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PHASE I STUDY TO EVALUATE THE SAFETY AND PHARMACOKINETICS OF SINGLE AND MULTIPLE ASCENDING DOSES OF INTRAVENOUS MINOCYCLINE IN HEALTHY ADULT SUBJECTS

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INTRODUCTION

- *Acinetobacter baumannii* is an important pathogen implicated in a number of hospital-acquired infections and is considered by the WHO and US CDC to be a serious antimicrobial resistance threat pathogen.
- Minocycline is highly active in vitro against *Acinetobacter* spp. with 72.3% of isolates testing susceptible (MIC ≤ 4 mg/L), including MDR and XDR isolates (66 and 63% respectively), and is FDA approved for the treatment of infections due to susceptible isolates (1).
- The current approved dosage regimen in the US is 100 – 200 mg twice daily. The purpose of this study was to determine the safety and pharmacokinetics of minocycline after single and multiple ascending doses at the current approved doses and then using higher exposures.

METHODS

- This was a double-blind, randomized, placebo-controlled, single- and multiple ascending dose study of up to 6 cohorts of different minocycline (Minocin®) IV doses. Each cohort consisted of 10 subjects (8 active drug and 2 placebo). Within each cohort, subjects received a single dose on Day 1, followed by the same dose on Day 4, then 7 days of twice-daily dosing (Days 4-10), followed by a single dose on Day 11.

Cohort	Single Dose (mg) Day 1	First Dose (mg) Day 4	Repeated Doses (mg) Days 4 – 11
1	100	100	100
2	200	200	200
3	300	300	300
4	400	400	400
5	500	500	300
6	600	600	300

- Within each cohort, subjects were randomly assigned to minocycline (n = 8) or normal saline placebo (n = 2). All infusions were administered over 1 hour. Plasma samples were obtained on Day 1 and Day 11 at 1 (end-of-infusion), 2, 4, 8, 12, 18, 24, 36, 48, and 72 hours after the start of dosing and at 1 (end-of-infusion), 2, 4, 8, 12 hours after the start of dosing on Day 4. All plasma samples were assayed for minocycline content using a validated LC-MS/MS method.

REFERENCES

1. Flamm RK, Castanheira M, Streit JM, Jones RN. Minocycline activity tested against *Acinetobacter baumannii* complex, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia* species complex isolates from a global surveillance program (2013). Diagn Microbiol Infect Dis. 2016 Jul;85(3):352-355.

RESULTS

Demographics

- 69 healthy subjects were randomized. In a planned cohort 3 (300mg), subjects received doses of 180 mg due to a dosing error. The 8 subjects were replaced by a new cohort 3 and were not included in the following analyses. 49 of the remaining 61 subjects were randomized to Minocin IV treatment and thus included in the PK analysis.
- A summary of baseline subject demographics is found in Table 3.
- Most subjects in the study were white (90.2%) and male (62.3%) with a mean age of 28.1 years.

Pharmacokinetics

- A summary of pharmacokinetic parameters by cohort is found in Table 1 and Table 2.
- Maximum concentrations of minocycline were achieved at the end of the 1-hour infusions.
- Minocycline exposures (C_{max}, and AUC) increased with dose (with the exception of the 500 mg dose).
- 300 mg BID dosing following a 300 mg, 500 mg or 600 mg first dose on Day 4 produced very similar exposures on Day 11 (Table 2, Column 7).

Safety

- Of the AEs observed in more than 10% of subjects (Table 4), the majority were assessed by the investigator as likely to be related to study drug.
- A total of 21 subjects out of 61 discontinued the trial.
- 6 of 10 subjects in cohort 4 discontinued study drug during the MAD portion (400 mg BID) of the trial due to mild to moderate dizziness. Dosing was discontinued in the remaining 4 subjects in that cohort and cohorts 5 and 6 were limited to 300 mg BID for the MAD portion of the trial.
- 4 subjects in cohort 6 (600 mg / 300 mg) discontinued study drug due to nausea.
- No serious adverse events were reported.

