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Study 1 was the best designed of the 5 studies and provides the most useful information. The investigators examined the degree of acid suppression in each individual after systematically administering an infusion of ranitidine and then determining corresponding serum drug concentrations. With this method pharmacodynamic response could be assessed based on each individual's baseline gastric acid output, as opposed to an arbitrary value. In addition, the subjects had confirmed active PUD, which is the proposed labeled indication for iv ranitidine.

Adults

Pharmacodynamic parameters from studies in adults are presented in Table 8.

Table 8. Pharmacodynamic data in adults subjects.

Ref.	Dose	Results
8	20, 40, and 80 mg po (tablet)	ED_{50}* after pentagastrin-stimulated gastric acid secretion = 165ng/ml (range of 95% CI, 123 to 204 ng/ml) with a duration of 2 hr
9	150 and 300 mg po (tablet)	ED_{50} after meal-induced gastric acid secretion =80±9 ng/ml. ED_{50} exceeded for 10 and 13 hr after 150 and 300 mg dose, respectively.
10	50, 100, 150, and 200 mg po (tablet)	ED_{50} and ED_{80} after meal-induced gastric acid secretion =73 ng/ml (range 38-111 ng/ml) and 180 ng/ml (range 134-212 ng/ml), respectively.
11	po (dose not reported)	ED_{50} 73-165 ng/ml with a duration of 8 hr
12	50 mg iv q8 hr 100 mg iv q 12 hr 10 mg/hr iv inf (all doses given over 24 hr)	ED_{50} under fasting conditions =44.9±3.1 ng/ml.

*ED_{50} is the serum ranitidine concentration needed to suppress baseline gastric acid secretion by ≥50%.

In general, mean ED_{50} values reported for ranitidine in adult subjects range from 45 to 165 ng/ml. There are large interindividual variabilities present in some of the studies. Differences arise due to the various study populations, doses of ranitidine given, routes of administration, test conditions, duration of PK/PD sampling, and assay methodologies. For example, Lebert[8] used normal men whereas Brater[8] and Sanders[12] employed asymptomatic patients with chronic duodenal ulcers. Sample sizes were small in all cases. The various doses and

8. Lebert PA, et al. Clin Pharmac Ther 1981;30(4):539.
9. Brater DC, et al. Clin Pharmac Ther 1982;32(4):484.
10. Mignon M, et al. Brit J Clin Pharmac 1982;14:187.
11. Richards DA. J Clin Gastroenterol 1983;5(Suppl 1):81.
12. Sanders SW, et al. Clin Pharmac Ther 1989;46:545.

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test conditions are included in Table 8. In addition, gastric acidity measurements were determined for times as brief as 2 hr[8] or for as long as 13 hr[9] depending upon the investigator. Comparison of the adult data to pediatric data is very difficult as none of the pediatric studies examined ED_{50} parameters. In conclusion, the inconsistencies between studies and the large variability often observed in the data renders any global predictions for "therapeutic" concentrations of ranitidine as somewhat difficult.

Dosing Recommendations

Intravenous

The proposed labeling for iv ranitidine recommends doses of 2 to 4 mg/kg/day, given every 6 to 8 hours, up to a maximum of 50 mg given every 6 to 8 hours, for the treatment of duodenal ulcers in pediatric subjects aged 1 month to 16 years. Six pharmacokinetic studies which examined iv ranitidine pharmacokinetics were reviewed. Four of these studies involved single iv doses only (Studies 6-9) which ranged from 1 to 2.5 mg/kg. Studies 1 and 5 included subjects with PUD; doses of 0.13-0.8 mg/kg q6 hr and 1.25 mg/kg q6 hr, respectively, were administered. These doses are consistent with the recommendations in the proposed label. Study 1 also examined adverse events and concluded that the doses given were safe.

Oral

The proposed labeling for oral ranitidine provides dosing recommendations based on diagnoses:

a. 2-4 mg/kg/day, bid to a maximum of 300 mg/day for active PUD
b. 2-4 mg/kg once daily to a maximum of 150 mg/day for maintenance of healing of PUD
c. 5-10 mg/kg/day, bid for GERD and erosive esophagitis

Three oral ranitidine studies were reviewed. Study 1 administered 1.25-1.90 mg/kg ranitidine q12 hr to patients with active PUD. No adverse clinical or laboratory events were noted and ulcers were healed at 6 weeks and 12 months. Subjects in Study 3 received 5 mg/kg ranitidine q12 hr for the treatment of GERD. No adverse events were noted over a 3 month period. Although patients in Study 2 did not have an "indicated" diagnosis, 2 mg/kg ranitidine q12 hr was considered to be safe. Overall, these studies support the dosing recommendations for oral ranitidine.

