Webinar Q&A Report:

From Mouse to Monkey: Revolutionizing Research via Preclinical Continuous Glucose Telemetry

1. **How long does the sensor last?**

   As a population, sensors typically lasts 6-8 weeks from the time they are implanted and when used within specifications. Each individual sensor is warranted for 28 days from the time they are implanted when used within specifications.

2. **Are there any specific difficulties in the implantation of blood glucose probes in lean versus obese mice?**

   In the lean animals we have occasionally experienced skin irritation/necrosis over a subcutaneously placed implant, particularly if the subcutaneous pocket is not made large enough to comfortably accommodate the implant. The pocket should be made very large, but kept lateral (not extended onto the ventral abdomen), to avoid the implant from dragging on the cage floor. A 3-cc syringe should easily fit into the pocket, and sterile saline should be instilled to lubricate the pocket before the implant is placed. The obese models tend to more accommodating of subcutaneous implants. If the mouse is large enough (ideally ≥ approximately 27 grams), the implant can be placed intraperitoneally to avoid skin issues.

   We have also seen some issues that we believe are related to a decreased ability to groom in lean mice with the device implanted in an intraperitoneal location and in obese strains. Some male mice have developed what appear to be proteinaceous penile plugs ± paraphimosis during the post-operative period. With careful daily monitoring and gentle removal of these plugs, the animals are able to recover without complication.

3. **Can you explain or clarify how to do the calibration?**

   Approximately one week after implantation a multipoint calibration is recommended in order to establish a linear calibration. Excluding that multipoint calibration single point references are recommended at least once every 7 days and preferably once every 3–4 days.

   In practice, a GTT or ITT with specific timing of blood draws is typically used for the multipoint calibration, though other methods are possible. An example of a multipoint calibration using a GTT can be seen at https://www.datasci.com/glucose/resources/videos.

4. **What animal models have you implanted with glucose telemetry?**

DSI surgeons have implanted continuous glucose telemetry within the below species and strains.

a. Mouse: Swiss Webster, C57Bl/6, ob/ob, db/db, DIO
b. Rat: Sprague Dawley +/- STZ, Fatty Zucker, ZDSD
c. LA: NHP, swine (minipig)

Additional species and strains have also been implanted by our customers; however, we have limited awareness of these details beyond posters and publications.

5. **As an extension, are any of the diabetic models more difficult to work with?**

We were concerned about potential delayed healing in diabetic animals due to their abnormal metabolism, but in practice this has seen limited impact. If possible, such as in a STZ-induced model, we wait until after surgery to induce the disease state. In the type II models, we monitor carefully for wound healing, skin irritation and general health and animal welfare.

We have occasionally seen animals with skin erosion or necrosis over the implant or sensor, in both diabetic and non-diseased animals. The steps we take to prevent this include ensuring a very large pocket is made on the animal's flank, so the skin isn't too tight over the device, or placing the implant intraperitoneally to protect the skin. In addition, we try to make sure the sensor lies flat under the skin of the neck. If it bulges up it can cause skin necrosis there as well.

6. **What's the maximum glucose level that this implantable device can detect?**

Our continuous glucose telemetry devices have been shown to be linear up to at least 900 mg/dl.

7. **If you were to implant both the blood pressure and glucose probe in a large animal, where would you suggest placing the catheter and sensor?**

The most important factor is maintaining the glucose-sensing tip of the glucose probe and pressure-sensing tip of the catheter in freely flowing blood. There may be a variety of acceptable surgical approaches that can achieve this. We have had success placing both the glucose sensor and tip of the pressure catheter in the descending aorta, but our preferred approach for this is a bilateral femoral cannulation. Specifically, we introduced the pressure catheter into the femoral artery of one leg and the glucose sensor in the femoral artery in the opposite leg. Alternatively, you could place one in the descending aorta via a femoral artery cannulation and one in the aortic arch via a carotid artery cannulation; however, that requires additional tunneling.

8. **How many samples are required or recommended during a glucose challenge?**

If using oral or intraperitoneal dosing two samples are required. The first sample should be collected prior to dosing when the animal is at a relatively steady state baseline. The second sample should be collected approximately 3 to 5 minutes after the peak glucose is observed using the real-time telemetry signal.