CONCLUSION

- Single IV doses of minocycline up to 600 mg were tolerated reasonably well, but the maximum tolerated multi-dose was 300 mg BID.
- The dose limiting AE during the multi-dose phase was dizziness.
- Most common AEs were mild nausea and dizziness.
- Exposure increased in a dose proportional fashion with exception of the 500 mg dose.
- The dosage regimen selected for further studies is a 600 mg loading dose followed by 300 mg BID.

Figure 1. Plasma Pharmacokinetics of Minocycline in Healthy Volunteers After a 1 hour IV Infusion

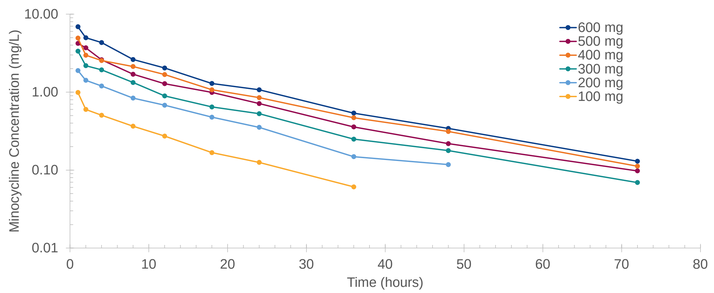

Figure 2. Plasma Pharmacokinetics of Minocycline in Healthy Volunteers After a Loading Dose then BID dosing of 7 days

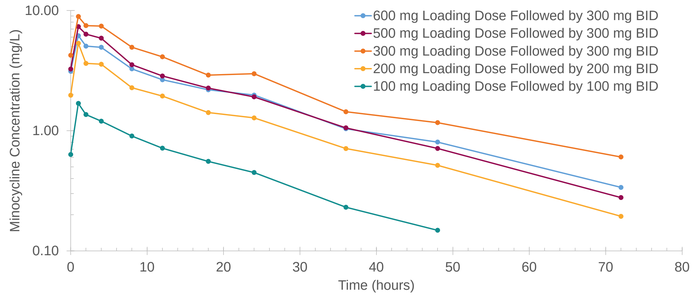

Table 1. Pharmacokinetic parameters of minocycline in the single ascending dose (SAD) phase

	Mean (SD) PK Parameters					
Dose (mg)	100	200	300	400	500	600
N	8	8	8	8	8	9
Cmax (mg/L)	0.99 (0.2)	1.89 (0.4)	3.35 (1.2)	4.93 (1.8)	4.36 (0.9)	7.03 (2.4)
$T_{1/2}$ (h)	11.05 (2.1)	13.70 (2.3)	16.62 (3.9)	17.55 (2.1)	14.44 (2.7)	17.27 (3.6)
$AUC_{0-\infty}$ (mg*h/L)	9.73 (1.4)	25.90 (6.9)	39.16 (13.8)	63.64 (18.2)	53.76 (20.3)	83.00 (29.4)
Cl (L/h)	10.48 (1.8)	8.21 (2.2)	8.28 (2.1)	6.71 (1.7)	10.25 (3.0)	8.07 (2.8)
Vss (L)	156 (36.7)	148 (36.6)	158 (45.4)	142 (38.0)	179 (46.5)	153 (52.8)

Table 2. Pharmacokinetic parameters of minocycline in the BID multiple ascending dose (MAD) phase

Single Dose (mg)	100	200	300	500	600	300, 500, or 600
BID Dosing (mg)	100	200	300	300	300	300
N	6	6	7	7	4	18
Cmax (mg/L)	1.71 (0.2)	4.59 (1.1)	8.91 (4.5)	7.58 (2.4)	6.17 (1.7)	7.79 (3.3)
$T_{1/2}$ (h)	15.89 (2.8)	18.22 (2.4)	19.78 (3.4)	18.15 (1.4)	20.19 (4.2)	19.24 (2.9)
AUC_{0-t} (mg*h/L)	27.5 (5.5)	80.7 (19.9)	173.7 (100.8)	124.1 (50.2)	119.0 (56.3)	142.3 (75.6)
Cl (L/h)	3.49 (0.7)	2.48 (0.8)	1.92 (0.7)	2.64 (1.1)	2.79 (1.3)	2.39 (1.0)
Vss (L)	72.05 (9.3)	58.42 (15.7)	47.05 (14.0)	58.06 (20.1)	67.81 (24.4)	55.94 (19.6)

