

Effect of Ethanol Intoxication on the Anti-hypoglycemic Action of Glucagon

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### **I. a. Background**

Glucagon is used clinically in the treatment for life-threatening hypoglycemia when the patient cannot take oral carbohydrates. In this context it is given by subcutaneous or intramuscular injection. It is also being delivered experimentally along with insulin by a bi-hormonal bionic pancreas for the automated control of blood glucose [1-4]. Glucagon antagonizes the effects of insulin in the liver by inhibiting glucose uptake from the blood and promoting glycogenolysis.

It is well known that the use of alcohol is associated with an increased risk of hypoglycemia [5]. It is proposed that ethanol impairs gluconeogenesis. This might be due to alcohol dehydrogenase increasing NADH production. A decrease in NAD/ NADH ratio decreases pyruvate concentration, which is one of the primary paths to gluconeogenesis [5,6]. There is a higher risk of hypoglycemia when hepatic glycogen deposits are depleted (during the fasting state or food deprivation) because glycogenolysis then plays a reduced role in glucose level regulation [7]. There is a risk of hypoglycemia with large dose alcohol intake and even with occasional drinking and low blood alcohol level in those who have missed or delayed food intake [8].

There is a paucity of data on the effects of alcohol on glucagon effectiveness in patients with type 1 diabetes. However, it is known that alcohol intake increases the risk of hypoglycemia [9]. This might be due to multiple factors including: inhibition of gluconeogenesis, which has the main role in glucose production during hypoglycemia in patients with diabetes, impairment of rapid and slow glucose counter regulatory hormones including epinephrine, glucagon, cortisol and growth hormone and hypoglycemia unawareness because of the central effects of alcohol

Because some people with type 1 diabetes drink alcohol and because the bihormonal bionic pancreas uses glucagon for management, it is essential to determine whether alcohol will impair the effectiveness of glucagon and subsequently impair the effectiveness of the bihormonal bionic pancreas in preventing hypoglycemia.

### **I. b. Rationale and Potential Benefits**

Alcohol reduces the production of glucose from the liver, mostly by reducing the rate of gluconeogenesis [6] Glucagon is thought to raise blood glucose primarily through glycogenolysis. Whether alcohol will reduce the ability of glucagon to prevent and treat hypoglycemia is not known. Since many people with diabetes drink alcohol, and because alcohol can reduce attentiveness to diabetes management, it is very important to know whether alcohol will impair the effectiveness of a bihormonal bionic pancreas in preventing hypoglycemia.

We will test the effectiveness of glucagon in raising blood sugar in the absence of ethanol and in the presence of defined blood alcohol content (BAC) levels in a random-order crossover design. An established alcohol infusion algorithm for a clamp study will be used (10). If there is a significant reduction in glucagon effectiveness in the presence of alcohol, this will be important information to give users. If glucagon remains equally effective in the presence of alcohol, this means that the bionic pancreas will provide an even larger margin of safety over usual care when people with type 1 diabetes chose to use alcohol because of the increased risk associated with the use of alcohol in usual care. Since the alcohol levels to be tested are relatively high, if there is no effect at these levels we can be confident that the lower alcohol levels associated with healthy consumption of alcohol (2 drinks a day or less) will have no effect on the effectiveness of the bihormonal bionic pancreas.

## **II. Hypothesis and Specific Aims**

We hypothesize that a BAC of 0.1 will not significantly alter the anti-hypoglycemic effect of micro-dose glucagon.

The specific aim of this study is:

Aim 1. To quantify the effect of a blood alcohol content on the anti-hypoglycemic efficacy of glucagon using a hyperinsulinemic-normoglycemic clamp technique in volunteers with type 1 diabetes in a random-order crossover trial.

### **III. Subject Selection**

#### **III. a. Inclusion Criteria**

- Age 21 to 80 years old with type 1 diabetes for at least one year.
- Diabetes managed using an insulin infusion pump using rapid-acting insulin such as insulin aspart (NovoLog), insulin lispro (Humalog), or insulin glulisine (Apidra) for at least one week prior to enrollment.
- Alcohol exposure on at least one occasion in the last year consisting of at least 4 drinks in one sitting.