It should be noted that not all individuals are expected to respond to the same degree when administered equivalent doses of ranitidine due to the large variability observed in pharmacodynamic parameters.

Labeling Comments (to be sent to firm)

A. *NDA 18-703 (Zantac Tablets)*
NDA 19-675 (Zantac Syrup)
NDA 20-095 (Zantac GELdose Capsules)
NDA 20-251 (Zantac EFFERdose Tablets and Granules)

1. A summary of the available pediatric pharmacokinetic information should be added to the *Pharmacokinetics* Section of the **CLINICAL PHARMACOLOGY** portion of the labeling. This information should be presented in both text and tabular form.

2. The *Pharmacokinetics* Section of the **CLINICAL PHARMACOLOGY** portion of the labeling should contain a statement regarding the potential for reduced plasma and renal clearances of ranitidine in the neonate (<1 month old).

3. The sentence under the *Pharmacokinetics* Section of the **CLINICAL PHARMACOLOGY** portion of the labeling should be modified as follows:

DRAFT LABELING

[redacted]

4. A *Pharmacodynamics* Section discussing the pharmacodynamics of ranitidine in pediatric subjects as compared with adults should be added to the **CLINICAL PHARMACOLOGY** portion of the labeling. The firm is also encouraged to update the adult pharmacodynamic data.

5. A statement regarding the use of ranitidine in neonates should be added to the *Pediatric Use* Section of the **PRECAUTIONS** portion of the labeling.

B. *NDA 19-090 (Zantac Injection)*
NDA 19-593 (Zantac Pre-mixed Injection)

1. A summary of the available pediatric pharmacokinetic information should be added to the *Pharmacokinetics* Section of the **CLINICAL PHARMACOLOGY** portion of the labeling. This information should be presented in both text and tabular form.

2. The sentence under the *Pharmacokinetics* Section of the **CLINICAL PHARMACOLOGY** portion of the labeling should be modified as follows:

DRAFT LABELING

[redacted]

3. A *Pharmacodynamics* Section discussing the pharmacodynamics of ranitidine in pediatric subjects as compared with adults should be added to the **CLINICAL PHARMACOLOGY** portion of the labeling. The firm is also encouraged to update the adult pharmacodynamic data.

4. A statement regarding the use of ranitidine in neonates should be added to the *Pediatric Use* Section of the **PRECAUTIONS** portion of the labeling.

5. The first sentence under the *Pediatric Use* section of the **DOSAGE AND ADMINISTRATION** portion of the labeling should be modified as follows:

DRAFT LABELING

[redacted]

The second sentence in this section is acceptable.

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II concludes that the supplements to NDAs 18-703, 19-090, 19-593, 19-675, 20-095, and 20-251 dated December 13, 1996 are approvable. The labeling comments listed above should be submitted to the firm and incorporated into the package insert.

Carol Cronenberger, Ph.D. .\S\ [redacted] 12/11/97
Gastrointestinal and Coagulation Drug Products
Division of Pharmaceutical Evaluation II

FT initialed .\S\ [redacted] 12/11/97
Mei-Ling Chen, Ph.D.
Director, Division of Pharmaceutical Evaluation II

cc:NDAs 18-703/SLR-056, 19-090/SLR-037, 19-593/SLR-028, 19-675/SLR-020, 20-095/SLR-007, 20-251/SLR-006, HFD-180, HFD-870 (Chen), HFD-870 (Cronenberger), HFD-850 (Lesko), Central Document Room (Barbara Murphy).

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APPENDIX

Pediatric Study Summaries

Proposed Labeling Changes for NDA 18-703, 19-675, 20-095, and 20-251

Proposed Labeling Changes for NDA 19-090 and

Study 1:

