Gentamicin Therapy for Pneumonic Plague: Important Considerations for Development using the Animal Rule

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- The views and information in this presentation are those of the author, and do not represent the views and/or policies of the U.S. Food and Drug Administration.

Outline of the Presentation

- Goal – address "Pillar 4" under 21 CFR § 314.610
- Development of the Animal Model for Pneumonic Plague
- Use of Animal Model for Dose Selection in Man
  - Gentamicin dose selection for treatment of plague in the African green monkey model; kinetics (PK), dynamics (PD [index & target])
  - Gentamicin systemic exposures from African green monkey-plague model compared to human exposures following various IV infusion regimens
  - In vitro methodology to explore the effect of differences in drug exposure on microbiological response
- Summary/Conclusions

The Animal Rule

- "New Drug and Biological Drug Products; Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible".
  - 21 CFR 314 Subpart I (Drugs)
  - 21 CFR 601 Subpart H (Biologics)
  - Proposed Rule: 64 Fed. Reg. 53,960 (October 5, 1999)
  - Final Rule: 67 Fed. Reg. 37,988 (May 31, 2002)

- Allows for the use of adequate and well-controlled animal studies as evidence of effectiveness for approval.

From MacGill, T., USPHS Scientific and Training Symposium, June 6, 2007

The Animal Rule (2)

- Subpart I can only be used when efficacy evaluations are not feasible under any other FDA regulation.
- Safety must still be established through the traditional path – animal toxicology and human safety.

From MacGill, T., USPHS Scientific and Training Symposium, June 6, 2007

The Animal Rule: Scientific Criteria

21 C.F.R. § 314.610 (§ 601.91)

- **"Pillar 1" – There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product;**
- **"Pillar 2" - The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans;**

The Animal Rule: Scientific Criteria (2)

- **"Pillar 3" - The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity; and**

- **"Pillar 4" - The data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allow selection of an effective dose in humans.**

Gentamicin Therapy for Pneumonic Plague

- **Pneumonic plague is caused by *Y. pestis*, a CDC Category A biological threat agent.**
- **Gentamicin has been recommended as preferred therapy for contained casualty situations.***
  - **Adults: 5 mg/kg IM or IV once daily or 2 mg/kg loading dose followed by 1.7 mg/kg IM or IV 3 times daily.**
  - **Children: 2.5 mg/kg IM or IV 3 times daily.**
- **Human trials of antibiotic efficacy against pneumonic plague are not feasible.**
  - **Animal rule studies required for FDA approval.**

*Ingelsby et. al., JAMA, 283: 2281-2290, 2000

Gentamicin Therapy for Pneumonic Plague: Non-Human Primate Studies

- ***Cercopithecus aethiops*, or African green monkeys (AGMs), selected as animal model.**
  - **AGMs are susceptible to *Y. pestis* through an aerosol route.**
  - **AGMs develop pneumonic plague that mimics human disease.**
  - **Used exclusively at USAMRIID since 1993.**

- **Need for natural history information to determine timing of intervention after exposure.**

- **Need for toxicity and PK data to design a dosage regimen.**

From MacGill, T., USPHS Scientific and Training Symposium, June 6, 2007

Natural History Study

- Design
  - Species: African green monkey
  - Group size: 6
  - Strain: *Y. pestis* Colorado (CO) 92
  - Dose: 100 ± 50 LD_{50}
    - Delivered by aerosol – MMAD 1 μm
  - Measurements:
    - Continuous telemetry monitoring
    - Daily bleeds - catheters
    - Clinical signs

Natural History Study (2)

