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Comparative Hemodynamic Effects of Selective Superior Mesenteric Arterial and Peripheral Intravenous Glucagon Infusions

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This experiment was designed to determine whether any hemodynamic benefits attend administration of equal pharmacologic doses of glucagon (1 μg/kg/m) by continuous intravenous infusion (Group I, $n = 6$) versus selective intraarterial infusion (Group II, $n = 6$) via the superior mesenteric artery (SMA) in dogs. Cardiac output, heart rate, mean arterial pressure, total peripheral resistance, pulmonary vascular resistance, superior mesenteric artery flow (SMAQ), SMA vascular resistance, and portal venous pressure were measured at baseline (BL) and at 5, 15, 30, and 45 min during glucagon infusion. SMAQ virtually doubled at 5 min from a baseline of 570 ± 60 ml/min to 1158 ± 146 ml/min in Group I ($P < 0.001$), and from a baseline of 527 ± 171 to 1018 ± 331 ml/min in Group II ($P < 0.002$). SMAQ was significantly higher in Group I at 30 and 45 min compared to Group II ($P < 0.03$) despite similar peripheral plasma glucagon levels. SMA vascular resistance was significantly lowered in both groups, with a greater reduction occurring during intravenous glucagon administration at 45 min ($P < 0.05$). Changes in systemic hemodynamic parameters, as well as glucagon and glucose levels were not statistically different between Groups I and II at any time period. Glucagon is a potent mesenteric vasodilator and the resultant profound splanchnic hemodynamic effects are as marked during intravenous administration as during selective SMA infusion.

The potential usefulness of mesenteric vasodilators in treating acute mesenteric ischemia became apparent from earlier reports of the efficacy of an aggressive therapeutic approach that included the adjunctive use of intraarterial papaverine [3]. Unfortunately, papaverine may not be a very potent mesenteric vasodilator [1, 11], and this agent may be ineffective when the superior mesenteric artery (SMA) becomes occluded proximal to collateral vessels [16, 19]. Furthermore, intraarterial papaverine has been reported to have a deleterious effect on oxygen consumption in an animal model of acute mesenteric ischemia [14]. Such disadvantages and the requirement that papaverine must be administered intraarterially in order to be effective, have led to studies of other potential splanchnic arterial vasodilators. Included among such agents has been glucagon which has been shown to improve survival in a rodent model of acute mesenteric ischemia involving temporary complete SMA occlusion [10].

Previous studies have verified that glucagon administered intravenously increases SMA flow out of proportion to the increase in cardiac output induced by this agent [9, 18]. Furthermore, we have documented that this increase in SMA flow is of a nonshunt, nutritive nature [9], in contrast to previous speculation that increases in SMA flow resulted from increased arteriovenous shunting [7, 8, 21]. The current work, representing an extension of earlier studies from our laboratory, assessed the comparative splanchnic hemodynamic effects of equal pharmacologic doses of glucagon administered by selective intraarterial infusion compared with those effects following parenteral intravenous infusion. Data from this study might have an impact on future clinical trials evaluating

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glucagon as a possible therapeutic agent for treating acute mesenteric ischemia.

MATERIALS AND METHODS

Twelve healthy adult dogs, weighing 22 to 35 kg, were anesthetized using intravenous pentobarbital (30 mg/kg) with supplemental doses (5 mg/kg) administered as needed during preparation of the subjects. No experimental manipulations or measurements were performed until a stable hemodynamic baseline was attained 30 to 40 min after either initial or supplemental doses of pentobarbital were administered [12]. Additional pentobarbital was not administered after this baseline was achieved. Dogs were intubated and mechanically ventilated in order to maintain physiologic arterial blood gases and normal blood pH (7.34–7.44). An esophageal probe monitored core temperature which was maintained with the use of an external heat source in all animals. Lactated Ringer's solution was infused at a rate of 25 ml/kg/hr during the course of the experiment. A carotid arterial catheter, a jugular central venous catheter, and a 7 French thermodilution Swan–Ganz catheter were properly positioned. After midline laparotomy, the superior mesenteric artery was exposed and a carefully precalibrated, nonoccluding electromagnetic flow probe was placed about its origin and appropriately zeroed for each subject. A 21-gauge polyethylene catheter for intraarterial glucagon administration was inserted into one of the mesenteric branches, and threaded into the SMA approximately 1 to 2 cm from its origin, proximal to all branches. An 18-gauge polyethylene catheter was threaded into the portal vein through a pancreaticoduodenal venous branch. The abdominal viscera were returned to the peritoneal cavity, and the abdominal incision was reapproximated prior to hemodynamic testing.