#### **III. b. Exclusion Criteria**

- Unable to provide informed consent.
- Unable to comply with study procedures.
- Unable to refrain from the consumption of alcohol at least 24 hours prior to study start
- Current participation in another diabetes-related clinical trial that, in the judgment of the principle investigator, will compromise the results of the clamp study or the safety of the subject.
- Pregnancy (positive urine HCG), breast feeding, plan to become pregnant in the immediate future, or sexually active without use of contraception.
- Aldehyde dehydrogenase deficiency as determined by a screening questionnaire
- End stage renal disease on dialysis (hemodialysis or peritoneal dialysis).
- History of pheochromocytoma (because glucagon has been reported to precipitate hypertensive crisis in the setting of pheochromocytoma). Fractionated metanephrines will be tested in patients with a history increasing the risk for a catecholamine secreting tumor:
  - Paroxysms of tachycardia, pallor, or headache. Personal or family history of MEN 2A, MEN 2B, neurofibromatosis, or von Hippel-Lindau disease
  - Episodic or treatment of refractory (requiring 4 or more medications to achieve normotension) hypertension.
- History of adverse reaction to glucagon (including allergy) besides nausea, vomiting, or headache.
- Inadequate venous access as determined by study nurse or physician at time of screening.
- Liver failure or cirrhosis
- Hemoglobin < 12 gm/dl.
- History of problem drinking or alcoholism, regardless of whether active or in remission.
- Use of benzodiazepines or barbituates or opiates or other central nervous system depressant drugs that could act synergistically with ethanol to lower the level of consciousness
- Any other factors that, in the judgment of the principal investigator, would interfere with the safe completion of the study procedures.
- Use of medications that are known to cause QT interval prolongation (See Appendix A)

No volunteers will be excluded on the basis of gender or race. The requirement that volunteers manage their diabetes using subcutaneous insulin infusion pump therapy is imposed because multiple daily injection therapy involves the use of medium-acting basal insulin (such as NPH insulin) or long-acting insulin (such as glargine) that would either require an extended washout period or would result in unwanted variation in the GIR due to the pharmacokinetics of longer acting insulins. The requirement significant

ethanol use in the last year is to reduce the likelihood that the subject will experience an adverse reaction to the blood alcohol content levels that will be reached in the study. The exclusion of potential subjects with a history of alcoholism is to avoid the risk of relapse associated with ethanol exposure in the study.

### **III. c. Source of Subjects**

Volunteers who fit the selection criteria will be considered as candidates for this study. Advertisements for the study will be posted at the MGH Diabetes Center and will be distributed in the weekly broadcast email of research studies seeking volunteers. We will post basic information about the trial along with contact information on our website [www.artificialpancreas.org](http://www.artificialpancreas.org) and the study will be posted on [www.clinicaltrials.gov](http://www.clinicaltrials.gov). We will also post information regarding the trial at online venues for people with type 1 diabetes, such as Glu (online community of the Type 1 Diabetes Exchange). We will also contact individuals who have previously inquired about participation in our studies and have asked us to have their contact information kept on file.

### **IV. Subject Enrollment**

#### **IV. a. Number of Subjects**

It is expected that we will have 20 volunteers complete two full-length clamp experiments with 15 of those volunteer's using a consistent protocol. The experiments are expected to be completed over a time period of 4-6 months.

Up to 35 volunteers with type 1 diabetes will be enrolled. The upper bound is based on the expectation that some volunteers will be excluded after the screening visit and blood tests, the possibility that some qualified volunteers will not be able to complete an experiment for scheduling reasons, the possibility that some experiments may have to be discontinued before completion (e.g. due to inability to maintain IV access or subject withdrawal), and the likelihood that minor modifications to the protocol for adjustment of the GIR, alcohol infusion rate, or the insulin infusion rate may be required during the first 2-3 experiments.

#### **IV. b. Enrollment Procedures**

Prospective participants may be briefed by a study staff member by phone regarding the study procedure and the inclusion and exclusion criteria. Potential volunteers may be sent an informed consent document to review by email or post.

#### **IV. c. Consent Procedures**

Potential volunteers will meet with a study physician or nurse practitioner who will explain the study and answer questions. Informed consent will be administered by an MD or NP. In the event that a volunteer is a patient of one of the study MDs or NPs, another staff MD or NP will answer questions and administer consent. If a nurse practitioner is administering the consent, a physician will be available as back-up for additional support if needed and subjects will be offered the chance to speak with a study physician if they wish.

