Comparison of intraperitoneal, intraportal and intravenous insulin infusion

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Abstract. In order to avoid complications induced by long-term infusions of insulin into the portal vein, we examined the effect of intraperitoneal (ip) insulin infusion on arterial plasma insulin and glucose concentrations in 6 pigs, made diabetic by a constant intravenous (iv) infusion of glucose, epinephrine and propranolol. Insulin was infused by an electromechanical programmable mini-pump (Pharmaject Micro Infusion System®, Pharmacia Electronics) as a booster injection of 46 mU highly purified porcine insulin Leo®/kg body weight, followed by 3 infusion periods of 30 min each with stepwise decreasing infusion rates of 1.6–0.8 and 0.2 mU/kg/min in a total volume of 192 μl. Insulin was infused in a peripheral vein, a portal vein and into the peritoneal cavity.

A steep rise of arterial plasma insulin was demonstrated followed by a slow and identical decline in the peripheral and portal experiments, whereas only a small increase of plasma insulin was seen in the ip experiment, indicating insufficient absorption of insulin from the peritoneal cavity. The decrease of plasma glucose was identical in the peripheral and portal vein experiments, indicating that insulin infused in the portal vein does not seem to have a higher hypoglycaemic effect, than insulin infused in a peripheral vein.

Intraperitoneal insulin infusion seems not to be a practical substitute for iv insulin infusion.

Subcutaneous (sc) insulin therapy does not lead to normal survival in insulin dependent diabetics (Deckert & Larsen 1979), probably because the normal plasma insulin fluctuations cannot be imitated in patients without endogenous insulin secretion. Therefore small portable programmable pumps are under development, whereby insulin can be infused iv at adequate rates, restoring normal plasma insulin fluctuations during the day (Bojesen et al. 1978). Since, however, long-term iv cannulation may lead to sepsis and/or thromboembolic complications, sc infusion of insulin in diabetics has been examined by several authors (Pickup et al. 1979; Tamborlane et al. 1979). Absorption of insulin from the sc tissue, however, is among other factors determined by sc blood flow. Therefore plasma insulin concentration might vary in an unpredictable way during e.g. exercise, which increases the absorption of insulin (Kølendorf et al. 1979). Also capricious local insulin degradation (Dandona et al. 1978) may lead to unpredictable insulin absorption.

In order to circumvent these problems and furthermore in order to imitate the natural route of insulin delivery to the portal system, we decided to examine the effect of ip infusion of insulin on plasma insulin and plasma glucose fluctuations in pigs.

Materials and Methods

Six pigs (3 female and 3 male, Danish Landrace), body weight 21–29 kg, were fasted 12–18 h prior to each experiment. General anaesthesia was induced after sedation with 4 mg azaperone per kg im, inhalation of trichlorethylene for 2–5 min and by iv administration of phenobarbitol (nembutal sodium injection) 10–15 mg/kg body weight. Anaesthesia was maintained by N2O/O2 (60/40 v/v), supplemented by small injections of pheno-
barbital through a catheter in an ear vein. Liver function was tested in each experiment after 2.5 h of anaesthesia by determination of plasma aspartate aminotransferase and alkaline phosphatases and found normal. Controlled ventilation was used and arterial blood gasses, pH and haematocrit were periodically monitored to assure that they remained normal.

Each pig went through 3 experiments with one week interval except one pig, which died after the first examination, where autopsy showed pneumonia and peritonitis. This pig was therefore replaced by another pig for the 2 following experiments. During all experiments blood was sampled at intervals from a superficial artery for determination of plasma glucose, plasma insulin, and plasma C-peptide. Between sampling clotting was prevented by a heparin plug (Heparine Leo® 50 units/ml). Before each sampling the plug was discarded. Plasma for C-peptide determination was collected into containers with Trasylol® (500 units/ml) and Heparin (50 units/ml). All samples were kept at 4°C until centrifugation. Plasma was stored at -20°C.

In order to inhibit the endogenous insulin secretion of the pigs and in order to prevent hypoglycaemia a catheter was placed in a superficial vein and connected to a peristaltic pump (Infusomat®) for constant iv infusion of glucose (120 mg/min), epinephrine (0.2 µg/kg/min with 0.02% ascorbic acid added in order to prevent oxidation of epinephrine), propranolol (Inderal®, 1.0 µg/kg/min) and highly purified porcine insulin (0.2 mU/kg/min) in porcine plasma (1%). This cocktail solution was infused continuously from 0 to 210 min. Intravenous glucose tolerance was determined after injection of 0.5 g glucose/kg body weight 10 min after start of the cocktail infusion. As expression of glucose tolerance the k-value was calculated after determining the half-life of glucose by plotting plasma glucose against time in a semilogarithmic scale, using the formula \( k = \frac{\ln 2}{t/2} \times 100 \) (\( \ln 2 = 0.693 \)).