Central venous, pulmonary artery, carotid arterial, and portal venous pressures were continuously recorded using pressure transducers connected to a multichannel recorder. Cardiac output was measured by thermodilution. SMA flow was measured using a square wave flowmeter and was continuously recorded. Heart rate and pulmonary capillary wedge pressure were determined, and blood samples were withdrawn through the central venous catheter for venous glucose and glucagon level measurements. Plasma glucose was determined by a standard automated hexokinase method. Plasma glucagon was determined by radioimmunoassay [20].

Cardiac output (CO—liter/m), mean arterial pressure (MAP—mm Hg), central venous pressure (CVP—mm Hg), mean pulmonary artery pressure (PAP—mm Hg), pulmonary vascular resistance (PVR = MPAP − PCWP/CO × 79.9—dynes-sec/cm^5), total peripheral resistance (TPR = MAP − CVP/CO × 79.9—dynes-sec/cm^5), SMA blood flow (SMAQ—ml/m), portal venous pressure (PVP—mm Hg), SMA resistance (SMAR = MAP − PVP/SMAQ (liter/m) × 79.9—dynes-sec/cm^5), and an estimate of left ventricular stroke work [LVSW = (MAP − PCWP) × CO/HR] were measured or calculated in the usual fashion at baseline (BL) and at 5, 15, 30, and 45 min during infusion of 1 μg/kg/m glucagon in a 45-ml volume of normal saline using a calibrated Harvard infusion pump. Infusions were administered through either a peripheral vein in six dogs (Group I) or directly into the SMA in six additional dogs (Group II). Data were subjected to statistical analysis using the University of Michigan MIDAS statistical program. The paired t test was used for evaluation of differences within a Group, with the unpaired t test and Mann–Whitney U median tests were used for assessing differences between Groups I and II. Creation of correlation matrices with calculation of the Pearson product–moment correlation coefficients were also used in the statistical analyses.

RESULTS

None of the baseline parameters measured in this study were significantly different between Group I receiving glucagon intrave-

nously compared to Group II receiving glucagon intraarterially.

During glucagon infusion CO did not differ between the two groups (Table 1), although changes within each group did occur. CO was increased significantly in both Groups at 5 min ($P < 0.03$), but subsequently was not significantly different from control values. Left ventricular stroke work was decreased by 15 min in both groups ($P < 0.02$), and subsequently remained lower than baseline values. Heart rate significantly increased throughout the infusions of glucagon regardless of the route of administration ($P < 0.005$). The degree of tachycardia was not different between the groups at any time period.

Mean arterial pressure decreased significantly following 15 min of intravenous infusion ($P < 0.02$), and remained below the baseline of 133 mm Hg, reaching 110 mm Hg at 45 min. Mean arterial pressure following intraarterial administration was also diminished at 15 min ($P < 0.01$), and likewise remained lower than control values for the remainder of the infusion, dropping from a baseline of 129 to 105 mm Hg at 45 min.

TPR decreased significantly throughout intravenous glucagon administration in Group I ($P < 0.04$). Total peripheral vascular resistance decreased at 5 min in Group II and remained lower than control values at 45 min in the group receiving glucagon intraarterially ($P < 0.03$). Differences in TPR between the two groups never attained significance. There was no significant change in mean pulmonary artery pressure, or pulmonary vascular resistance within or between the groups.