The study physician or nurse will also answer any questions that the volunteer may have during their participation. They will share any new information in a timely manner that may be relevant to the volunteer's willingness to continue participating in the trial. The volunteers may choose to discontinue their participation at any time.

Documentation of the informed consent process will be noted using the Documentation of Informed Consent Form in each volunteer's research record, including documentation of the option to speak with a study physician

## V. Study Procedures

### V. a. Screening data

- Age
- Sex
- Race and ethnicity
- Urine HCG for female volunteers
- Date of diabetes diagnosis
- Medical, surgical, and social history, allergies, and review of systems relevant to inclusion and exclusion criteria
- Subject's customary drinking history
- Date of last menstrual period in female volunteers
- Medications (prescription and non-prescription) and date of last change in medication regimen
- Duration of insulin pump use
- Insulin regimen (basal rate, sensitivity factor, and carbohydrate ratio)
- Average total daily dose of insulin in the last 30 days (from pump history)
- Height and weight
- Blood pressure
- Hemoglobin
- Fractionated metanephrines (in patients with history increasing the risk for a catecholamine secreting tumor)

### V. b. Drugs

The study involves subcutaneous administration of *Eli Lilly glucagon*. Lilly glucagon is commercially available by prescription and is indicated for patients with type 1 diabetes.

The clamp procedure involves intravenous administration of *regular human insulin*, which is commercially available indicated for patients with type 1 diabetes. The insulin infusion includes 2% *human serum albumin*, which is added to the solution to prevent inactivation of insulin or loss of insulin on the walls of the administering syringe and IV tubing (10).

The clamp procedure also includes ethanol infusion solution (6 % v/v ethanol in ½ normal saline). Sterile pyrogen free IV ethanol 98% is diluted to 6 % v/v with ½ normal saline prior to use.

Intravenous infusion of *dextrose 20% solution* will also be administered.

Per MGH hypoglycemia procedures, one ampule of 50% dextrose will be given in the event of a hypoglycemic episode. Some side effects associated with taking dextrose include: dehydration, mental confusion, hyperglycemia and possible hyperosmolar syndrome which may result from too rapid administration.

In the event of any nausea, subjects will be given a small dose of ondansetron to alleviate symptoms of nausea. Ondansetron will only be administered upon the subject's request. Pain medications such as acetaminophen and ibuprofen will also be offered for pain and administered upon the subject's request. Adverse effects associated with taking acetaminophen include: rash, hives, redness of skin, itching, swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles, or lower legs. Common side effects associated with taking ibuprofen include: nausea, vomiting, diarrhea, bloating and abdominal pain.

### V. c. Devices

**Ethanol clamp algorithm:** Alcohol Infusion System Software. This is the software system, developed by the Indiana Alcohol Research Center (Dr. Sean O'Connor) that runs the PBPK (Physiologically Based

Pharmacokinetic) model, integrates breath alcohol measurements, computes the ethanol infusion rate profile to achieve the desired result, converts the profile into computer-controlled infusion pump instructions, runs the pump, and displays the results throughout the experiment (10, 11). The algorithm will be run on a laptop computer that will directly control the ethanol infusion pump.

**Ethanol infusion pump:** The Alaris Imed Gemini PC-2TX Infusion Pump is a computer controllable 2 channel pump that can be controlled by a computer using a serial connection.

**Saline, and glucoseinfusion pumps:** Standard hospital infusion pumps.

**Breathalyzer:** The handheld Alco-Sensor FST (Intoximeter, Inc) Breath alcohol analyzer will be used to measure Breath Alcohol Content (BrAC) at an accuracy of  $\pm 0.005\%$  BAC at  $0.100\%$  BAC. Each subject will use a disposable mouth piece. A push on the ejection tab on the mouthpiece hygienically expels it from the Breathalyzer without any contact between the subject's saliva and the meter or the operator's hand. The meter will be professionally calibrated at least annually.

**Intravenous catheters:** Each volunteer will have two intravenous catheters introduced. One will be dedicated to withdrawal of samples and the other for infusion of insulin, ethanol and dextrose.

**Nova Biomedical StatStrip Xpress Glucose Meter:** The StatStrip Xpress glucose meter is FDA approved for outpatient and inpatient use and is commercially available. The meter will be cleaned between subjects according to the manufacturer's instruction.

**HemoCue Hb 201 + Analyzer:** The HemoCue is an FDA approved meter used to measure hemoglobin through blood obtained via finger stick.

