Therapy of Intestinal Ischemic (SMA) Shock with Vasoactive Drugs

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Based on hemodynamic considerations, the therapy of shock with vasoactive drugs could be more effective than present experience indicates if agents with more selective actions on specific types of microvessels were used. Recent synthesis of analogues of naturally-occurring vasoactive amines and polypeptides and blocking agents provides a new source of drugs with suitably selective actions.

Rats were subjected to intestinal ischemic shock, divided into nine groups and studied according to the therapy used. Groups 1 and 2, controls, received no therapy and saline solution, 2.0 ml/50 minute, respectively. Groups 3 to 9 received saline solution plus the following drugs alone or in combination; isoproterenol, phenoxybenzamine, PLV-2 (2-phenylalanine-8-lysine vasopressin). Blood pressure was monitored continuously in selected experiments in each group and survival was determined at 48 hours in all other experiments. Compared with controls, significantly increased survival was noted in the groups treated with isoproterenol, PLV-2, and isoproterenol + PLV-2, the latter with the highest survival. The remaining groups all demonstrated sustained, profound hypotension.

GENERAL EXPERIENCE with vasoactive drugs as acute therapy in shock has not been satisfactory; their use is regarded with considerable uncertainty.[1, 2] The principle of correcting the critical impairment of tissue blood flow in shock by altering pressure-resistance relationships in the terminal vascular bed is unquestionably valid, however. Vasoactive drugs in common use, on which most present laboratory and clinical evidence is based, do not alter these pressure-resistance relationships appropriately, as demonstrated by their unfavorable effects on microcirculatory perfusion.[3, 4] However, the advent of an almost limitless number of analogues of natural catecholamines and polypeptides and other unnatural blocking and potentiating agents suggests the very real possibility of attaining drugs which, singly or in combination, do have suitably selective vasomotor actions. One of these, PLV-2, a polypeptide which has been studied in our laboratory[3, 4, 5] and by others,[6, 7] predisposes to more favorable microcirculatory function and survival of animals after several types of experimental shock. We considered it worthwhile to combine its properties with those of either isoproterenol or phenoxybenzamine, synthetic dilators, used to treat shock, which have specific vascular actions[8, 9, 10, 11] that should complement the effects of PLV-2 on peripheral perfusion.

Methods

Wistar-strain female rats, 150 ± 15 Gm. body weight, were anesthetized with pentobarbital sodium, 3.0 mg./100 Gm., and a femoral vein was cannulated with a plastic catheter. In selected experiments, not included in the survival data, the accompanying artery also was cannulated for connection to a conventional mercury manometer for continuous blood-pressure recording. In all experiments the venous catheter was connected to a calibrated syringe controlled by a Harvard infusion pump. Through a midline laparotomy, a fine silk ligature was passed around the superior mesenteric artery (SMA) close to its

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origin from the aorta and the free ends of the ligature were threaded through a short length of plastic tubing. Intestinal ischemia was induced and maintained for 60 minutes by occluding the artery by tensing and clamping the silk suture through the plastic tubing.[4] Effectiveness of ligation and resumption of blood flow were determined by onset of intestinal pallor, fall in rectal temperature (thermistor probe) and return of color with rise in temperature. The abdominal incision was closed temporarily during the period of occlusion and sutured permanently after removal of the ligature. One hour after ligature release, 2.0 ml. of saline solution, alone or containing the various drugs (table 1), were infused at a constant rate over a 50-minute period, and observations were continued for an additional hour. Then the femoral vein was ligated, the incision was closed and the animals were observed for 48 hours for survival. Drug doses were based on previously-reported effective therapeutic ranges.[2, 4, 12] The volume of saline solution in which they were dissolved (approximately 15–20 per cent of the estimated normal blood volume) was limited deliberately to less than full replacement of fluid probably lost into the bowel and cannulated limb. Aseptic technique was used and necropsies of all animals were done at death or when sacrificed to eliminate from consideration those with inadvertent intestinal infarction or vascular laceration. Animals dying within 15 minutes of the start of infusion were not included. Survival data were compared for significance by the chi-square test.

Results

Figure 1 is a composite of the blood-pressure patterns in controls, saline- and drug-treated animals in the selected experiments not considered in the survival data. Each point on the curves represents mean value of recorded mean blood pressures versus time. During infusion, only the saline and PLV-2 groups showed sustained elevations in blood pressure which, in the period following infusion, reverted to the hypotensive levels observed in the untreated and isoproterenol groups. Animals receiving phenoxybenzamine alone or in combination with the other drugs, particularly following the infusion period, rapidly developed profound hypotension which was sustained. Isoproterenol combined with PLV-2, after completion of infusion, led to a more gradual onset of hypotension which reached a level intermediate between those of the above groups.