Mesenteric hemodynamics were markedly altered in both groups (Table 2). Intravenously administered glucagon doubled SMA blood flow from a baseline of 570 ± 60 ml/m to 1158 ± 146 ml/m by 5 min ($P < 0.001$). This increase in SMAQ persisted throughout intravenous drug infusion. Similarly, intraarterial glucagon nearly doubled SMA flow ($P < 0.002$), but there appeared to be a less sustained response to glucagon in this group (Table 2). At the 30- and 45-min periods,

TABLE 1

SYSTEMIC HEMODYNAMIC ALTERATIONS DURING GLUCAGON INFUSION[a]

	BL		5 min		15 min		30 min		45 min	
	IV	IA	IV	IA	IV	IA	IV	IA	IV	IA
MAP (mm Hg)	133 ± 17	130 ± 11	135 ± 18	130 ± 12	118 ± 15*	114 ± 11*	114 ± 8	103 ± 11*	110 ± 14*	105 ± 15*
CO (liter/m)	3.97 ± 0.56	4.47 ± 1.17	4.58 ± 0.77*	5.39 ± 1.05*	4.45 ± 1.01	4.86 ± 1.36	4.35 ± 0.80	4.89 ± 1.13	4.41 ± 0.79	4.60 ± 1.06
HR	156 ± 24	154 ± 24	195 ± 33*	197 ± 27*	212 ± 37*	214 ± 20*	220 ± 26*	210 ± 26*	210 ± 39*	210 ± 19*
TPR (dynes-sec/cm^5)	2793 ± 353	2498 ± 565	2476 ± 452*	2022 ± 310*	2299 ± 552*	2013 ± 429*	2225 ± 391*	1803 ± 310*	2132 ± 507*	1928 ± 333*
PVR (dynes-sec/cm^5)	126 ± 23	152 ± 54	131 ± 28	112 ± 28	115 ± 36	134 ± 49	127 ± 22	124 ± 38	113 ± 32	121 ± 46
LVSW (mm Hg)	3.4 ± .7	3.8 ± .6	3.2 ± .4	3.6 ± .6	2.4 ± .5*	2.6 ± .7*	2.3 ± .4*	2.5 ± .6*	2.3 ± .4*	2.3 ± .6*

[a] Data expressed as $\bar{X} \pm 1$ SD; IV, intravenous; IA, intraarterial.
* Statistically significant differences from BL, $p < 0.05$; no statistically significant differences IV ($n = 6$) vs IA ($n = 6$).

TABLE 2

SPLANCHNIC HEMODYNAMIC ALTERATIONS DURING GLUCAGON INFUSION[a]

	BL		5 min		15 min		30 min		45 min	
	IV	IA	IV	IA	IV	IA	IV	IA	IV	IA
SMAQ (ml/m)	570 ± 60	527 ± 171	1158 ± 146	1018 ± 331*	1123 ± 171*	927 ± 160*	1105 ± 183*†	840 ± 179*†	1067 ± 154*†	803 ± 168*†
SMAR (dynes-sec/cm^5)	18484 ± 1817	20859 ± 5287	9079 ± 1252*	10587 ± 2526*	8192 ± 1626*	9656 ± 2045*	8080 ± 1446*	9743 ± 1949*	7955 ± 994*†	10480 ± 2494*†
PVP (mm Hg)	1.8 ± 1.3	1.3 ± 2.3	4.5 ± 1.4*	3.8 ± 1.9*	5.9 ± 2.2*	5.2 ± 1.7*	4.8 ± 1.9*	3.8 ± 1.7*	4.8 ± 1.5*	3.2 ± 1.7

[a] Data expressed as $\bar{x} \pm 1$ SD; IV, intravenous; IA, intraarterial.
* Statistically significant differences from BL, $P < 0.05$.
† Statistically significant differences IV ($n = 6$) vs IA ($n = 6$), $P < .05$.

SMAQ was significantly greater in dogs receiving glucagon intravenously compared to those receiving the drug intraarterially ($P < 0.03$), and the difference in SMAQ between groups already approached significance as early as 15 min ($0.05 < P < 0.10$). Reductions of SMAR were present in both groups throughout glucagon infusion ($P < 0.01$). SMAR was significantly lower at 45 min in the dogs receiving glucagon intravenously ($P < 0.05$) compared with those receiving intraarterial glucagon.

The rise in portal venous pressure, thought to reflect increased SMAQ [9, 11], not necessarily arteriovenous shunting, was higher than control values ($P < 0.03$) in Group I, and was also higher than controls during intraarterial administration in Group II until 45 min when the values were not different from controls.

Glucose levels were elevated above control values throughout the study within both groups, but there was no difference in the degree of hyperglycemia achieved between the two groups (Table 3). Despite the minor differences in splanchnic hemodynamics between the two groups, no difference in blood glucagon levels occurred between the two methods of glucagon administration at the dosage level used in this study. Within each group over the course of study, glucagon levels correlated directly with SMAQ, PVP, HR, and glucose levels and inversely with TPR, SMAR, and LVSW ($P < 0.05$).