**Hot box:** A hot box will use warm air to warm the forearm and hand of the subject in which the sampling IV catheter is placed for the purpose of arterializing venous blood.

#### **V. d. Experimental Procedures and Data Collection**

##### **Screening Visit**

- All volunteers will have a screening visit to confirm eligibility
- Female volunteers will have urine tested for HCG. If the test is positive, the volunteer will be informed of the result and the visit will be ended.
- The volunteer will be interviewed and the case report form will be completed by a study nurse or study physician to establish whether the volunteer is eligible to continue with the screening.
- A finger stick will be performed to test hemoglobin using the HemoCue Hb 201+ Analyzer. A blood draw will be performed in the event that the Hemocue measurement is out of range and, if indicated, plasma for metanephrines.
- A study physician or nurse practitioner will review the case report form and laboratory results to determine volunteer eligibility. If volunteers are not eligible to continue in the study, the results of abnormal tests will be reported to the volunteers and to a health care provider of their choosing.

##### **Hyperinsulinemic-normoglycemic Clamp**

We will test the effect of glucagon in the absence and presence of ethanol in a random-order crossover design. We will give each volunteer two identical injections of glucagon, one with a blood alcohol content of approximately 0 at one visit and another with a BAC of approximately 0.1 at another separate visit.

##### **In Both Visits**

- Subjects will report to the Clinical Research Center (CRC) by approximately 7:00 AM in the fasted state from 10pm the previous night. Subjects will be asked not to take any bolus insulin after 4 am, but to keep their basal insulin running.
- A urine HCG test will be performed for all female subject who are able to become pregnant. If the test is positive, the PI will inform the subject of the test result and the visit will be cancelled.

- A dipstick drug test will be performed to ensure that subjects are not under the influence of benzodiazepines or barbiturates or opiates that could synergize with ethanol to cause central nervous system depression.
- A Breathalyzer measurement will be obtained prior to the start of the visit to ensure the subject is not under the influence of alcohol.
- Two intravenous (IV) catheter lines will be placed, one in each arm. The sampling IV will be placed on the dorsal surface of the hand or the forearm. The catheters will typically be 20 gauge or smaller.
- Blood will be drawn for measurement of hemoglobin A1c, creatinine and estimated GFR, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum albumin, and free fatty acids.
- Regular human insulin will be added to the solution of 2% human serum albumin in normal saline to allow an infusion rate of 5-20 ml/hr based on the desired hourly insulin dose. Mixing of the insulin infusate will be performed by the research pharmacy and the final desired insulin concentration will be communicated to the research pharmacy in advance of the visit. The range of insulin concentrations in the infusate are expected to be from 0.2-1.2 u/ml, depending on the mean basal insulin rate of the subject.
- The subject will remove their own insulin pump and a primed continuous insulin infusion will be started using the insulin/saline/albumin mixture. The continuous rate will be between one-fold and four-fold higher than the mean basal insulin rate of the subject with the goal to use a minimum rate of 0.02 units/kg/hour. The insulin infusion may be used to give insulin boluses if the subject is hyperglycemic at arrival to reduce the time necessary to reach steady state. Once the appropriate rate is established (with a dextrose infusion rate that is neither too low nor too high), it will remain stable throughout the experiment. For a 70 kg, 5'10" tall man with a usual basal rate of 1 u/hr, an infusion at two-fold the usual basal rate would be 17 mU/m<sup>2</sup>/min. Therefore, for a 5 ml/hr infusion 19.88 units of insulin would be added to 50 ml of saline/albumin solution (~0.4 u/ml). A bolus of insulin that is three times the subject's mean basal rate will be given at the start of the clamp to accelerate the rise of insulin levels in the blood.
- An infusion of 20% dextrose in water will be started. BG values will be measured every 5 minutes using arterialized blood measured with the StatStrip Xpress. The dextrose infusion will be adjusted so that the blood glucose is stabilized at  $90 \pm 5$  mg/dl. If the dextrose infusion rate is less than 2 mg/kg/min or greater than 8 mg/kg/min (for the 70 kg, 5'10" tall man, 42-168 ml/hr) then the insulin infusion rate may be adjusted. Initial stabilization is expected to take less than 3 hours.
- Blood samples (5ml) will be processed for plasma for later insulin and glucagon measurement every 20 minutes throughout the experiment.