At 60 min a preprogrammed insulin infusion was started by an electromechanical syringe pump (Pharmajecct Micro infusion system®, Pharmacia Electronics) (Bojesen et al. 1978). The infusion programme was identical in all experiments: After a booster injection of 46 mU insulin/kg, insulin was infused in three stepwise decreasing rates of 30 min each, namely 1.6, 0.8 and 0.2 mU/kg/min respectively. The insulin solution was prepared from highly purified porcine insulin Leo Neutrale® (the concentration depending on the pigs body weight), 0.5 mol phosphate buffer, pH 7.4, equilibrated to isosmolarity with NaCl. Two per cent porcine plasma was added in order to avoid absorption of insulin to tubes and syringes. The infusion volumes during the 3 x 30 min were 192, 96 and 24 µl respectively.

During one of the three experiments the preprogrammed insulin infusion was given iv in a peripheral vein, during the second experiment ip, i.e. the catheter was placed in the peritoneal cavity through a small slit in the parietal peritoneum. During the third experiment the preprogrammed insulin infusion was given into the portal vein through a catheter placed in the splenic vein. The order of the experiments was randomized.

Plasma glucose was measured by the glucose oxidase

### Table 1.
Clinical data of 6 pigs, made diabetic by an iv infusion of epinephrine, propranolol and glucose and treated by insulin infusion A: in a peripheral vein; B: intraperitoneal and C: intraportally.

<table>
<thead>
<tr>
<th>Pig No. (sex)</th>
<th>Body weight (kg)</th>
<th>K-value1</th>
<th>Δ-C-peptide2 (pmol/ml)</th>
<th>Glucose-insulin3 ratio in plasma (mol/U)</th>
<th>Pump-insulin4 (U/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>1 (M)</td>
<td>21.0</td>
<td>21.8</td>
<td>23.0</td>
<td>0.12</td>
<td>0.35</td>
</tr>
<tr>
<td>2 (F)</td>
<td>23.5</td>
<td>26.0</td>
<td>25.5</td>
<td>0.22</td>
<td>0.83</td>
</tr>
<tr>
<td>3 (F)</td>
<td>23.0</td>
<td>27.5</td>
<td>30.5</td>
<td>0.35</td>
<td>0.07</td>
</tr>
<tr>
<td>4 (F)</td>
<td>25.0</td>
<td>23.0</td>
<td>24.0</td>
<td>0.23</td>
<td>0.44</td>
</tr>
<tr>
<td>5 (M)</td>
<td>25.0</td>
<td>25.5</td>
<td>29.5</td>
<td>0.13</td>
<td>0.30</td>
</tr>
<tr>
<td>6 (M)</td>
<td>24.0</td>
<td>27.0</td>
<td>23.5</td>
<td>0.09</td>
<td>0.19</td>
</tr>
<tr>
<td>X</td>
<td>23.6</td>
<td>25.2</td>
<td>26.0</td>
<td>0.19</td>
<td>0.36</td>
</tr>
<tr>
<td>SEM</td>
<td>0.7</td>
<td>1.1</td>
<td>1.6</td>
<td>0.04</td>
<td>0.11</td>
</tr>
</tbody>
</table>

1 Half-life of glucose (k = \( \frac{\ln 2}{t/2} \times 100 \), normal value in men > 1.0).
2 Plasma C-peptide (max) = plasma C-peptide (10 min) (normal value in men > 0.8 pmol/ml).
3 Plasma glucose area above basal/plasma insulin area above basal within the period of 60-150 min.
4 Concentration of insulin solution in the pump.
method, plasma insulin by immunoassay ad modum Heding (Heding 1972) and porcine C-peptide ad modum Faber (Faber & Binder 1977).

Results

Table 1 shows that secretion of endogenous porcine insulin was prevented by the infusion of epinephrine and propranolol in spite of the increased plasma glucose concentration since plasma C-peptide did not increase during the experiments. Plasma insulin variations therefore were assumed to originate from variations of the insulin infusion rate. Table 1 demonstrates furthermore that every pig was made diabetic indicated by k-values below 1.0 after infusion of epinephrine and propranolol.