TABLE 1. Influence of Vasoactive Drugs on Survival of Rats in Intestinal Ischemic Shock

Drug(s)†	Dose, μg./100 Gm.	Survivors/ Total	% Survivors
Untreated		54/113	48
Normal Saline	2.0 ml.	35/58	43
Isoproterenol	10	17/26	65*
PLV-2	1.56	32/52	63*
Phenoxybenzamine (Dbz)	100	10/30	33
Isoproterenol +PLV-2	10+1.56	17/21	81**
Isoproterenol +Dbz	10+100	9/28	32
PLV-2+Dbz	1.56+100	7/18	39
Isoproterenol +PLV-2+Dbz	10+1.56+100	7/14	50

† Isoproterenol = Isuprel hydrochloride(R), 1:5000 solution (0.2 mg./ml.). Phenoxybenzamine = Dibenzyline(R). PLV-2 = 2-phenylalanine-8-lysine vasopressin, 100 μgm. of active peptide/ml.

* $P < 0.04$ compared with untreated and saline-treated groups.

** $P < 0.005$ compared with untreated and saline-treated groups.

Table 1 summarizes the survival data. Only those animals treated with isoproterenol or PLV-2, alone or in combination with each other, showed significantly higher survival rates than untreated controls or those given saline alone. Simultaneous administration of these two drugs yielded the highest survival rate. Phenoxybenzamine alone or combined with isoproterenol and/or PLV-2 either did not improve or seemed to lower survival rate.

Discussion

Pharmacologic manipulation of the terminal vascular bed, the net effects of which improve exchange-vessel blood flow, is a valid therapeutic approach to shock. This approach is based on the accepted thesis that failure to maintain tissue perfusion, as mediated by the microcirculation, is the principal hemody-

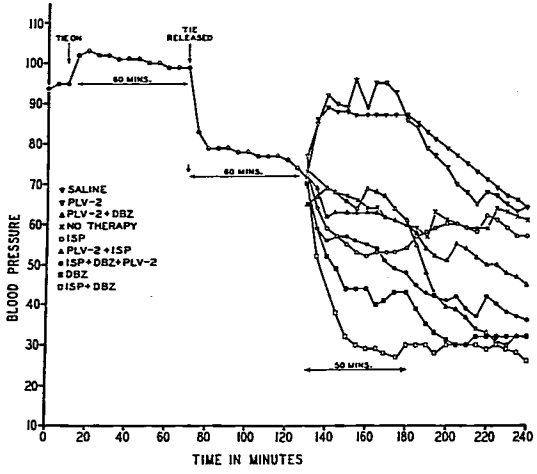

FIG. 1. Composite of mean blood pressure patterns in rats after intestinal ischemic shock treated with vasoactive drugs. No. of rats before therapy = 75. No. of rats in each therapy group: untreated = 8; saline = 8; isoproterenol = 7; PLV-2 = 13; Dbz = 7; isoprot. + PLV-2 = 9; isoprot. + Dbz = 9; PLV-2 + Dbz = 7; isoprot. + PLV-2 + Dbz = 7.

namic event leading to death.[13, 14, 15] It follows, therefore, that the choice of vasoactive drugs used to treat shock should be based not only on their effects on cardiovascular components proximal to the terminal vascular bed, but also on their effects on the various types of microvessels which regulate capillary blood flow. Use of these drugs on the basis of their microcirculatory effects has been limited, however, because documentation of their vasomotor effects during intestinal ischemia or other types of shock is meager.

The survival data, *per se*, add further support for the general therapeutic approach to which these experiments were directed. More specifically, the data demonstrate the correlation between the effects of these drugs on survival and their selective macrovascular and microvascular actions. The results with isoproterenol and PLV-2 were anticipated, having been reported previously.[3, 4, 12] The observation that in joint use these drugs complemented each other in supporting survival was also predictable from their known cardiovascular actions.[8, 9, 10, 16] The mild vasodilating effect of isoproterenol on the inflow side of the terminal bed would not be expected to negate the excitatory microvascular effects of PLV-2. Additionally, the cardiac beta-adrenergic activity of isoproterenol should increase the pressure at which blood is delivered to the periphery. The inability of phenoxybenzamine, given acutely, to improve survival was not surprising. Its potent alpha-adrenergic blocking action on all peripheral macro- and microvessels[9, 11] lowers resistance in perfusion pathways to expand the capacity of the capillary bed, and presumably alters pressure-resistance relationships to a level of hydraulic insufficiency in the absence of large blood-volume expansion. When phenoxybenzamine is combined with isoproternol, the net change in dynamics derived from the latter's cardiac effect similarly could not be expected to overcome the hydraulic factor. The effects of phenoxybenzamine and PLV-2 were disappointing since we had reasoned that each would modulate the other's actions almost ideally relative to pressure-resistance. The inaccuracy of this prediction probably can be explained by recent microcirculatory observations of our own and a report from De Jong and McLeod[17] showing that the acute administration of phenoxybenzamine renders the smallest microvessels markedly hypersensitive to PLV-2 for relatively long periods. Furthermore, there seems

to be a significant dose-dependent interrelationship in the net vasomotor behavior induced by the combined use of these drugs.