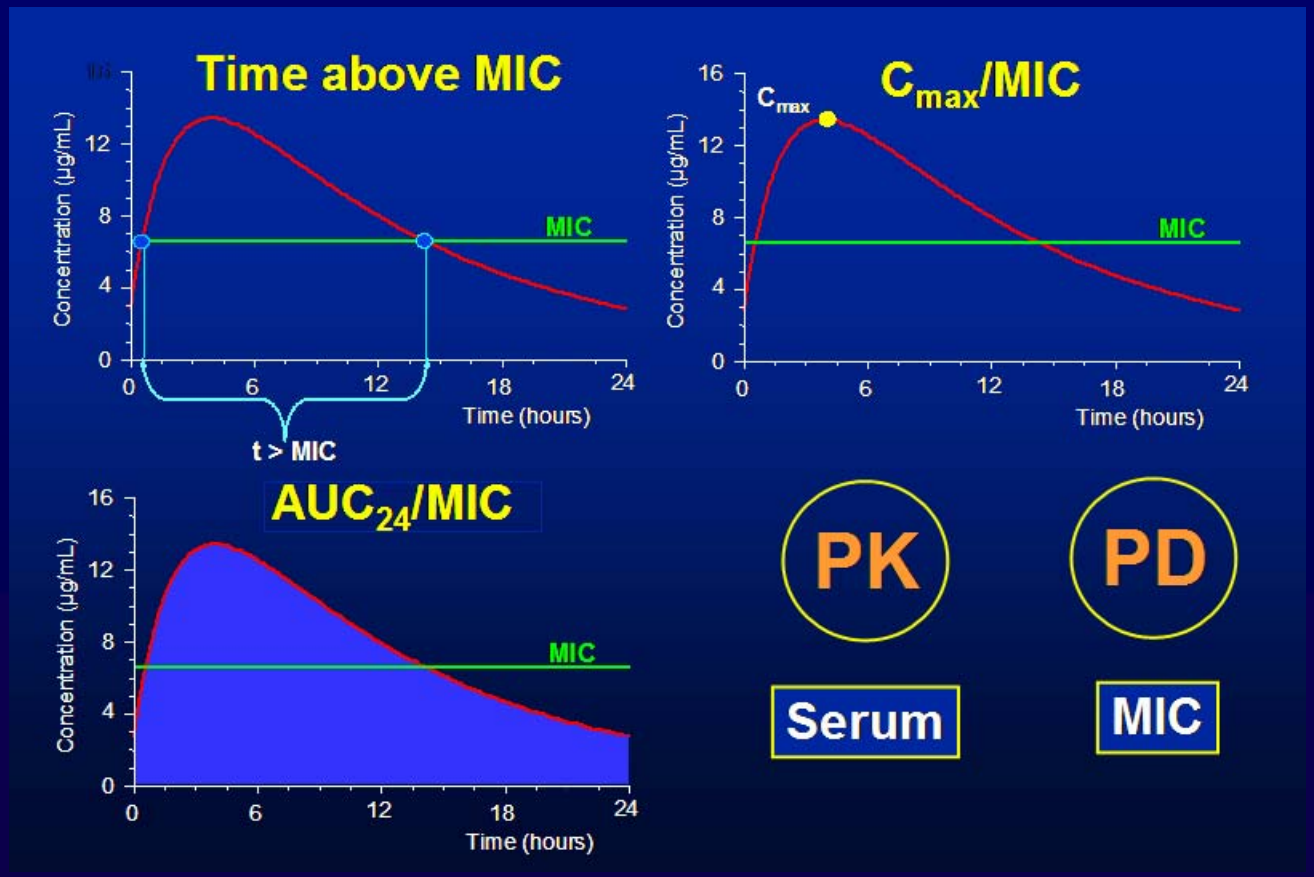
- **Results**
  - **All animals (4/6) which became bacteremic did so by 72 hours following exposure to aerosolized *Y. pestis*.**
  - **Fever was the most consistent early clinical sign of disease.**
  - **No bacteremia or disease in animals (2/6) exposed to < 20 LD_{50}**

- **Conclusions**
  - **Initiation of Treatment**
    - **76 hours after exposure to *Y. pestis***
    - **or development of consistent fever (≥ 1.5°C above baseline temperature for 2 hours) in the majority of animals in the exposure cohort.**

From MacGill, T., USPHS Scientific and Training Symposium, June 6, 2007

Terminology

Pharmacokinetics (PK) and Pharmacodynamics (PD) applied to Antimicrobial Drugs – PK/PD Index

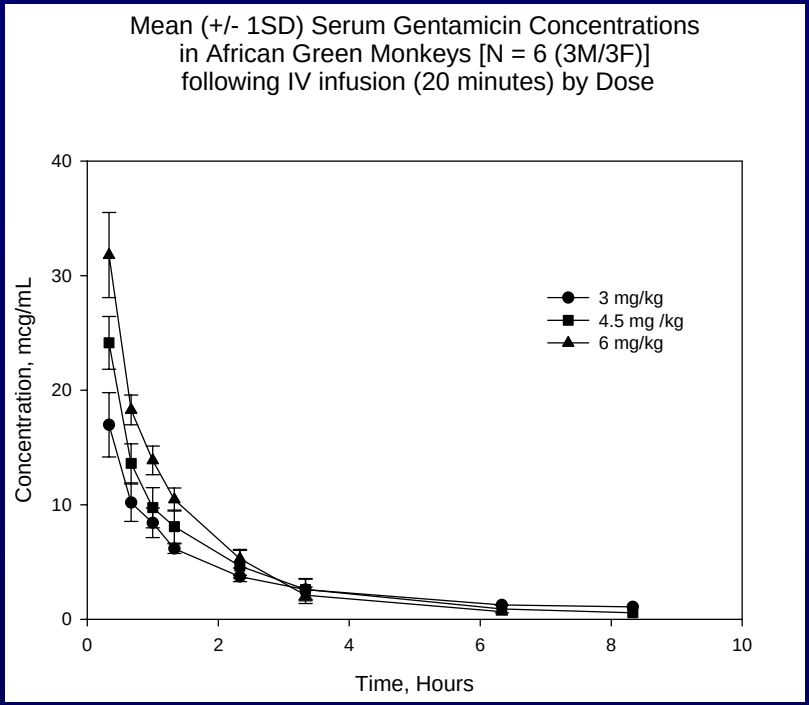


From Derendorf, H.., IDSA/ISAP/FDA Workshop, April 16, 2004

Gentamicin PK Study in African Green Monkeys

- **Design**
  - N = 6 (3M/3F)
  - Single Dose; 20 min IV infusion
  - Dose Levels: 3 mg/kg, 4.5 mg/kg, 6 mg/kg
    - 1 week washout between doses
  - Blood Sampling: predose, end of infusion, 20, 40 minutes and 1, 2, 3, 6 and 8 hours post-infusion