If using intravenous dosing, four samples are recommended. The first sample should be collected prior to dosing. The second sample should be collected approximately 3 to 5 minutes after the peak glucose is observed using the real-time telemetry signal. The third should be collected 5 minutes after the second sample. And the fourth should be collected 5 minutes after the 3rd sampled. During calibration optimization, not all of those samples will necessarily be used.

9. Do the animals experience problems when housed in pairs such as tangling or other strain on wires?

Our implantable telemetry devices are wireless, so no tangling or strain on wires would be expected.

With regards to pair housing of small animals, the solution only allows one implant to be on and recording at a time, so if pair housing is required a non-implanted companion animal would be recommended.

10. What is the success rate of implantation in mice? Have you experienced any unique challenges?

Our success rate is approximately 80% or better, depending on the strain. A robust strain such as a Swiss Webster should have a greater success rate, and a more compromised strain may be lower. It is difficult to predict surgical success in genetically modified animals, and a small pilot is recommended to better understand how much overage should be accounted for during a full study.

11. Do mice gain weight similarly to normal mice after implantation of the probe?

With this and similar surgeries, we expect to see a small (<20%) decrease in the first few days post-operatively. Animals typically return to their pre-operative weight within the first week post-operatively and then continue on a typical growth curve

12. How much do the probes weigh?

The mouse and rat continuous glucose telemetry devices weigh 2.2 grams. The large animal continuous glucose telemetry devices weight 13.7 grams.

13. Are similar systems available for other species?

DSI's HD-XG implant is available for the mouse, rat, and similar-sized small animals. DSI's M series glucose implants are suitable for large animal such as non-human primates, swine, canine, or rabbits.

14. Is there any diminished glucose signal over time due to clot formation on the catheter?

The glucose sensor has been specifically designed to avoid clot formation. Occasionally some type of biological material does form around the sensor which could diminish the signal. Our calibration algorithm should compensate for this appropriately.

15. **Have you tried anticoagulant coatings on the glucose catheters to prevent clotting?**

    The glucose sensor incorporates such a coating already.

    In practice we find that clotting is not an issue, as long as the tip of the sensor is located in freely flowing blood. If the tip of the sensor is in an area of stagnant blood (i.e. not placed deeply enough beyond a ligated artery/branch) the entire vessel becomes clotted, and no anticoagulant coating will prevent this.

16. **What statistical analysis do you recommend for comparing treatments longitudinally?**

    The type of analysis will depend upon your hypothesis and study design. Ultimately, DSI would recommend that you consult with a statistician. Before that if one desires to interact with DSI to understand what others have done, an email could be sent to glucose@datasci.com.

17. **Using this method, is it possible to measure glucose in socially housed animals?**

    The glucose implant for large animal species is part of the PhysioTel Digital platform and allows for social housing. In small animals, the solution only allows one implant to be on and recording at a time so if pair housing is required a non-implanted companion animal would be recommended.

18. **Is temperature measured with the same probe? What is the temperature measurement principle (is it a digital or analog sensor)?**

    Temperature is measured within our continuous glucose telemetry devices using a thermistor which is calibrated during our manufacturing process. This thermistor data is sampled frequently and sent via telemetry by the device along with the other signals. As such, the resulting temperature data is digital in nature.

19. **How sensitive is the sensor placement to the physical stress of exercise, for example using a treadmill on a daily basis over an extended period of time?**

    I'm not aware of the device being used with treadmills; however, it has been used with running wheels without any obvious artifact being present. As such, I estimate that the glucose and temperature measurements should not be negatively impacted by the use of a treadmill and as such should only document the physiologic effects of treadmill use on the animal's actual glucose and temperature.

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Data Sciences International (DSI)
Headquarters and North America Sales
119 14th St NW
Suite 100
St. Paul, MN 55112 U.S.A.

Tel: 1-800-262-9687 (U.S.)
Tel: +1-651-481-7400 (International)
Fax: +1-651-481-7404

Sales Email: sales@datasci.com
Support Email: support@datasci.com