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Pharmacokinetics of the Novel Antifungal Agent F901318 in Mice, Rats and Cynomolgus monkey

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Abstract

Background: F901318 is the first member of the orotomide class of antifungal agents which act via inhibition of DHODH, an important enzyme in pyrimidine biosynthesis. F901318 has a mould spectrum of activity and is highly potent *in vitro* against clinical aspergilli. F901318 is currently being developed for the treatment of invasive aspergillosis. As part of the development process, detailed PK studies are required from multiple animal species to help interpret *in vivo* efficacy and toxicological data.

Methods: PK profiling in the mouse, rat and cynomolgus monkey was carried out to determine total drug concentrations in plasma following both IV and oral dosing. All doses were administered at 10mg/kg. Blood samples were taken at appropriate time intervals for analysis by LC MC/MS.
In a separate study mice were dosed IV with F901318, 8mg/kg TD for four days and levels were measured in key tissues after one and four days, to examine distribution of F901318 in tissues.

Results: The PK parameters of F901318 following a single IV or PO 10mg/kg IV and PO dose in mice, rats and cynomolgus monkey are shown in the Table.

Species	Mouse	Mouse	Rat	Rat	Cyno	Cyno (F)	Cyno (M)
Route	IV	Oral	IV	Oral	IV	Oral	Oral
AUC 0-24 (ng.hr/ml)	21005	13382	13489	6610	18190	8182	14915
C max (ng/ml)	9706	1696	5356	809	5460	605	914
T1/2 (hr)	3.0	3	3.2	3.7	5.1	5	5.6
Bioavailability		64%		49%		45%	82%

F901318 shows a typical pharmacokinetic profile when dosed by the IV route. When dosed orally, bioavailability in all species was good with values > 45%. A difference in bioavailability between male and female cynomolgus monkey was noted.
In mice dosed with 8mg/kg F901318 TD there was good distribution in tissues after both single and repeat dosing. Levels in kidney and liver were higher than those in plasma, Levels in lung were similar to those in plasma. Levels in brain and spleen were lower than plasma levels, however, after repeat dosing potentially therapeutic levels of F901318 were seen in the brain.

Conclusion: F901318 shows good pharmacokinetics and oral bioavailability in various animal species, it also distributes well into the tissues of mice. The ability to achieve therapeutic concentrations in plasma and tissue is a clear advantage for therapeutic use.

Introduction

F901318 is the first member of the orotomide class of antifungal agents which act via selective inhibition of DHODH, a critical enzyme in pyrimidine biosynthesis. F901318 is highly potent *in vitro* against clinical aspergillus isolates and other pathogenic filamentous fungi and is currently being developed for the treatment of invasive aspergillosis. As part of the development process, detailed PK studies are required in multiple animal species to help interpret *in vivo* efficacy and toxicological data.

Methods

PK studies were carried out in the mouse, rat and cynomolgus monkey following both IV and oral dosing at a dose level of 10mg/kg. For IV dosing the drug was formulated in hydroxy propyl β cyclodextrin and for oral dosing as a solution in PEG300. Following dosing to animals by the appropriate route, blood samples were taken at appropriate time intervals for analysis by LC MS/MS. Pharmacokinetic parameters were calculated using PK solutions software. To examine the distribution of F901318 in tissues, mice were dosed with F901318, 8mg/kg TID for four days and levels were measured in key tissues and plasma after the first and seventh doses. Levels in tissue were determined following homogenisation of tissue in phosphate buffered saline followed by processing in the same manner as serum samples.

Results

Figures 1, 2 and 3 show the IV and oral PK profiles of F901318 when administered to mice, rats and cynomolgus monkeys at 10mg/kg. Table 1 shows the relevant pharmacokinetic parameters.