Fig. 1 demonstrates plasma insulin variations during the three experiments. After starting the cocktail infusion at 0 time (0.2 mU insulin/kg/min), plasma insulin increased slowly from about 4 μU/ml to 10 μU/ml at 60 min. Thereafter a steep rise to arterial plasma insulin was demonstrated following the booster and preprogrammed insulin infusion given either into the peripheral or the portal vein.

The course of plasma insulin during the decreasing infusion rates of insulin were identical in these 2 experiments. However, when infused ip only a small but instant and significant increase ($P < 0.05$) of arterial plasma insulin could be demonstrated, indicating insufficient absorption of insulin from the peritoneal cavity. If absorption of insulin from the peritoneal cavity would be optimal, arterial plasma insulin after ip and portal vein infusion should be identical.

Fig. 2 demonstrates mean plasma glucose during the three experiments. It is seen that decrease of plasma glucose is almost identical in two experiments (peripheral vein and portal vein), whereas the decrease was slower in the peritoneal experiment in accordance with the lower plasma insulin concentration in this experiment.

Glucose insulin ratio, determined by dividing the glucose area by the insulin area, was identical during peripheral and portal infusions (Table 1), indicating identical effects of insulin independent of whether insulin was infused in a branch of the portal vein or in a peripheral vein. During ip infusion glucose insulin ratio was high and variable in accordance with the small arterial plasma insulin area during ip infusion.
Discussion

The experiments have shown a highly significant difference in arterial plasma insulin concentration after ip and portal iv infusion of insulin. In spite of a combined insulin booster and high rate insulin infusion the arterial plasma insulin concentration only increases about twice instead of tenfold during the ip experiment. This indicate that absorption of porcine insulin from the peritoneal cavity of young pigs either is rather bad, or reduced considerably because of local degradation. The tailing of arterial plasma insulin after discontinuation of ip insulin infusion at 150 min (see Fig. 1) supports the former view. This is in accordance with experiments in man (Greenwood et al. 1979; Cerasi, personal communication), where insulin was injected into the peritoneal cavity. Our results are however, in discrepancy to the preliminary report by Schade et al. (1979), who found steep increases of plasma insulin after ip infusion of insulin in one insulin-dependent male, maintained on peritoneal dialysis. The discrepancy might be explained by different infusion volumes being only about 500 ml in our experiment. Also species differences in insulin absorption capacity from the peritoneal cavity might play a role and differences in peritoneal drainage. Whether infusion of epinephrine combined with propranolol might impair the absorption of insulin from the peritoneal cavity is not known, but unlikely, since the heart rate of the pigs increased indicating that higher heart minute volumes neutralized the epinephrine induced reduction of the splanchnic blood flow (Reynolds et al. 1975). Also 2 pilot experiments did not indicate any improvement of the peritoneal insulin absorption when a slightly modified insulin preparation without zinc and phenol was used and epinephrine and propranolol were excluded. In these experiments arterial plasma insulin concentration increased slowly from 7 μU/ml to max. 29 μU/ml at 40 min after starting ip infusion using the same booster and infusion rate as shown above.

The experiments have also shown arterial plasma insulin to be identical during iv infusion of insulin in a peripheral and a portal vein. This is in agreement with Botz et al. (1976) who also induced identical peripheral plasma insulin concentrations by identical intraportal and peripheral iv insulin infusion, but difficult to understand, if about 50% of portal insulin is extracted by the liver during one passage as generally assumed (Sherwin et al. 1974). However, recent studies with portal and peripheral insulin infusions in humans indicate that the first pass fractional hepatic uptake of insulin is highly dose dependent, resulting in identical plasma clearance rates at the insulin dose used in our experiments (Tranberg & Thorell 1979).

Also the decrease of plasma glucose and the glucose insulin ratio were identical in the peri-
Peripheral and portal vein experiments. This means that insulin infused in the portal vein does not seem to have a higher hypoglycaemic effect than insulin infused in a peripheral vein. This is in accordance with the experiences of Botz et al. (1976) who showed that hypoglycaemic responses to constant insulin infusions were not appreciably different with either peripheral or portal route.

In conclusion: Intraperitoneal infusion of insulin can not replace iv insulin infusion in short term experiments, however, long term studies should be performed before this question is finally settled.

Acknowledgments

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Addendum

In a more extensive paper on intraperitoneal insulin infusion in man Schade D S, Eaton R P, Friedman N & Spencer W (1979): The intravenous, intraperitoneal and subcutaneous routes of insulin delivery in diabetic man, Diabetes 28: 1069–72, found considerably degradation of insulin in the peritoneal cavity (ca 50%) but an earlier onset of the hypoglycaemic effect of insulin infused in the peritoneal cavity compared to insulin infused in sc tissue.

References


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