DISCUSSION

The purpose of this experiment was to assess the splanchnic vasoactive effects of glucagon administered intravenously compared to direct intraarterial SMA administration. Others have suggested that intraarterial administration of glucagon may provide a beneficial vasodilatory effect in the management of nonocclusive mesenteric ischemia [6, 22, 24]. Data from the present canine study supports the conclusion that intravenous glucagon in pharmacologic doses is as effective in increasing total SMA flow and

TABLE 3

PLASMA GLUCOSE AND GLUCAGON LEVELS DURING GLUCAGON INFUSION[a]

	BL		5 min		15 min		30 min		45 min	
	IV	IA	IV	IA	IV	IA	IV	IA	IV	IA
Glucose (mg/dl)	108 ± 5	133 ± 31	187 ± 22*	188 ± 36*	234 ± 42*	227 ± 60*	236 ± 62*	243 ± 62*	220 ± 77*	232 ± 60*
Glucagon (pg/ml)	1508 ± 1312	812 ± 1436	34160 ± 15133*	51620 ± 2160*	54280 ± 24838*	69540 ± 17520*	57920 ± 15678*	66440 ± 17718*	56360 ± 20818*	70000 ± 10670*

[a] Data expressed as $\bar{x} \pm 1$ SD; glucose $n = 6$, glucagon $n = 5$; IV, intravenous; IA, intraarterial.
* Statistically significant differences from BL, $P < .05$; no statistically significant differences IV ($n = 6$) vs IA ($n = 6$).

reducing splanchnic vascular resistance as is selectively administered glucagon. If one were to use glucagon as an adjunct in the clinical treatment of acute mesenteric ischemia, there might be no advantage to infusion of glucagon directly into the SMA compared with simple parenteral intravenous administration. Further, the potentially deleterious side effects of hyperglycemia and tachycardia resulting from intravenous glucagon administration were equally evident in this study during intraarterial infusion.

The rationale for the use of vasodilators in treating mesenteric ischemia relates primarily to the presence of reversible vasospasm. Lauffman introduced the concept of vascular spasm persisting after intestinal vascular occlusion [16, 19]. Turner reported significantly reduced intestinal blood flow following relief of both mesenteric arterial and venous occlusions [23]. Vasoconstriction has also been postulated to play an important role in the pathogenesis of nonocclusive mesenteric ischemia [1–3, 6, 14, 15, 16, 19, 24]. Although controlled trials demonstrating improved survival of patients with acute mesenteric ischemia treated with vasodilators are nonexistent, the adjunctive use of such agents appears theoretically sound. Clearly, the best vasodilator has not been determined, but intravenous glucagon appears to be a suitable agent for study in humans.

The hemodynamic effects of glucagon, in pharmacologic doses, include positive inotropic and chronotropic actions as well as reductions in LVSW such as documented in the current study [9, 18]. Glucagon increases celiac and superior mesenteric blood flow, as well as liver perfusion by increasing both portal venous and hepatic arterial blood flow [13, 18]. The hormone significantly enhances intestinal villous tip blood flow, and effectively increases SMA blood flow despite SMA stenoses and digoxin-induced vasoconstriction [4, 17]. Glucagon-induced reductions in intestinal motility may theoretically lower the bowel's energy requirements, and the accompanying inhibition of gastric, biliary, and pancreatic secretion may be beneficial in

lessening the so called "enzymatic phase" of intestinal injury associated with vascular insufficiency [5, 15].

Recently, we have shown that intravenously administered glucagon improves survival in a rat model of acute mesenteric arterial insufficiency [10]. It would seem that the adjunctive use of intravenous glucagon in pharmacologic doses deserves study in clinical instances of acute mesenteric ischemia. This agent has been safely administered to humans [25]. The intravenous route of administration would allow rapid initiation of adjunctive therapy prior to obtaining confirmatory angiography in patients suspected of having acute mesenteric ischemia, and theoretically would not mandate prolonged use of an indwelling arterial catheter. The results from this canine study suggest that intravenously administered glucagon is at least as effective as glucagon administered by a select intraarterial route in increasing mesenteric blood flow and reducing mesenteric vascular resistance.

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