
Bon respondos pressori esseva effete a 51 ex 68 cases de choc tractate con mixtures de levarterenol e phentolamina. Nulle necrosis se disveloppava in 33 ocorrentias de extravasation del mixtura, sed un tal eseva notate in le caso de un extravasation de 8 mg./L de levarterenol sol (ab que le admixtion de phentolamina hubeva essite omittita accidentalmente). Currentemente nostre practica es adder 5 mg de phentolamina a omne litro de solution de levarterenol.

References
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One of the fine traditions of the practice of medicine, which may be giving shelter to something quite unsatisfactory, is the tradition of charity. Charity, like a loving mother, may override the rights of others in the protective solicitude, not to say the selflessly selfish ambition, she has for her own. Operating as charities, the hospitals have accepted or demanded, in the name of charity, the services of nurses, interns, and even patients in ways and to a degree that raise, at least retrospectively, questions as to who was giving what and in whose name. The time and care that nurses and interns have given hospital patients were required in the name of education and dispensed in the name of charity. Patients were called charity cases, but if they were used for teaching, it was not so often explained to them that this improved their care as that it was justified as a substitute for hospital fees. Doctors, for all that hospital positions enlarged their experience and enhanced their professional prestige, gave an enormous amount of time and effort in the name of charity. Even universities were expected to contribute to the care of the sick poor, which was charity though usually charged and considered as education.—Alan Gregg, M.D.  Challenges to Contemporary Medicine.  New York, Columbia University Press, 1956, p. 86.
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