Gentamicin PK in African Green Monkeys



Parameter	3 mg/kg	4.5 mg/kg	6 mg/kg
C_{max}, mcg/mL	17.0 (2.8)	24.1 (2.3)	31.8 (3.7)
AUC(0-∞), mcg*hr/mL	27.8 (4.0)	32.9 (6.2)	37.9 (4.0)
Cl, L/h/kg[1]	0.108 (.012)	0.142 (.023)	0.162(.020)
Vc, L/kg[1]	0.111 (.061)	0.125 (.003)	0.099 (.042)
$t_{½\beta}$, hr[1]	1.8 (0.6)	1.3(0.2)	0.8 (0.1)

[1]Estimated values (2 Stage) – 2 Compartment Model using ADAPT II, rel 4

Gentamicin Population PK* in African Green Monkeys

MODEL	OFV	Population Estimate (%SE)	Between Subject Variability (%SE)
	145.3		
CL (L/hr/kg)		0.139 (5.2)	52% (3)
V1 (L/kg)		0.121 (6.9)	17% (38)
Q (L/hr/kg)		0.249 (14.3)	
V2 (L/kg)		0.086 (9.4)	
Residual Variability			
Proportional Error		5% (85)	
Additive Error		0.63 µg/mL (44)	

*NONMEM ver. 5 using ADVAN 3 and TRAN 2, Method = 0

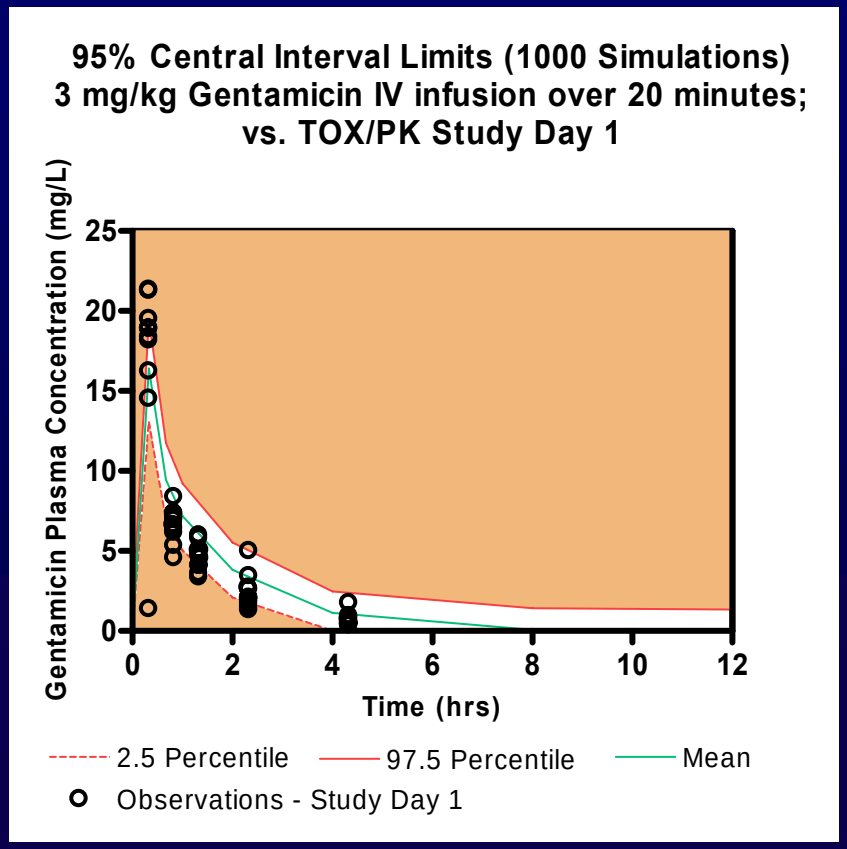
Gentamicin Toxicity Study in African Green Monkeys