#### **During the Ethanol Infusion Visit Only**

- Once the insulin infusion rate is established and the dextrose infusion rate has been stable for 15-20 minutes with the BG in the target range, the ethanol infusion will be started.
- The ethanol loading dose will be infused over 30 minutes, followed by a maintenance infusion. The target BAC is achieved by a specific dose and rate of alcohol infusion that is computed for each subject by estimating physiological parameters that include subject's alcohol elimination rate. An established computer model will be used (10) which is physiologically based on alcohol pharmacokinetic modeling. The parameters are based on height, weight and gender.
- We will use a breathalyzer to estimate BAC and will adjust the maintenance infusion accordingly to reach and maintain a BAC of  $0.1 \pm 0.01$ . This is expected to take 30 to 45 minutes. Breathalyzer readings will be collected every 5 minutes until the BAC of 0.1 is reached, and then the levels will be checked every 10 minutes.
- The ethanol infusion will be continued for a maximum of up to 4 hours
- A mock ethanol infusion will be delivered during the non ethanol visits, consisting of the half-normal saline vehicle that the ethanol is normally delivered in. This will be done in order to keep the total amount of fluid infused the same. This will be started at approximately the same time, when the insulin infusion rate has been established and the dextrose infusion rate has been stable for 15-20 minutes. The computer model will run a standard profile based on the subject's height, weight and gender without any BAC measurements needed. When the computer model predicts that the BAC has reached the desired value, and the GIR remains stable for 15-20 minutes, the

injection will be given. Note that BAC measurements in the ethanol visits will modify the standard profile to achieve a true BAC of 0.1%, but the deviations from the standard profile are usually not large, so that the volume of half-normal saline delivered will be approximately the same during ethanol and non-ethanol visits.

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**In Both Visits**

- Once the GIR has been stable for 15-20 min (and the BAC has been stable at  $0.1 \pm 0.01$  for at least 10 minutes in the Ethanol Infusion Visit or the predicted BAC has been stable for at least 10 minutes in the non-ethanol visits) two baseline plasma samples will be obtained 5 minutes apart and the glucagon injection will be given.
- A bolus of 50 mcg of Lillyglucagon will be administered by subcutaneous injection using a syringe and a small gauge needle at a depth of less than 1 cm.
- In the 60 minute period after the glucagon injection, the frequency of BG checks will be increased to every 2 minutes and blood samples will be processed for plasma at every other check (every 4 minutes).
- The dextrose infusion rate will be adjusted to maintain the BG in the target range. Since glucagon antagonizes the effects of insulin in the liver, the dextrose infusion rate will be reduced and then increased again to baseline as the glucagon effect waxes and wanes. Given what is known about the pharmacokinetics of glucagon given by the subcutaneous route, it is expected that it will take 60-90 minutes for the dextrose infusion rate to stabilize again.
- After the initial 60 minute period, the sampling interval for BG measurements will return to 5 minutes and the sampling interval for blood samples to be processed for plasma will be extended to every 10 minutes.
- At 90 minutes after the injection, the experiment will be ended and the insulin infusion will be stopped. The dextrose infusion will either be stopped or titrated down by the provider.
- In the ethanol infusion visit the ethanol infusion will be stopped. The BAC will be monitored until it falls below 0.04%. In the non-ethanol infusion visit the mock ethanol infusion will be ended.
- The subject's insulin pump will be replaced and restarted at the end of the experiment. The subject will be given a small meal. The provider will help the patient determine how much of their own insulin (from their insulin pump) they should bolus, if any. Both IV lines will now be removed.
- The total clamp time is expected to be up to 8 hours and total experiment time is expected to be up to 11 hours
- The total blood obtained is expected to vary from 150- 200 ml per visit. In no case will more than 400 ml of blood be taken total.
- Subjects will not be allowed to sleep during the clamp visit, as sleep can affect glucose metabolism. Ambulating to the bathroom will not be permitted. A urinal and a bedside commode will also be made available to subjects should they need it.
- If the subject's BG is  $>250$  mg/dL for two consecutive measurements and no correctable fault is found the clamp procedure will be stopped. The subject will be treated and return to their usual care per PI discretion.
- If the subject's BG is  $< 60$ mg/dL for two consecutive measurements and no correctable fault is found the clamp procedure will be stopped. Hypoglycemia will be treated using either oral or IV carbohydrates and the subject will return to their usual care per PI discretion.
- Subjects will not be released until their BAC falls below 0.04% and someone is available to accompany the subject.
- Subject will instructed upon discharge to monitor their blood glucose values closely for approximately 24 hours post discharge. The contact information for the covering provider will be given to the subject.