Although blood-pressure patterns do not resolve the uncertainty of the therapeutic effects of vasoactive drugs, they suggest several features relevant to such therapy. At relatively comparable blood pressure levels some drug-treated animals showed higher survival rates than the untreated and saline-treated rats in which the vasomotor apparatus had not been altered by drugs. Although pressure-flow-resistance relationships in the periphery are extremely complex, this observation suggests that the drugs modified tissue blood flow favorably. Such an interpretation of this observation is compatible with the concept of the unfavorable relationship of excessive vasoconstriction to tissue perfusion proposed by Wiggers *et al.*[18] and supported by Nickerson.[1] However, when vasoactive drug therapy results in an abrupt drop in blood pressure to drastically low levels (below 40 mm. Hg, fig. 1) the outcome was not improved. This suggests that there is a critically low pressure level at which hydrodynamic and rheologic factors lead to insufficiency of tissue flow for which vasomotor mechanisms cannot compensate.[19]

Summary and Conclusions

The effects of isoproterenol, phenoxybenzamine and PLV-2 (analogue of vasopressin) on survival of rats subjected to intestinal ischemic shock was studied. The drugs, in saline solution, were infused intravenously singly or in combination and survival rates and mean blood-pressure patterns were compared with those of animals given saline solution alone or no therapy. Isoproterenol and PLV-2, or a combination of the two, resulted in significantly increased survival, the combination yielding the highest figures. Animals receiving phenoxybenzamine alone or combined with the other two drugs did not show improved survival. The latter groups also developed sustained, profound hypotension, suggesting hydraulic insufficiency of the terminal vascular bed. A critical assessment of these drugs and other synthetic vasoactive agents requires more comprehensive microcirculatory and survival studies. These preliminary findings with combined-drug therapy, and previous findings with single-drug therapy, suggest that appropriately selective pharmacologic manipulation of the microcirculation is a valid approach to the therapy of shock.

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Anesthesia

MALIGNANT HYPERPYREXIA Idiopathic explosive malignant hyperthermia, which occurs after anesthesia is administered, is a syndrome of increasing prevalence. It is a separate entity from the "postoperative heatstroke" reported in the days prior to temperature and humidity control of operating rooms. Reviews of 40 cases from the literature and the authors' own experience reveal a 73 per cent mortality in an otherwise healthy and young (average 21 years) age group. The only reasonable explanation of the etiology appears to be an uncoupling of oxidative phosphorylation. Treatment, even with early diagnosis, is difficult. (*Wilson, R. D., and others: Malignant Hyperpyrexia with Anesthesia, J.A.M.A. 202: 183 (Oct.) 1967.*)

CESAREAN SECTION Twenty-six term patients for elective section were anesthetized with thiopental, nitrous oxide and succinylcholine. The flow rates of nitrous oxide and oxygen were 3 l./min. and 1.5 l./min. Blood samples were taken from a maternal artery before anesthesia; from a maternal artery and uterine vein before incision of the uterus; from the umbilical artery and vein at birth; from the umbilical artery shortly after birth and at one hour of age. Analyses consisted of determinations of oxygen, carbon dioxide, *p*H, lactate, pyruvate, glucose and thiopental. The mean pre-anesthesia maternal oxygen content was 6.00 millimoles/l.; maternal artery before incision of the uterus, 6.78; umbilical vein 4.17; umbilical artery at one hour, 7.15. The transplacental CO_2 difference was 9.2 mm. Hg. No *p*H values were reported. Mean carbon dioxide partial pressure in the pre-anesthesia maternal artery was 34.6 mm. Hg; umbilical vein 44.9; umbilical artery 48.6; umbilical artery shortly after birth 50.4; umbilical artery at one hour, 40.2. Thiopental concentration in the maternal artery eight to 16 minutes after injection was 0.49 mg./100 ml.; uterine vein 0.5; umbilical vein 0.3; umbilical artery 0.2; umbilical artery at one hour of age 0.18. Eighty per cent of the infants had a one-minute Apgar score of 7 to 10. Those with Apgar scores of less than 5 were thought to be depressed from nitrous oxide narcosis. The levels of the various metabolites measured were at least as close to the accepted normal ranges as those found in women undergoing cesarean section and exposed to spinal, epidural and cyclopropane anesthesia. (*Stenger, V. G., and others: Observations on Pentothal, Nitrous Oxide, and Succinylcholine Anesthesia at Cesarean Section, Amer. J. Obstet. Gynec. 99: 690 (Nov.) 1967.*)