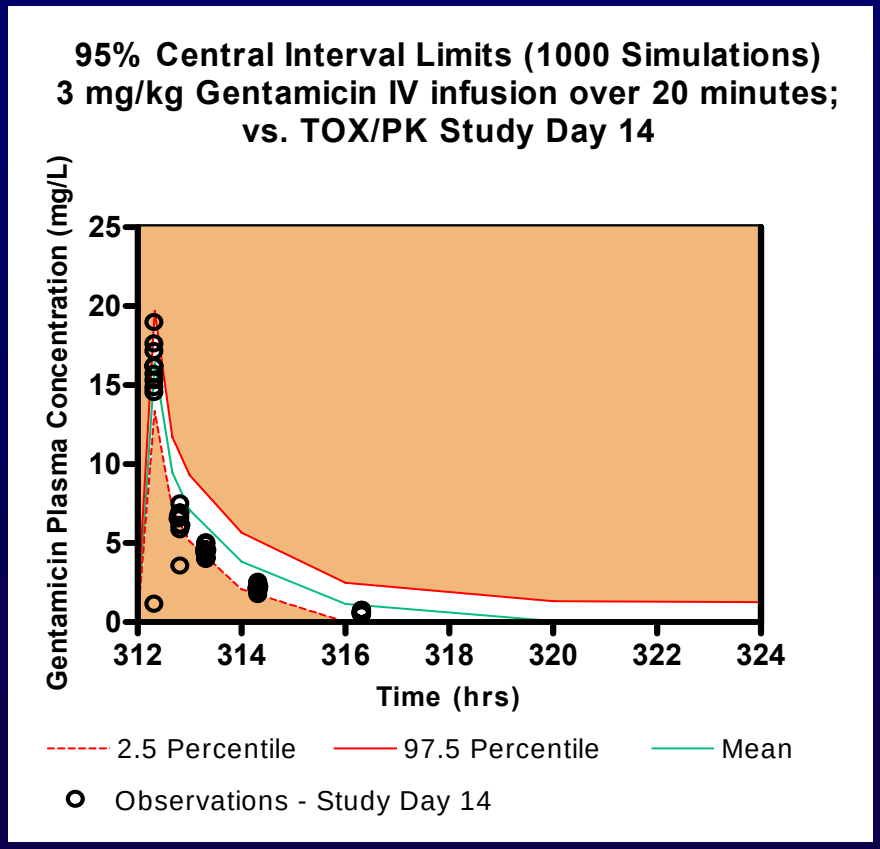
- **Design**
  - N = 6 (3M/3F) control; 10 (5M/5F) treated
  - Multiple Dose; 20 min IV infusion twice daily x 14 days
  - Dose Levels: 0 mg/kg, 1.5 mg/kg, 2.25 mg/kg, 3 mg/kg
  - Blood Sampling for Toxicokinetics (TK): (Days 1 and 14) predose, end of infusion, 0.5, 1, 2 and 4 hours post-infusion

- **Results**
  - There was an absence of major toxicity at maximum tested 3 mg/kg twice daily for 14 days.

Population Gentamicin Concentrations;

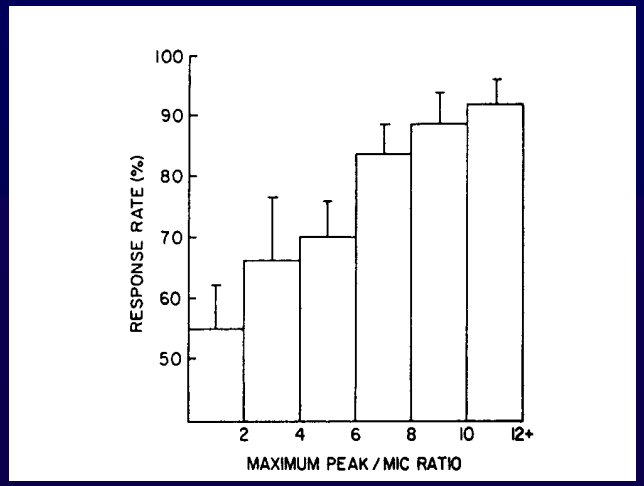
African Green Monkey – Simulation of Systemic Exposure *vs.* Results from 14-Day TOX Study





Gentamicin PK/PD Index – Target (1)

- C_{MAX}/MIC Ratio = 10:1
- Source: N = 188 patients with Gram- infections*
  - treated with gentamicin (44%), tobramycin (36%), or amikacin (20%)



- MIC [*Y. pestis* CO 92]
- Range: 0.2 - 1 mcg/mL from various sources
  - 0.5 mcg/mL at 37 °C,
  - 1 mcg/mL at 28 °C

  [Personal communication with Dr. H. Heine, USAMRIID]

*Moore, RD, *et al*.,J..Infect. Dis.,155:93, 1987

Gentamicin PK/PD Index - Target (2)

Treatment of Experimental Pneumonic Plague in Mice exposed to 100 ± 50 LD_{50}s of *Y. pestis* CO92

	Dose, mg/kg IP *q6h* for 5 days	
	12	20
PD Index (Steady-State)		
T > MIC*, minutes	57	66
C_{MAX}/MIC, mcg/mL	6 – 7.2	22.7
$AUC_{24\ hour}$ /MIC, hr*mcg/mL	21	37
Effectiveness	**No. of Survivors/Total (%)**	
Early Treatment[a]	32/40 (80)	16/20 (80)
Late Treatment[b]	12/38 (32)	17/20 (85)