**V. e. Response to adverse events**

Euphoria, sedation, ataxia, nausea, vomiting, delayed reactions, impaired memory, blurred vision, impaired fine muscles and dizziness might occur with blood alcohol content (BAC) of 0.1. If patient wants to stop receiving the ethanol infusion they can withdraw at any time.

Nausea is a potential side effect of glucagon administration. Minimal nausea was noted in clinical trials of the bi-hormonal closed-loop system in which up to 80 mcg of glucagon was given at intervals of as little as 5 minutes. The mean glucagon dose in these trials was ~1 mg over 24 hours. Therefore, we do not anticipate significant nausea associated with one 50 mcg doses of glucagon. However, if nausea is experienced by subjects, they are allowed up to 8 mg of ondansetron every 8 hours.

If vomiting occurs, a study physician or nurse practitioner will be notified. If the glucagon dose has already been given at the time of vomiting, then the experiment will be completed if the subject is willing since completing the experiment will not involve administration of more glucagon. If the vomiting occurred prior to glucagon injection, and may therefore be related to pre-existing illness or to ethanol, a study physician or nurse practitioner will assess if the study needs to be stopped prior to the glucagon administration. The subject may withdraw at any point of the study.

#### **V. f. Supervision by Study Staff**

A study physician or nurse practitioner will order all changes to the insulin infusion and glucose infusion rates and to the ethanol infusion, and will be on site at all times once the clamp has begun and until it is ended.

### **VI. Biostatistical Analysis**

#### **VI. a. Data Collected**

##### **At the time of enrollment:**

- Age
- Sex
- Race and ethnicity
- Urine HCG for female volunteers
- Date of diabetes diagnosis
- Medical, surgical, and social history, allergies, and review of systems relevant to inclusion and exclusion criteria
- Date of last menstrual period in female volunteers
- Medications (prescription and non-prescription) and date of last change in medication regimen
- Duration of insulin pump use
- Insulin regimen (basal rate, sensitivity factor, and carbohydrate ratio)
- Average total daily dose of insulin in the last 30 days (from pump history)
- Height and weight
- Blood pressure
- Hemoglobin A1c
- Hemoglobin
- Creatinine and estimated GFR
- Serum Albumin
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Fractionated metanephrines (in subjects with history increasing the risk for a catecholamine secreting tumor)
- Free fatty acids

##### **During the hyperinsulinemic-normoglycemic clamp:**

- Venous BG measurements
- Timing and size of glucagon dose
- Insulin infusion rate
- Glucose infusion rates

- Ethanol infusion rate
- BAC according to breath alcohol meter
- BAC according to blood alcohol measurement
- Plasma insulin levels during the hyperinsulinemic-normoglycemic clamp
- Plasma glucagon levels during the hyperinsulinemic-normoglycemic clamp
- Any adverse events

## **VI. b. Study Endpoints**

### **Primary endpoint analysis:**

- Area over the curve for the glucose infusion rate in the hour following a subcutaneous glucagon dose ( $AOC_{GIR}$ ) with a blood alcohol content of 0 vs. approximately 0.1%

### **Secondary endpoint analyses:**

- Maximum change in GIR from baseline after glucagon injection in the presence and absence of ethanol

We will calculate means, median, percentages, standard deviations, standard errors, inter-quartile ranges, and 95% confidence intervals in descriptive analyses. We will use paired t-test for comparison of means. We will use multivariate regression models with repeated measurements to compare means and percentages while adjusting for patient demographics characteristics such as age, gender, body mass index, and body surface area.

## **VI. c. Power Analysis**

Assuming that the standard deviation in each arm is 20% of the mean, and a within-patient correlation of 0.5, a sample size of 15 achieves 95% power to detect equivalence when the margin of equivalence is from -20% to 20% assuming the actual mean difference is zero. The significance level ( $\alpha$ ) is 0.05 using two one-sided paired t-tests. These results are based on 2000 Monte Carlo samples.

