Use of Externalized Magnetic Ports in Mice: A Refinement for Long-term, Repeat-dose Intravenous Bolus Injections

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1 ABSTRACT

Long-term daily intravenous dosing in mice presents many challenges. Generally, the maximum number of consecutive days mice can be successfully dosed via tail vein is 14 days. Procedurally, intravenous tail injections require a restraint device, and sometimes warmed gauze or water baths to dilate the vessels. Complications can include necrosis of tissues surrounding the injection site, injury due to heating methods, and stress from restraint devices. A method development study was conducted in preparation for 2 developmental and reproductive toxicology studies involving male and female fertility. The studies were to receive daily doses for a minimum of 8 weeks (males) and between 3 and 5 weeks (females). Tail vein dosing was not an option due to study length, so jugular catheters attached to externalized ports with magnetic protective caps were evaluated. The protective caps allow for breeding or social housing without damaging the ports. Twenty-five male CD1 mice were implanted with jugular catheters attached to an externalized port. Male mice only were used since there was no expected difference in dosing administration between males and females and the male portion of the study would be the longest. The mice were bolus dosed 0.2 mL of 0.9% saline approximately 5 days per week for 13 weeks. The ports were not locked with an anticoagulant between doses. After 9 weeks, 84% of the externalized ports were still patent for dosing. At week 13, 52% remained patent for dosing. Complications included patency loss (2 animals), catheter dislodgement (7 animals) and skin erosion around the port (3 animals). Surgically implanted catheters and externalized ports allow for more consecutive daily IV bolus injections. In addition, this system would be beneficial when dosing irritating materials since the circulating blood volume is greater than in a peripheral vessel.

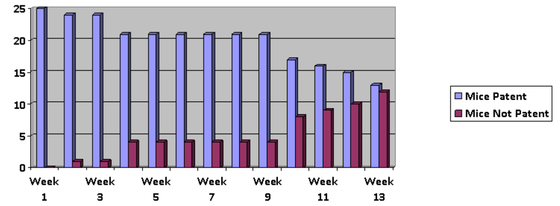
2 METHODS

To evaluate the long term maintenance and feasibility of surgically implanted jugular catheters attached to an externalized port for mouse daily bolus intravenous dosing, a method development study was designed. Twenty five male CD-1 mice were ordered for study. The animals were implanted at the vendor with polyurethane catheters placed in the jugular vein, advanced to the atrium and exteriorized to an external port. The rounded tip catheter was bonded to the subcutaneous pin of the port prior to implantation. The ports were protected by a metal cap that attaches magnetically to prevent damage from chewing. At the start of the study, animals were approximately 8 weeks of age and weighed 28-35 grams. Animals were identified by microchip and single housed in polycarbonate mouse caging to mimic conditions of the planned fertility studies. Room conditions were set to maintain a temperature of 68°-78° F and a humidity of 30%-70%. Animals had access to certified rodent pellets and water ad libitum. During the study, the animals were dosed once daily by bolus injection for approximately 5 days per week (4 days on holiday weeks) for thirteen weeks with 0.2mL of sterile 0.9% saline to simulate a dose. The protective red cap was removed using a tool that attached magnetically to the base of the port. (See Fig. 1) The button port septum was swabbed with 70% Isopropyl alcohol prior to accessing with a syringe attached to an injector. (See Fig. 2-3) A positive pressure push of approximately 0.03 mL of sterile 0.9% saline was given when completing each dose to simulate a flush and lock of the system post dose and no anticoagulant was used in between daily doses. Animals were given dietary enrichment as positive reinforcement following dosing. Body weights and detailed observations were collected once weekly, daily observations were collected during the dosing period. Five animals were selected for hematology and five animals were selected for serum chemistry blood collections following the dosing period. The blood samples were collected from the retro-orbital sinus immediately prior to euthanasia by CO2 inhalation.

3 RESULTS

After nine weeks of dosing, 21 out of 25 animals (84%) were still patent for dosing. Seventeen of those animals were bi-directionally patent (68%). By week thirteen, 13 out of 25 animals (52%), remained patent for dosing. Two animals experienced total patency loss during the dosing period, one during the first week and the second during week eleven. Seven animals had the catheter become dislodged from the jugular vein, two during the second week, one during the third week, three during week nine and one during week ten (see Table 1). Scabbing around the port and skin erosion were seen in three animals: two in week twelve, and one in week thirteen. There were no effects on body weights compared to the Charles River Ashland historical control data base for CD-1 mice. Hematology and serum chemistry blood samples were collected at week thirteen for evaluation. Mean ALT and AST values were mildly elevated when compared to the Charles River Ashland historical control data base for 20 week old mice while mean platelet and absolute reticulocyte counts were minimally elevated.

Table 1



4 CONCLUSION

Surgically implanted jugular vein catheters with externalized ports were successful for daily bolus intravenous dosing of mice. This was an improvement over daily tail vein dosing, especially for longer than a 14 day period. There was loss of patency seen in the catheters, especially past the ten week time point. Daily dosing through the ports seemed viable up to ten weeks, it is recommended to have an increase in the number of animals placed on study to compensate for the loss of patent animals when dosing past the eight week timeframe. There was no need to lock the ports with an anticoagulant between doses even when dosing occurred two or three days apart. This system would be beneficial when daily bolus IV dosing of mice is needed for periods greater than 14 days. In addition, it would be beneficial when dosing irritating materials since the circulating blood volume is greater than in a peripheral vessel.

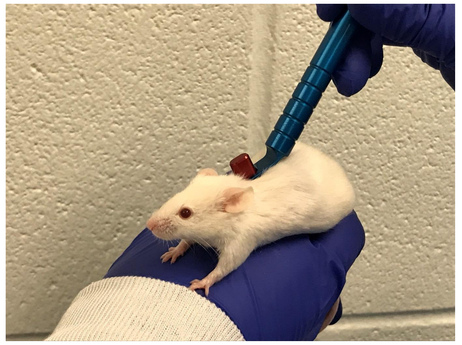


Fig. 1

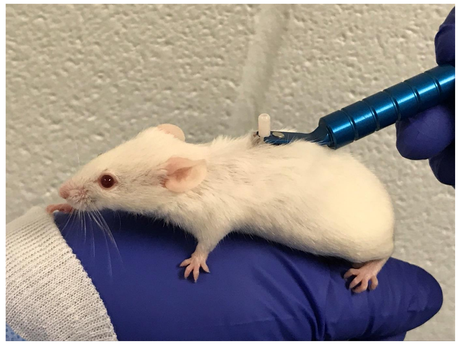


Fig. 2

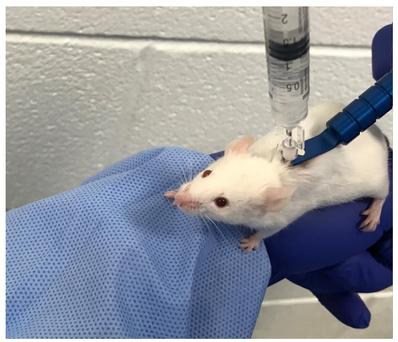


Fig. 3