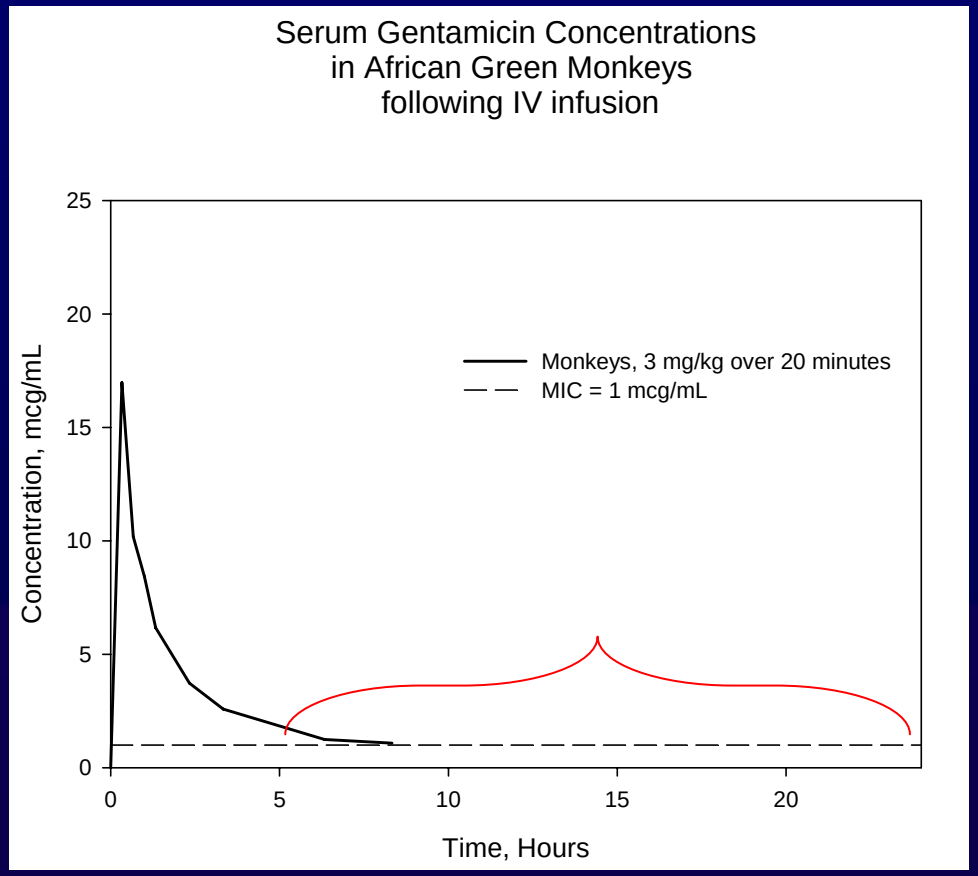
*MIC = 2 mcg/mL
[a]Treatment initiated 24 hours after aerosol infection.
[b]Treatment initiated 42 hours after aerosol infection.

Derived values

Byrne, WR *et.al.*, Antimicrob. Agents Chemother., 42:675-681, 1998

Gentamicin PK/PD Target in the African Green Monkey - Plague Model

C_{MAX}/MIC > 10:1

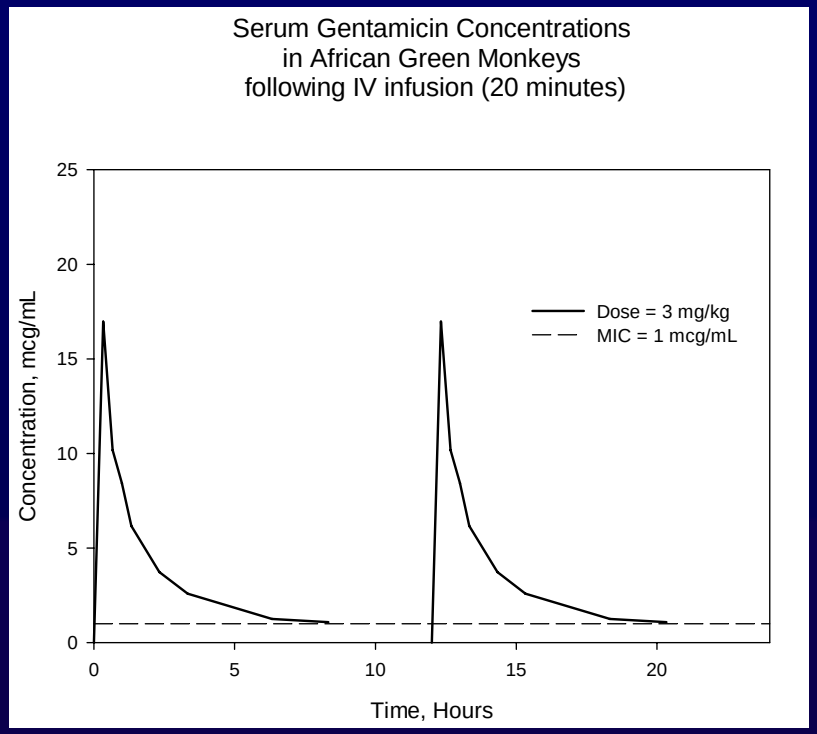


Issue:

