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Insulin: Appropriate Placement in the Portal Vein

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Abstract Subcutaneous insulin administration in the diabetic patient causes peripheral hyperinsulinemia, which contributes to vascular disease, hyperlipidemia and coagulation abnormalities. In the non diabetic patient, insulin is released from the pancreas into the portal system. The majority of this endogenous insulin is taken up by the liver in the first pass so that portal insulin exceeds peripheral insulin. Avoiding peripheral hyperinsulinemia requires that insulin be given orally or administered intra-portally; the latter we have done in diabetic dogs. We propose portal insulin placement in diabetes as physiologic and appropriate in an effort to avoid peripheral hyperinsulinemia and its sequellae.

Keywords Portal, Insulin, Placement

1. Introduction

Insulin has been placed peripherally in the patient with diabetes for 90 years saving and prolonging lives. However, present peripheral subcutaneous administration of insulin results in peripheral hyperinsulinemia which itself is undesirable. Diabetic patients suffer multiple morbid sequellae of this route of insulin treatment: atherosclerosis[1,2], hypertension[3], altered lipid metabolism[3], cardiovascular disease[4] and impaired hemostasis.[5] We wished to place insulin into the portal vein of the diabetic animal, comparing peripheral insulin levels in those animals subsequent to insulin injection given peripherally, portally or via hepatic artery. These short term studies do not compare the long term complications of insulin placement; rather we compare insulin levels in our attempt to avoid the peripheral hyperinsulinemia routinely seen with subcutaneous injection of insulin. With this in mind, we wish to explore insulin placement in the portal vein, measuring and avoiding peripheral hyperinsulinemia acutely.

2. Research Method & Design

Mongrel dogs weighing 18-30 Kg were pancreatectomized under general anesthesia with simultaneous placement of catheters in branches of the portal vein and a peripheral vein as previously reported.[6] In a further group a catheter was also placed in the hepatic artery. All catheters were connected to pumps placed on the dorsal spine.

Our protocol was approved by Evanston Hospital's animal review committee and institutional review board. Pancreatic enzymes were replaced with oral lipase, protease and amylase, adjusted to animal weight. Healthy, weight stable animals were studied after overnight 12 hour fast. Diabetic study animals received subcutaneous intermediate acting insulin twice daily on days not tested.

All animals with and without diabetes were healthy, weight stable, and rapidly consumed the trial meal on the morning of study.

A total of fourteen animals were studied. Ten had diabetes, confirmed by elevation of glucose values into the diabetic range. Catheters in the portal vein, distal and proximal, hepatic artery and peripheral vein were placed. The catheters, tunneled subcutaneously, were maintained with low flow heparin injection between studies. Appropriate heparin dosage for catheter patency was given using Autosyringe model AS2C. Portal and peripheral glucose and insulin levels were measured fasting and over five hours after a meal given simultaneously with regular insulin 0.3 u/Kg administered subcutaneously, portally or via hepatic artery. Diabetes was confirmed with elevated blood glucose values daily (test day average FBS 278 and average NADIR 93 mg/dl).

3. Results

In control animals, portal insulin levels exceeded peripheral insulin levels in the fasting and fed state.

In contrast the peripheral insulin levels of diabetic insulin treated animals always exceeded portal insulin levels when given insulin subcutaneously or via hepatic artery. However, if insulin was given via the portal vein, peripheral insulin levels more nearly resembled control values (Table I).

4. Discussions and Conclusions

In intact animals and humans insulin is released from the pancreas directly into the portal venous system and thence to the liver where the majority of such insulin is extracted on the first pass. The concentration of insulin in the portal vein is 3 to 10 times greater than in peripheral veins.[7] Contrariwise peripheral hyperinsulinemia occurs after subcutaneous insulin administration. Insulin given subcutaneously causes only a modest subphysiologic portal insulin level increase even as it results in this peripheral hyperinsulinemia.[1]

Peripheral hyperinsulinemia is associated with deleterious effects on vessel walls[2], ischemic heart disease[4], hypertension[3], hyperlipidemia[3], and impaired hemostasis.[5]

