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Prevention of Levarterenol Necrosis in Rabbits by Use of Levarterenol-Phentolamine Mixtures.* (25480)

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Levarterenol (Levophed), administered by slow intravenous drip, is the vasopressor drug most frequently employed in treatment of shock. Accidental extravasation may produce such intense local vasoconstriction that ischemic necrosis of the skin may ensue. Vasoconstriction can be reversed by prompt injection of the anti-adrenergic drug phentolamine (Regitine) into the area of extravasation (1,2). The method is not effective when extravasation has been overlooked for several hours and irreversible tissue damage has occurred. Neglect of an extravasation might not be serious if phentolamine could be given intravenously with levarterenol. Preliminary clinical studies indicate that levarterenol-phentolamine mixtures may be used effectively(3). The purpose of our study is to determine the least amount of phentolamine that will inhibit the local vasoconstrictor action of doses of levarterenol usually employed in treatment of shock.

Methods. The method described by McGinn and Schluger(4) was used for producing sloughs on rabbit abdomen. Solutions were prepared in 1000 cc of 5% glucose in water. They were administered through 22 gauge 1½ inch needles inserted subcutaneously at center of shaved abdomen and directed caudally. The drip was adjusted so that 250 cc were infiltrated during 2 hour period. The needles were then removed. Experiments were carried out on 36 adult rabbits, divided into 6 groups of 6 rabbits each. Group A served as control receiving only levarterenol.† Of this group, 2 were injected with 8 mg/l levarterenol, 2 with 16 mg/l, and 2 with 32 mg/l. Each of the other 5 groups was similarly subdivided. However, the levarterenol solutions for these animals contained increasing amounts of phentolamine‡: Group B, 0.5 mg; Group C, 1 mg; Group D, 2.5 mg; Group E, 5 mg and Group F, 10 mg.

Results. Group A: Subcutaneous infiltration of levarterenol solutions without phentolamine produced a well-demarcated swelling. After 24 hours, there was a mottled, warm area of induration. After 72 hours, necrosis with scaling and crusting occurred. Size of slough varied directly with concentration of levarterenol. The smallest measured 3 x 4 cm and the largest 12 x 20 cm.

Group B: The 2 rabbits that received the mixture with 8 mg levarterenol developed no necrosis. The 2 injected with 16 mg and the 2 with 32 mg developed areas of necrosis approximately the same size as those in corresponding animals in Group A.

Group C: No necrosis was observed in 2 rabbits that received the mixture with 8 mg levarterenol or in one with 16 mg. A 1 x 1 cm slough developed in the second rabbit of latter group. Necrosis appeared in both rabbits given the mixture with 32 mg levarterenol. One measured 2 x 2 cm and the other 0.5 x 2 cm.

Groups D. E. F: Necrosis did not develop in any of the animals.

Discussion. Experiments have confirmed

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‡ Phentolamine (Regitine) was furnished by Ciba Pharm. Products, Summit, N. J.

OUTCOME OF SUBCUTANEOUS INFILTRATION OF LEVOPHED-REGITINE SOLUTIONS IN 36 RABBITS

LEVOPHED, mg./L.	GROUP: A	B	C	D	E	F
32	++	++	++	oo	oo	oo
16	++	++	+o	oo	oo	oo
8	++	oo	oo	oo	oo	oo

0 0.5 1.0 2.5 5.0 10.0

REGITINE, mg./L.

+ NECROSIS o NO NECROSIS

FIG. 1. Effect of varying concentrations of phentolamine in prevention of levarterenol necrosis.

the previously reported observations that ischemic necrosis uniformly follows slow subcutaneous infiltration of 250 cc of levarterenol solution into the rabbit abdomen. McGinn and Schluger(4) used a solution equivalent to 16 mg of levarterenol/liter. Similar changes were produced in our study with solutions containing 8, 16, and 32 mg levarterenol. Size of sloughs varied directly with concentration of levarterenol.

Phentolamine given simultaneously with levarterenol has a potent inhibitory effect on cutaneous vasoconstriction of the latter (Fig. 1). As little as 0.5 mg counteracted the effect of 8 mg of levarterenol. A concentration of 1 mg phentolamine diminished the vasoconstriction produced by 16 and 32 mg levarterenol judging by the small size of resultant slough. The lowest phentolamine dose to abolish the ischemic effect of all 3 strengths of levarterenol was 2.5 mg. The same beneficial response was obtained with 5 and 10 mg phentolamine.

These experiments were carried out to determine smallest amount of phentolamine that will abolish the local vasoconstrictor action of doses of levarterenol usually administered to patients in shock. If results in normal rabbits can be extrapolated to patients in shock, then mixtures containing 2.5 mg phentolamine might be free from the ischemic hazard. However, circulation in extremities of patients in shock is not comparable to that in the skin of abdomen of normal rabbits. Intense vasoconstriction commonly associated with shock may increase the requirement for phentolamine.

Summary. 1. Subcutaneous infiltration of 250 cc of solutions containing 8, 16, or 32 mg levarterenol/liter for 2 hours regularly produced slough of skin on abdomen of rabbits. 2. All levarterenol-phentolamine mixtures that contained 2.5, 5, and 10 mg phentolamine did not produce slough. Those containing 0.5 and 1 mg phentolamine prevented slough only for mixtures with 8 mg levarterenol. Sloughs were reduced with mixtures containing 16 and 32 mg levarterenol and 1 mg phentolamine.

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Serotonin Studies on Mouse Tissues.* (25481)

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Anaphylaxis in the mouse apparently differs from that observed for other species with respect to difficulty of sensitization and shock organs and mediators concerned. Since histamine is believed to be of relatively little importance in this reaction(1), attention has

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