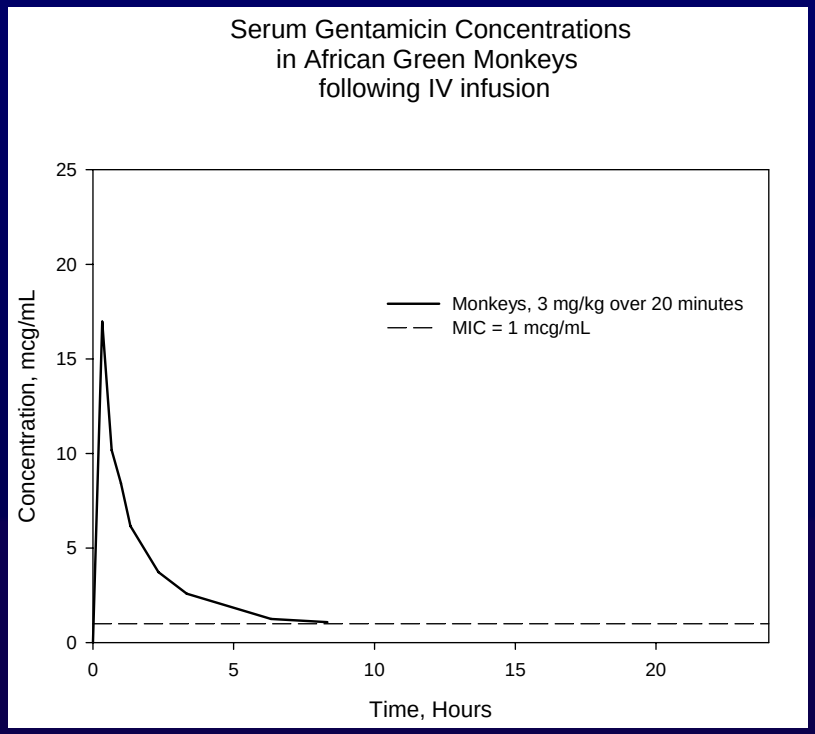
Time interval between drug exposures ?

Gentamicin PK/PD Target in the African Green Monkey - Plague Model

Dosage Regimen: Study 1 *vs.* Study 2



Efficacy Study 1



Efficacy Study 2

Gentamicin Treatment in African Green Monkey – Plague Model

Study Design (PK Perspective)

- **Efficacy Study 1**
  - N = 6 (3M/3F) control; 10 (5M/5F) treated
  - Multiple Dose; 20 min IV infusion *twice* daily x 10 days
  - Dose Levels: 0 mg/kg, 3 mg/kg
  - Blood Sampling: Study Days 2, 4, 6, 8, 10; 5 minutes post-infusion
- **Efficacy Study 2**
  - N = 2 (1M/1F) control; 10 (5M/5F) treated
  - Multiple Dose; 20 min IV infusion *once* daily x 10 days
  - Dose Levels: 0 mg/kg, 3 mg/kg
  - Blood Sampling: Study Days 2, 4, 6, 8, 10; 5 minutes post-infusion and Study Days 2, 6, 10; 3 hours post-infusion

Gentamicin Population PK*
in African Green Monkey – Plague Model
Efficacy Studies 1 & 2

MODEL	OFV	Population Estimate (%SE)	Between Subject Variability (%SE)
	261.843		
CL (L/hr/kg)		0.147 (4.5)	12% (46)
V (L/kg)		0.192 (4.9)	19% (63)
Residual Variability			
Proportional Error		18% (26.3)	
Additive Error		0.25 µg/mL (82.0)	