## **VII. Risks and Discomforts**

There is a potential risk of nausea or vomiting in volunteers due to the administration of exogenous glucagon. The experiments, however, involve small subcutaneous glucagon doses. The recommended dose of glucagon for treatment of severe hypoglycemia in an adult with diabetes is 1000 mcg, given as a single subcutaneous or intramuscular injection. In practice, a smaller dose of 500 mcg is sometimes used initially to reduce the risk of nausea and vomiting. The total dose to be administered in our study is 50 mcg.

There is a risk of euphoria, sedation, ataxia, vomiting, delayed reactions, impaired memory, blurred vision, impaired fine muscles and dizziness with infusion of ethanol to achieve a blood alcohol content (BAC) of 0.1. We will exclude without previous alcohol exposure comparable to the study amount to avoid severe reactions. If patient wants to stop receiving the ethanol infusion they can withdraw at any time.

There is a risk of headaches, fatigue, malaise, and constipation with administration of ondansetron. Subjects will only be given this medication upon their request for nausea or vomiting.

There is a potential risk of hypoglycemia, since exogenous insulin will be administered. Given frequent BG monitoring (every two to five minutes), corresponding adjustment of a continuous dextrose infusion, and direct supervision by an NP or MD at all times, the risk of a hypoglycemic episode leading to significant harm to volunteers is expected to be very low. We do not expect to see a wide range of BGs. If two consecutive measurements are more than 250 mg/dL or less than 60 mg/dL the study provider will be informed and the clamp infusions will be checked. A small meal will be provided to subjects after completion of the study.

There is a theoretical risk of infection associated with the use of albumin, a protein purified from donated blood. The risk of transmitting disease is reduced by testing blood donors for infections, and by heat treating and purifying the albumin. Because of these measures, the risk is considered to be very small; no cases of disease transmission have ever been identified for albumin.

Subjects may experience mild discomfort associated with the insertion of the infusion into the SC tissue. Any discomfort is expected to be similar to that associated with injection of insulin. Once the infusion set is in place, there should be no significant discomfort. The risk for developing inflammation in the SC tissue at the insertion site is expected to be extremely low.

Subjects may experience discomfort with insertion of the peripheral intravenous line and the risks of intravenous lines remaining in place for about 10 hours include thrombosis and phlebitis of the peripheral vein.

Subjects may also experience mild discomfort associated with the subcutaneous injection of glucagon.

There is a risk of risk of dizziness or lightheadedness from blood loss. However, typical blood loss will be ~200 ml and loss of blood will be limited to no more than 400 ml.

### **VIII. Potential Benefits**

The data derived from this study will allow us to determine if there is a significant reduction in glucagon effectiveness in the presence of alcohol or not. This will be important information to give to users of the bionic pancreas. If glucagon effectiveness does decrease, this information will be important for users of the bionic pancreas. If it does not, this means that the bionic pancreas will provide an even larger margin of safety over usual care when people with type 1 diabetes chose to consume alcohol. There is no direct benefit for the subject participating in this study.

### **IX. Data and Safety Monitoring**

#### **IX. a. Monitoring of Source Data**

The principal investigator (PI), a study clinical research fellow (physician), or a study nurse practitioner will review the eligibility of each volunteer based on the case report from the screening visit.

All data from study visits will be combined in a single database that will be compared against the primary data files for integrity. The computer database will be backed up at least monthly and the backup media stored in a secure location.

The study will be conducted by the staff of the MGH Diabetes Research Center (DRC) in cooperation with the staff of the CRC. The PI will conduct meetings with study staff at least twice a month to review study progress, discuss any issues in study conduct, and review procedures. Study staff will be encouraged to raise any concerns they may have or problems they have identified at these meetings. The PI will decide a course of corrective action, and resolution or progress will be assessed no later than the next bimonthly meeting. An audit of procedures, regulatory documentation, and a sample of volunteer files will be performed by a member of the DRC at least biannually. The audit will be conducted by a DRC staff member not directly involved in the conduct of the study. This audit will include a review of regulatory documentation, such as IRB correspondence, and a review of files, including a review of consents, case report forms, and other data from study visits.

A numeric code will be substituted for the volunteers personal identifying information in the study database, which will be password protected. The key linking the medical record number of the volunteer with the numeric code, along with case report forms, and all information that is personally identifiable, will be kept in a locked filing cabinet in an investigator's locked office. All electronic records will be kept in a password protected computer database. All printed computer data will be disposed of confidentially when no longer needed. Only the study staff will have access to the study database. Subjects may not withdraw

from the de-identified database, but they may elect to have the key linking their medical record to the de-identified database destroyed.