Table 3. Baseline Demographics

Cohort		1	2	3	4	5	6	Placebo	Total
Age, years	Mean	26.6	31	25	29.6	25.8	30.6	27.4	28.1
	SD	7.8	7.5	7.5	8.7	8.8	12.1	8.2	8.7
Race: White	N	8	7	8	7	6	7	12	55
	%	100	87.5	100	87.5	75	77.8	100	90.2
Race: Black	N		1			2	1		4
	%		12.5			25	11.1		6.6
Race: Asian	N				1		1		2
	%				12.5		11.1		3.3
Sex: Male	N	5	5	6	5	6	5	6	38
	%	62.5	62.5	75	62.5	75	55.6	50	62.3
Sex: Female	N	3	3	2	3	2	4	6	23
	%	37.5	37.5	25	37.5	25	44.4	50	37.7
Height, cm	Mean	179.3	175.8	178.1	175.4	178	176.4	178.1	177.3
	SD	9.8	7.6	7.1	9.2	6	11	10.1	8.9
Weight, kg	Mean	75.1	71.7	71.6	69.9	72.6	73	70.9	72.1
	SD	10.6	9	10.1	11.6	8	12.7	14.6	11
BMI, kg/m2	Mean	23.3	23.2	22.5	22.7	22.9	23.4	22.1	22.9
	SD	2.6	2.7	2.4	2.9	2.5	3	2.8	2.7

Table 4. Adverse events (incidence >10%) by decreasing frequency

Cohort		1	2	3	4	5	6	Placebo	Total
Dose (mg)		100	200	300	400	500/300[1]	600/300[2]		
N Total		8	8	8	8	8	9	12	61
Overall									
Subjects with any AE	% (N)	75 (6)	100 (8)	100 (8)	100 (8)	100 (8)	100 (9)	91.7 (11)	95.1 (58)
Dizziness	% (N)	12.5 (1)	50 (4)	100 (8)	100 (8)	100 (8)	77.8 (7)	25 (3)	63.9 (39)
Nausea	% (N)	25 (2)	75 (6)	75 (6)	62.5 (5)	75 (6)	88.9 (8)	16.7 (2)	57.4 (35)
Infusion site reaction	% (N)	62.5 (5)	87.5 (7)	87.5 (7)	12.5 (1)	75 (6)	66.7 (6)	0	52.5 (32)
Headache	% (N)	12.5 (1)	50 (4)	0	37.5 (3)	50 (4)	55.6 (5)	25 (3)	32.8 (20)
Dysgeusia	% (N)	0	0	0	50 (4)	40 (4)	66.7 (6)	25 (3)	27.9 (17)
Decreased appetite	% (N)	12.5 (1)	37.5 (3)	25 (2)	25 (2)	37.5 (3)	0	8.3 (1)	19.7 (12)
Dizziness postural	% (N)	12.5 (1)	25 (2)	0	37.5 (3)	0	11.1 (1)	8.3 (1)	13.1 (8)
Fatigue	% (N)	0	12.5 (1)	25 (2)	12.5 (1)	25 (2)	11.1 (1)	8.3 (1)	13.1 (8)
Vomiting	% (N)	0	25 (2)	25 (2)	0	12.5 (1)	33.3 (3)	0	13.1 (8)
Diarrhoea	% (N)	0	25 (2)	12.5 (1)	25 (2)	0	11.1 (1)	8.3 (1)	11.5 (7)

[1] Single dose (d1) and loading dose (1st dose d4): 500mg; subsequent doses: 300mg
[2] Single dose (d1) and loading dose (1st dose d4): 600mg; subsequent doses: 300mg

Disclosures

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