*NONMEM ver. 5 using ADVAN 1 and TRAN 2, Method = 0

Gentamicin PK/PD Index

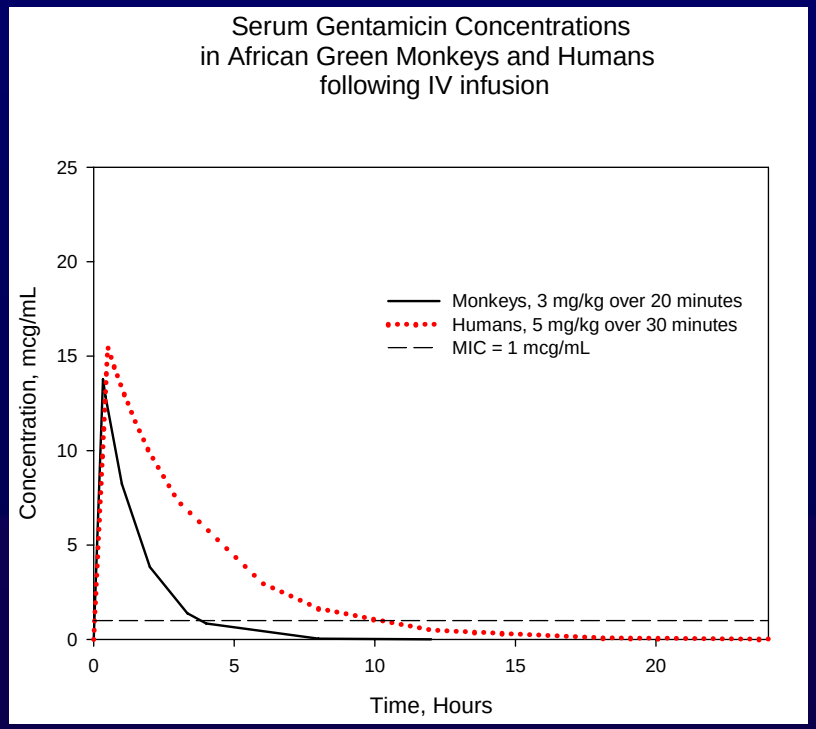
Treatment of Experimental Pneumonic Plague in African Green Monkeys exposed to 100 ± 50 LD_{50}s of *Y. pestis* CO92

Efficacy Study 1 (N = 10) 3 mg/kg IV *q12h* for 10 days	Observed Values Mean (1 SD)	Estimated Values Mean (1 SD)
$C_{5\ \text{minutes post-infusion}}$	12.6 (4.1)	12.7 (2.5)
$C_{MAX,\ \text{Steady-Steady}}$ /MIC*		13.6 (2.9)
$AUC_{0\text{-}24,\ \text{Steady-State}}$ /MIC		43.9 (1.3)
Survivors/Total (%)	8/10 (80)	
Efficacy Study 2 (N = 10) 3 mg/kg IV *q24h* for 10 days		
$C_{5\ \text{minutes post-infusion}}$	13.0 (2.2)	12.8 (1.0)
$C_{3\ \text{hours post-infusion}}$	1.4 (0.4)	1.4 (0.3)
$C_{MAX,\ \text{Steady-State}}$ /MIC		13.8 (1.1)
$AUC_{0\text{-}24,\ \text{Steady-State}}$ /MIC		22.1 (2.2)
Survivors/Total (%)	6/10 (60)	

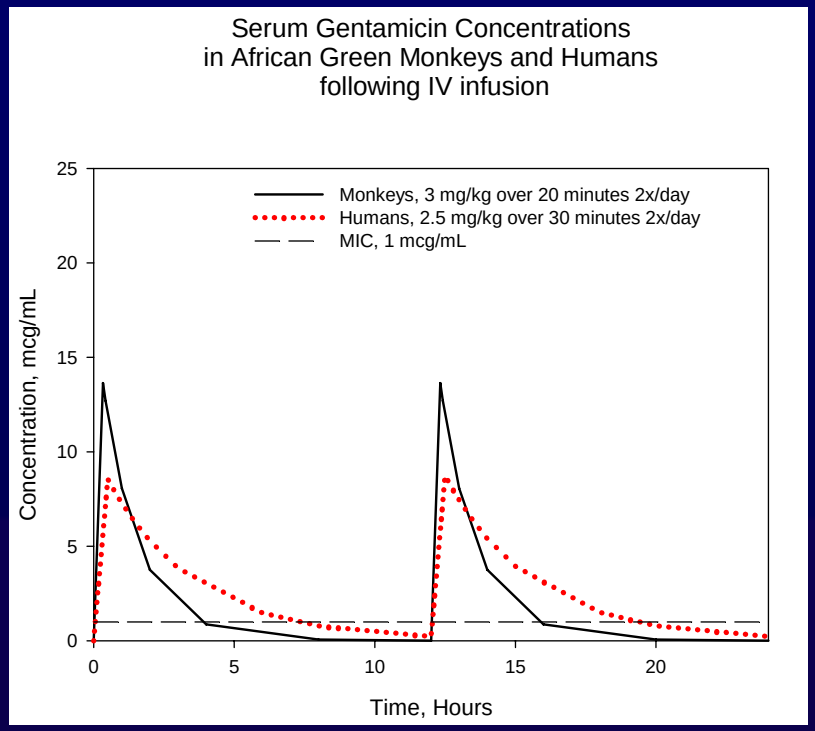
*MIC = 1 mcg/mL

Gentamicin Systemic Exposure: Monkey Dosage vs. Human Dosage

Efficacy Study 2



Efficacy Study 1



Gentamicin PK in Humans

- Parameters
  - Clearance ~ 4.3 L/hr
  - Volume of Distribution ~ 20 L
  - Half-life varies 2.5 – 4 hr
- Covariates
  - Creatinine Clearance, Age
  - Body Weight
- Dosage regimens
  - 5 mg/kg/day in divided dosing (approved)
  - 5 mg/kg/day once daily
  - 7 mg/kg/day once daily
  - others

Gentamicin Systemic Exposure: Simulation in Humans

- **Source:**
  - **Adult Humans – Hospitalized patients with at least 1 measured serum gentamicin concentration***
    - **Dose = 7 mg/kg IV infusion over 1 hour**

Table 1
Demographic data of 939 study patients receiving once-daily dosing of gentamicin

M/F	509/430
Weight (kg)[a]	70.2 ± 17.4
Age (year)[a]	55 ± 20
S_{CR} (mg/dl)[a]	0.99 ± 0.42
CL_{CR} (ml/min)[a]	92.0 ± 45.2

[a] Mean (S.D.).