The study data may be shared with collaborators outside of Partners, but only in a form in which all personally identifiable information has been removed. Shared data will be in the form of a database in which only a number identifies volunteers.

### **IX. b. Safety Monitoring**

A study physician or nurse practitioner will directly supervise each experiment. The PI will be informed of any adverse events immediately and will make any adjustments to the study protocol as needed to maintain subject safety.

The Research Pharmacy will mix the insulin and ethanol solution. The calculations for the insulin infusion rate and the mixing of the insulin solution will be done in advance and checked by another physician or nurse practitioner. The calculations for the alcohol infusion rate will be done in advance and checked by another physician or nurse practitioner.

This study will be conducted under an Investigational New Drug application sponsored by the PI.

This study is considered moderate risk. The Principal Investigator and co-investigators will evaluate each experiment. Unanticipated problems, including adverse events, will be reported to the Partner's IRB in accordance with the PHRC policy on Unanticipated Problems Involving Risks to Subjects or Others including adverse events. An external Data and Safety Monitoring Board will oversee the conduct of the study and review its results on a regular basis. Additionally, the DSMB will be informed after any experiment that has to be discontinued due to hypoglycemia, hyperglycemia, or any unexpected adverse event. DSMB review will occur before any further experiments are performed. The DSMB will be informed if there are any changes to the study protocol that could significantly impact the safety or scientific validity of the study. A final DSMB meeting will convene after the completion of the study. After the first DSMB meeting, subsequent meetings may be convened via e-mail or conference call. Safety and efficacy data will also be reported to the FDA in compliance with applicable regulations.

### **IX. c. Adverse Event Reporting Guidelines**

The PI will review any adverse events after each experiment. Adverse events will be reported to the Partner's IRB, the DSMB, and to the FDA.

### **X. Subject Compensation**

Financial compensation of \$50 will be provided to all subjects who complete a screening visit. Subjects will be compensated \$200 after completion of each visit for a total of \$450 for the entire study.

### **XI. References**

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I. Appendices

Appendix A.

The last revision date: December 17, 2015



**Filters:**

TdP Risk Category: **Drugs with known TdP risk**

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use	Risk Category	Route
Amiodarone	Cordarone®, Pacerone®, Nexterone®	Antiarrhythmic	Abnormal heart rhythm		oral, injection
Anagrelide	Agrylin®, Xagrid®	Phosphodiesterase 3 inhibitor	Thrombocytopenia		oral
Arsenic trioxide	Trisenox®	Anticancer	Cancer (leukemia)		injection
Astemizole (Removed from US Market)	Hismanal®	Antihistamine	Allergic rhinitis		oral
Azithromycin	Zithromax®, Zmax®	Antibiotic	Bacterial infection		oral, injection
Bepidil (Removed from US Market)	Vascor®	Antianginal	Angina Pectoris (heart pain)		oral
Chloroquine	Aralen®	Antimalarial	Malaria		oral
Chlorpromazine	Thorazine®, Largactil®, Megaphen®	Antipsychotic / Antiemetic	Schizophrenia, nausea, many others		oral, injection, suppository
Cilostazol	Pletal®	Phosphodiesterase 3 inhibitor	Intermittent claudication		oral
Ciprofloxacin	Cipro®, Cipro-XR®, Neofloxin®	Antibiotic	Bacterial infection		oral, injection
Cisapride (Removed from US Market)	Propulsid®	GI stimulant	Increase GI motility		oral
Citalopram	Celexa®, Cipramil®	Antidepressant, SSRI	Depression		oral
Clarithromycin	Biaxin®, Prevpac®	Antibiotic	Bacterial infection		oral
Cocaine	Cocaine	Local anesthetic	Anesthesia (topical)		topical
Disopyramide	Norpace®	Antiarrhythmic	Abnormal heart rhythm		oral
Dofetilide	Tikosyn®	Antiarrhythmic	Abnormal heart rhythm		oral
Domperidone (On non US Market)	Motilium®, Motilium®, Motinorm Costi®, Nomit®	Antinausea	Nausea, vomiting		oral, injection, suppository
Donepezil	Aricept®	Cholinesterase inhibitor	Dementia (Alzheimer's Disease)		oral