Pharmacokinetics (PK) and Safety of a 120-day Implantable Risperidone Device in Rats

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ABSTRACT SUMMARY
A small titanium implant device loaded with a formulation of risperidone and 3 PLGA polymers and implanted subcutaneously (SC) in rats is shown to maintain constant plasma levels of the active moiety for 4 months. The device is reversible and well tolerated.

INTRODUCTION
Poor medication adherence is a major limitation of oral antipsychotic therapy.[1] A two-week long acting injectable (LAI) formulation of risperidone (Risperdal Consta™) provides objective clinical benefit relative to oral dosing by improving compliance. However, the PK profile is less than optimal; following injection there is a 3-wk lag period before risperidone reaches therapeutic levels, steady-state peak-to-trough fluctuations average 1.7, clearance after the last dose takes 7 wks, and the system is not reversible should patients develop adverse events. Despite these limitations, the success of Consta validates the clinical benefit of LAI risperidone and clearly establishes the therapeutic window for this agent.[2]

To address the weaknesses and leverage the PK benefits validated by the 2-week Consta system, we are developing a drug delivery device (PROZOR™) that has the promise to deliver risperidone at a constant rate for 3-6 months in humans and offers the advantage of complete reversibility.

The device is a small titanium reservoir (5 mm in diameter and 40 mm in length) loaded with a dry powder formulation of risperidone plus a mixture of three PLGA polymers. The polymers are not included to entrap drug in a matrix, rather the selected polymers act by donating soluble acid equivalents as they hydrolyze. The reservoir is sealed on each end with conventional polymer membranes, and hydrated immediately before use creating an aqueous suspension within the reservoir. Although risperidone is virtually insoluble at neutral pH, its aqueous solubility increases substantially as the pH is lowered. The mechanism of release is simple concentration gradient-based diffusion of the active from the reservoir. Output is boosted to therapeutic levels by maintenance of a low pH environment within the reservoir (provided by the continual release of soluble acid as the polymers hydrolyze).

Here we report results of a pilot parallel group PK study in rats comparing the plasma level of risperidone active moiety for four months following SC implantation of 4 variants of the PROZOR device in rats. Systemic safety and local tolerance at the implantation site was followed and histology conducted in two groups.

EXPERIMENTAL METHODS
Risperidone (GMP) was mixed with PLGA polymers in methylene chloride and the solvent removed under reduced pressure. The dried material was mechanically ground and sieved to yield a free-flowing powder (particle size 20-100µ). The powder was loaded into reservoirs and sealed at each end with pressed-on caps fitted with conventional membranes. The systems were hydrated before use by placing devices under vacuum and backfilling with PBS.

In vitro release was following by submerging each device in a petri dish containing 13 mL bicarbonate buffer. Dishes were placed in a CO2 incubator (37°C, pH 7.4) equipped with a planetary rotator (100 rpm). The receiving buffer was replaced daily and released risperidone was measured by UV spectroscopy (270 nm).

Based on in vitro screening of several hundred formulation variants and membrane configurations, four groups were selected for PK evaluation. A 120-day non-GLP local tolerance and PK study was conducted at Pacific Bio Labs (Hercules, CA) in compliance with the final rules of the Animal Welfare Act. Six male Sprague Dawley rats were assigned to each group. In vitro release was also followed for sets of devices representing each group. A small incision was made in anesthetized animals and a single device implanted in the dorsal subcutaneum using a custom implanter tool. The incision was closed with a suture. Whole blood was collected at 4hr, 24 hrs, and weekly thereafter. Blood was also collected at 4hrs. and 24 hours following explantation at day 118.

An LC-MS/MS based bioanalytical assay was used to quantify risperidone and 9-hydroxy risperidone in rat plasma. The linear range of the assay was 0.05 ng/mL (LLOQ) to 1500 ng/mL.
RESULTS AND DISCUSSION

The plasma concentration of active moiety (risperidone + 9-OH risperidone) vs. time curves for the four groups of animals (n=6) are presented in Figure 1. In vitro release and PK parameters are shown in Table 1. Low variation among replicates was seen. A small initial peak (burst) was apparent in all groups; by 24-hours post implantation plasma levels reached a steady-state which was maintained for four months. Following explantation, plasma concentrations fell to below LLOQ within 24 hrs. Group 3 provided the highest exposure with a C_{ave} of 62 ng/mL and AUC of 7780 ng*day/mL.

During the in-life phase, animals exhibited no adverse clinical signs and gained weight normally. At necropsy, no erythremia, swelling or any other gross signs of inflammation or local site adverse reactions were observed in any group. As expected, during the implantation period a thin transparent fibrous capsule formed around each device in all animals (Figure 2). The capsules were avascular, had no evidence of fluid accumulation and, in a recovery group, the remaining fibrous tissue was substantially reabsorbed within two weeks.

The most notable finding from the histopathology was fibrosis in sections taken from the capsule in all animals. These scores reflected the maturity and amount of fibrous connective tissue present and represent the expected tissue response to the implant (namely the formation of a fibrotic capsule around the implant). The presence of moderate granulation tissue was seen in the Head and/or Tail sections of capsules in 4 animals. The granulation tissue in the Head and Tail sections most likely resulted from animal movement which may have led to incomplete tissue remodeling at both ends of the device. Based on these histologic findings, the implant capsules evaluated were consistent with capsules surrounding other implanted biocompatible devices and no findings were considered to be adverse.

The formation of the fibrotic capsule around the implant.

Figure 1: Plasma conc. of active moiety vs. days after implantation

Figure 2: Rat following implantation (right) and device exposed at necropsy showing transparent, avascular capsule (left)

CONCLUSION

These findings provide preclinical proof-of-concept for a small cylindrical titanium device which enables the delivery of a constant therapeutic dose of risperidone for four months after subcutaneous implantation in rats. The device is well tolerated with no indications of systemic or local adverse effects. Active moiety appears immediately after implantation and clears within 24 hours of explantation. The device is completely reversible.

REFERENCES


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