With a functioning endocrine pancreas, portal insulin increases markedly after feeding, suppressing hepatic glucose production and promoting ingested glucose deposition in the liver.[7,8] Only modest subphysiologic portal insulin increase is found in the diabetic patient given insulin subcutaneously.[9] Insulin placed in the portal system causes proportionately less hypoglycemia, appears to lead to less local vessel stenosis at site of infusion, better vessel neointimal growth after injury is found, and peripheral hyperinsulinemia is decreased or avoided.[10] Control peripheral: portal insulin radios are more nearly achieved in the diabetic animal when insulin is administered portally rather than peripherally.[10]

Insulin placement by injection or catheter in the portal vein is not without complications. The portal vein and its branches lie deep within the abdomen and are mobile, leading to difficulty of foreign body catheter placement and potential for needle or catheter displacement.

Oral insulin absorption will occur into the portal system once barriers to such absorption are overcome, including gastric breakdown of polypeptide hormones and inadequate small bowel absorption.[11] Not only for convenience but for physiological appropriateness oral insulin is desirable. As we have stated previously, "the promise of a resultant potential decrease in ischemic heart disease, lipid abnormalities, abnormalities in hemostasis and less frequent, less severe hypoglycemia lend urgency to development of a means to place or to deliver insulin into the portal venous system."[6] Arterial stiffness is associated with cardiovascular, renal, retinal and autonomic disease in Type 1 diabetes[12] and this arterial stiffness correlates with these diseases in diabetics and non diabetics, independent of other risk factors correlating with duration of type I diabetes. Appropriate peripheral "euinsulinemia" should be achieved by direct insulin administration into a branch of the portal system, whether in umbilical vein or a more deeply placed stent or catheter in the portal system, or with orally administered insulin absorbed into the portal system.

The CONFIRM study recently again documented the increased prevalence, extent, severity and mortality risk of individuals with diabetes.[13] Fasting insulin levels are positively associated with the incidence of hypertension among American young adults.[14] In 1,695 non diabetic adults followed over 29 years, fasting insulin in the upper quartile confirmed a 37% increased risk for total mortality among cancer patients compared with that of lower quartile.[14]

We previously delivered insulin by catheter through a branch of the portal vein into the portal system in the diabetic animal resulting in lower peripheral insulin levels over 5 hours than is seen when insulin is given subcutaneously, more nearly imitating that seen in the non diabetic control animal.[6] Now when we deliver insulin via the hepatic artery in the same animals, peripheral insulin levels rise markedly (52.7 μ U/ml) as would be seen when insulin as delivered subcutaneously (56.6 μ U/ml) (see Table I).

Table I. Peripheral Insulin Levels 2 Hour Post Injection/Meal in Control and Diabetic Animals

	Peripheral Insulin μ U/ml	p value vs controls
Controls Diabetic Animals Injection Route	N=6 $32^{5} \pm 15^{3}$	
Subcutaneous Insulin	N=7 $56^{6} \pm 18^{6}$	01
Hepatic Artery Insulin	N=6 $52^{7} \pm 25^{2}$	.02
Portal Vein Insulin	N=9 $38^{0} \pm 26^{2}$	NS

Only portal vein placement of insulin does not result in elevated peripheral insulin levels in the injected animal at 2 hours post injection

Peripheral insulin replacement will result in peripheral hyperinsulinemia. The goal in treatment of the diabetic patient should be not only euglycemia, but peripheral euinsulinemia for all the reasons enumerated above. Because insulin is released from the pancreas into the portal venous system, and because insulin carries risks of concomitant harm when present in excess amounts in peripheral vessels, it would be best to administer insulin orally[11] or intra-portally in diabetic patients. Delivery through portal catheter placement or orally should be achievable in patients with diabetes. Measurement of peripheral glucose would continue then to be used as guideline to insulin dosage administration, although periodic measure of peripheral insulin levels could then also guide insulin intra-portal dosage.

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