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### **Introduction:**

In light of the interest on the relationship between glycaemia control in critically ill subjects and outcome, we set up a study to investigate if benzodiazepine, commonly used in anesthesia and intensive care units, interfere with glucose metabolism and to explore the mechanism.

### **Methods:**

A total of 40 sedated and paralyzed Sprague Dawley rats (301±55 gr) were investigated in four consecutive studies. 1) To investigate the effects of diazepam on blood glucose, 15 rats were randomly assigned to intraperitoneal anaesthesia with Tiopental 80 mg/kg (DZP0), Tiopental 40 mg/kg + Diazepam 5 mg/kg (DZP5) or Tiopental 40 mg/kg + Diazepam 15 mg/kg (DZP15). Blood levels of glucose (GEM premier 3000, IL) were measured at time intervals over two hours. 2) Ten animals randomized to DZP0 or DZP5 underwent an intravenous glucose tolerance test with glucose bolus (0.5 g/kg). Acute Insulin Response, the mean value of blood insulin (Insulin ELISA kit, Millipore) from 2 to 10 minutes after glucose bolus, was measured as index of insulin secretion. 3) An hyper-insulinemic euglycemic clamp obtained by a continuous intravenous infusion of insulin (130 mUI/kg/min) was run in 10 animals randomised to DZP0 or DZP5 and Glucose Infusion Rate (GIR, mg/kg/min) was assessed [1]. 4) The effect of midazolam on blood glucose was tested in five additional animals (M5: Tiopental 40 mg/kg + Midazolam 5 mg/Kg).

Data are presented as mean±SEM. Statistical analysis (ANOVA, t-test) was conducted with Sigma Stat 3.1 (Systat Software).

### **Results:**

1) Diazepam was associated with higher levels of blood glucose in a dose response fashion: DZP0 128±7 mg/dL, DZP5 166±7.3, DZP15 197±7 (P<0.05). 2) Acute Insulin Response to Intravenous Glucose Tolerance Test was similar in DZP0 and DZP5 (DZP0 3.97±0.42 ng/mL, DZP5 3.68±0.44, P=0.68), while blood glucose levels were different (DZP0 192±5 mg/dL, DZP5 217±5, P<0.05). 3) During Hyperinsulinemic Euglycemic Clamp, blood glucose levels were similar (109±3 mg/dL, P=0.2), but DZP5 group showed a trend through lower values of GIR (DZP0 30.8±2 mg/kg/min, DZP5 24.7±2, P=0.08). 4) Infusion of midazolam was associated with higher blood glucose levels (DZP0 128±5 mg/dL, M5 151±6, P<0.05).

### **Conclusions:**

Both diazepam and midazolam significantly alter plasma glucose levels in rats. Peripheral disposal of glucose rather than altered pancreas secretion of insulin explain the benzodiazepine-associated hyperglycaemia.

### **References:**

1) DeFronzo, Am J Physiol, 1979, 273(3):E214-23