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2010 AAPS Annual Meeting and Exposition

TITLE (QPS 2010-004)

Pharmacokinetic Screening of Monoclonal Antibodies in Mice and Rats using Small Volume Serial Sampling and Discovery Criteria

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ABSTRACT

Introduction

This presentation describes a generic discovery pharmacokinetic screening approach for mAb, with small volume serial sampling in rats and mice to enable determination of individual rather than composite pharmacokinetics. The advantages of this approach include a reduction in the numbers of animals used and a corresponding reduction in the amount of test article required.

Methods

The test article was human IgG1 at 1 mg/mL in phosphate buffer solution (Eureka Therapeutics). Pharmacokinetics were evaluated in male Sprague Dawley rats and male CD-1 mice, with 3 of each dosed IV at 1 mg/kg and 3 of each dosed subcutaneously (SC) at 1 mg/kg. Rats were dosed *via* a jugular vein cannula. Mice were dosed by injection into the dorsal metatarsal vein. Serial blood samples were collected into a 70 µL capillary by tail snip. Serum samples were analyzed for human IgG1 using a sandwich ELISA method.

Results

In both rats and mice human IgG1 showed a biphasic serum concentration *vs.* time profile after IV injection. The mean terminal elimination half-life was 10.4 days in rats and 9.5 days in mice. Systemic clearance was low. After subcutaneous injection dosing, human IgG1 showed a slow absorption phase, with an observed C_{max} at 7 days post-dose in rats and at 1 day post-dose in mice. Subcutaneous bioavailability averaged 64% in rats and 111% in mice. The terminal elimination half-life after subcutaneous dosing averaged 2.8 days in rats and 7.5 days in mice. The inter-animal variability in serum concentrations in rats was low. In mice, 2 of the 3 animals in both IV and SC groups eliminated human IgG1 rapidly after approximately 8-12 days post-dose.

Conclusions

The data clearly demonstrated that it is feasible to serially sample individual mice at minimally 7 time-points, which will provide superior PK data compared to composite PK using multiple animals. Without this, the inter-animal differences in the elimination profiles could be masked. Coupling IV dosing *via* the metatarsal vein and tail snip sampling, with a sensitive and selective ELISA method, can provide a routine PK screening approach for monoclonal drug candidates.