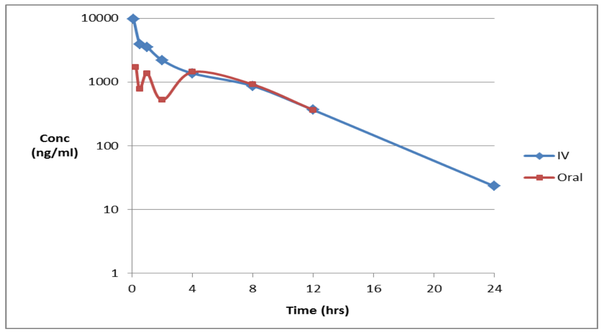

Fig.1
Mouse PK profile

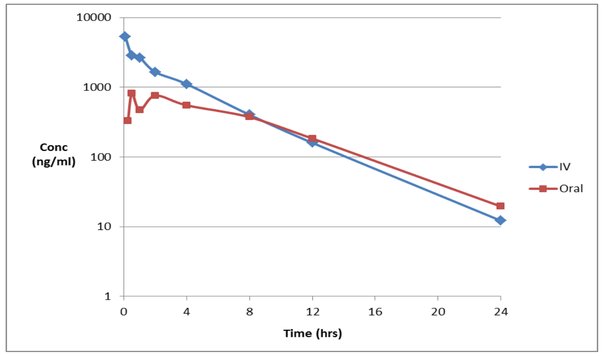

Fig.2
Rat PK profile

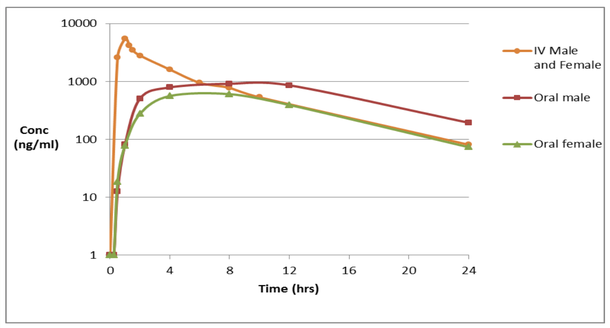

Fig.3
Cyno PK profile

Table 1 PK parameters of F901318 dosed at 10mg/kg in mouse rat and cynomolgus monkey

Species	Mouse	Mouse	Rat	Rat	Cyno	Cyno (F)	Cyno (M)
Route	IV	Oral	IV	Oral	IV	Oral	Oral
AUC 0-24 (ng.hr/ml)	21005	13382	13489	6610	18190	8182	14915
C max (ng/ml)	9706	1696	5356	809	5460	605	914
T1/2 (hr)	3.0	3	3.2	3.7	5.1	5	5.6
Bioavailability		64%		49%		45%	82%

When dosed by the oral route F901318 shows good bioavailability in all three species. In the cynomolgus monkey a difference was noted in the pharmacokinetics between sexes when F901318 was dosed orally, with the AUC being lower in the female, however, no differences were observed in between sexes by the IV route. The terminal half-life of F901318 increased as species weight increased.

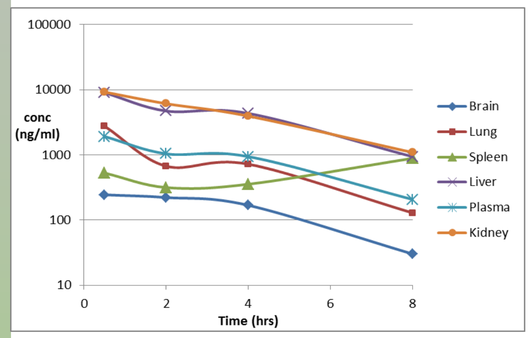

Fig. 4 Shows the concentration of F901318 in the tissues of mice after a single IV dose of F901318 8mg/kg.

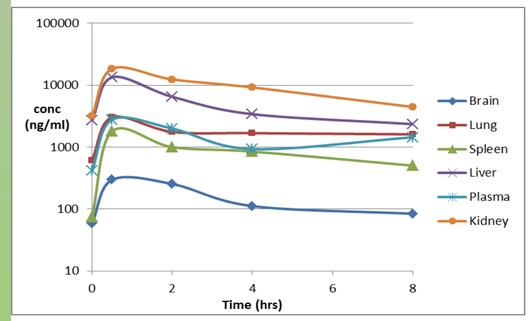

Fig. 5 Shows the concentration of F901318 in tissues of mice after the 7th IV dose of F901318 8mg/kg TID

There is variability in levels of F901318 seen in different tissues; levels in lung are similar to those in plasma whilst levels in kidney and liver are higher than those in plasma (Fig 4). After repeat dosing (8 mg/kg TID) levels in all tissues increase by approximately two fold by the 7th dose (Fig 5). Although the levels in brain are lower than in other tissues examined, potentially therapeutic levels may be obtained following repeat dosing.

Conclusions

F901318 demonstrates good pharmacokinetic profiles in various animal species allowing efficacy and toxicological studies to be carried out.
Bioavailability is in excess of 45% in all three species using simple solution of drug in solvent.
F901318 also distributes well into the tissues of mice. The ability to achieve therapeutic concentrations in both plasma and tissues is a clear advantage for treatment of disseminated infections.
Further studies to determine tissue distribution utilising radio-labelled material are currently ongoing in rats and cynomolgus monkey.