*Xuan, D *et.al.*, Int. J. Antimicrob. Agents, 23:291-295, 2004

Gentamicin Systemic Exposure: Simulation in Humans* (continued)

CL = 4.32 L/hr
V1 = 19.6 L

Table 2
Final population pharmacokinetic parameter estimates of gentamicin in 939 patients receiving once-daily dosing

Parameter	Parameter estimate	Relative standard error (% R.S.E.)	95% Confidence interval
Theta (1)	0.047	7.5	0.040–0.054
Theta (2)	0.28	7.6	0.24–0.32
Theta (3)	0.092	12.1	0.070–0.11
Theta (4)	0.071	48.6	0.0033–0.14
Inter-individual variability (% CV)			
CL	29.6	9.9	26.6%–32.4
V	5.8	350	–
K12	69.9	43.0	27.6%–94.8
K21	63.9	49.0	12.6%–89.4
Residual error			
σ1-Proportional (%)	23.7	12.0	20.8–28.0
σ2-Additive	0.23 mg/l	49.9	0.034–0.33

Final PK Model: CL = Theta (1)*CLcr; V1 = Theta (2)*WT; K12 = Theta (3); K21 = Theta (4).

*Xuan, D *et.al.*, Int. J. Antimicrob. Agents, 23:291-295, 2004

Gentamicin Systemic Exposure:
Human Simulated Exposures *vs.* PK/PD Targets from African Green Monkey - Plague Model
1000 Simulated Exposures; % > = Target

		Target: $C_{MAX, Steady-State}$/MIC
Dosage, IV inf	**Estimated Human $C_{MAX, Steady-State}$/MIC**	**13.6** [9.0 – 19.6]
5 mg/kg *q24h*	16.2 (4.0)	**72.8%** [97.2 - 19.6%]
2.5 mg/kg *q12h*	9.3 (2.2)	**4.3%** [51.1 – 0.0%]
1.67 mg/kg *q8h*	7.0 (1.8)	**0.3%** [12.3 – 0.0%]
		Target: $AUC_{24-hour, Steady-State}$/MIC
	Estimated Human $AUC_{24-hour,Steady-State}$/MIC	**43.9** [42.0 - 46.7]
5 mg/kg *q24h*	90.2 (20.0)	**98.8%** [99.2 – 97.8%]
2.5 mg/kg *q12h*	86.5 (26.8)	**98.0%** [98.6 – 97.5%]
1.67 mg/kg *q8h*	87.3 (27.6)	**97.8%** [98.5 – 97.1%]

*Xuan, D *et.al.*, Int. J. Antimicrob. Agents, 23:291-295, 2004

Further Evaluation of Gentamicin Dosage Regimens

- *In Vitro* Hollow Fiber Infection Model (HFIM)
  - Measure Microbiological Response
  - Simulate Human and Animal PK
  - HFIM model of *B. anthracis* available*
    - Used to compare microbiological response to ciprofloxacin and levofloxacin exposure based on Rhesus monkey PK and human PK
    - "model permits the evaluation of treatment regimens that humanize antibiotic exposure in animal models"
    - "enhancing the confidence with which animal models may be used to reliably predict the efficacies of proposed antibiotic treatments in humans … where human trials cannot be performed"
  - HFIM model of *Y. pestis* now available
    - Used to compare microbiological response to levofloxacin and streptomycin exposure based on human PK
      - [Louie, A, *et al*, Antimicrob. Agents Chemother., 51:2661-2667, 2007]

*Deziel, MR, *et al*, Antimicrob. Agents Chemother., 49:5099-5106, 2005

Summary

Gentamicin Therapy for Pneumonic Plague in Humans: Considerations for Development using the Animal Rule

1. Identify animal model that best represents the disease course in man.
2. Determine PK/TOX/TK of the test drug in the animal model.
3. Determine PK/PD index/target:
   a. Based on varying dose schedules in the animal model.
   b. Use in vitro systems to further evaluate potential animal/human dosing regimens.
4. Use of population PK and simulations to estimate frequency of achieving PK/PD target with human dosing regimens.

Conclusions

- The African green monkey model for pneumonic plague is critical to the development of drugs for treatment of pneumonic plague in humans.
- An understanding of the similarities and differences in PK/toxicity between the animal model and humans is essential.
- The determination of PD Indices and Target Values is necessary to the design of potential dosage regimens for antimicrobial drug therapy.
- Population PK and simulation are useful tools to evaluate animal and human dosing regimens.

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