Title	Pharmacokinetic determination of ranitidine pharmacodynamics in pediatric ulcer disease.
Reference	Blumer, J. et al. J Pediatrics, 1985;107:301.
Objective	To evaluate the pharmacokinetics/pharmacodynamics, safety, and efficacy of ranitidine in the treatment of peptic ulcers in children.
Study Population	12 children (5F,7M)(7W,5B) ages 3.5 to 16 yr, 15.5 to 56 kg with endoscopically documented peptic ulcer disease.
Study Design	Three-phase ranitidine treatment schedule: 1. Dose Ranging - iv loading dose at 0.6 mg/kg for 15 min followed by a continuous infusion at 0.2 mg/kg/hr. At the end of each hr, 20% increase in loading dose infused over 20 min along with 20% increase in continuous infusion. Regimen continued until gastric acid secretion (output) inhibited by ≥90% of baseline, then infusion discontinued. Blood sampled for 12 hours post-infusion and PK parameters determined. Gastric secretion volume and pH and pepsin output monitored during iv infusion and for 12 hr post-infusion. 2. IV Treatment - dose of ranitidine required to suppress gastric acid secretions by ≥90% given as iv infusion for 15 min q 6 hr. Blood sampled after the first dose for 6 hr and PK parameters determined. Gastric secretion volume and pH and pepsin output monitored for 6 hr after infusion started. 3. Oral Treatment - 150 mg tablets q 12 hr for 6 wk. Dose adjusted to achieve serum concentrations that decrease gastric secretions by ≥90%. Blood was sampled for 6 hr after 1st dose and weekly thereafter. Urine was collected over a 12 hr period during each pharmacokinetic phase.
Analytical Method	Serum ranitidine concentrations assayed by (b)(4) Urine assay not stated.

Results

PK data (mean±SD)

	Vd (L/kg)	$t_{½}$ (hr)	CL (ml/min/1.73 m²)	F
iv (n=11)	2.3 (0.9)	1.8 (0.3)	795 (334)	
po (n=12)	2.5 (1.0)	2.0 (0.5)	788 (333)	0.48 (0.20)

PD data (range)

	Total dose	C_{max} (ng/ml)	$C_{90\%}$ (ng/ml)	$t_{90\%}$ (min)
Phase 1	0.3 to 2.1 mg/kg	75 to 419	not reported	not reported
Phase 2	0.13 to 0.80 mg/kg	50 to 968	40 to 60	45
Phase 3	po dose yielding $C_{90\%}$	54 to 492	not reported	not reported

Conclusions	1. The values for half-life, total CL, and F are similar to those reported in healthy adults. A large range was noted in reported F values (0.22-0.96). 2. A distinct range of ranitidine serum concentrations was associated with a ≥90% inhibition of gastric acid secretion after iv dosing (40-60 ng/ml). 3. No adverse clinical or laboratory effects were seen with the use of either po or iv ranitidine and all ulcers were healed at end of the study and at 12 months follow-up. Therefore, ranitidine appears to be safe and efficacious for the treatment of peptic ulcer disease in children and adolescents at iv doses of 0.3-2.1 mg/kg and oral doses of 1.25-1.90 mg/kg q 12 hr.
Reviewer Comments:	1. The text states that there were no statistically significant differences found in Vd, Cl, and half-life after iv and po dosing, however, the results of data analysis are not reported in the paper. 2. According to the text urine was collected, however, no data are reported; i.e.,urine volume, renal clearance, etc. 3. No values are reported for AUCs after either iv or po dosing, although results are discussed in the text. The authors report linear pharmacokinetics of ranitidine after both iv and po dosing as evidenced by direct correlations between AUC and dose administered (r=0.95 for iv and r=0.89 for po dosing). 4. Marginal blood sampling scheme. 5. No formal PK/PD modeling was performed. However, there does appear to be a serum concentration-pharmacologic effect relationship. 6. Although the study population was small, overall, this study provides useful information as to the pharmacokinetics and pharmacodynamics of ranitidine in children and adolescents. No data is provided for neonates nor infants.

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Study 2:

Title	Pharmacokinetics of ranitidine syrup in children.
Reference	Protocol #69-RAN-1149, Vol.4, Supplemental NDA for Pediatric Labeling, NDA 18-703 Zantac® Tablets.
Objective	To establish the pharmacokinetic parameters and assess the safety profile of ranitidine syrup in children.
Study Population	Eight hospitalized patients with variable diagnoses, aged 7 mo-14 yrs, (2F,6M) who required H_2-blockers as part of normal clinical care. Diagnoses were variable and included both medical and surgical patients.
Study Design	Patients received 2 mg/kg ranitidine syrup (15 mg/ml) q12 hr for as long as considered therapeutic. Blood sampled at 3,4,5,6,8, and 12 hr after the first and eighth doses.
Analytical Method	Plasma ranitidine samples assayed (b)(4)

Results:
*Given as means ±SD. Adult data taken from Report D870067; results are dose-adjusted.

	Pharmacokinetic Parameters*			
	C_{max} (ng/ml)	t_{max} (hr)	$AUC_{12\ hr}$ (hr*ng/ml)	Half-life (hr)
Single dose				
Pediatrics (7mo-14yr)	244 (109)	1.61 (0.50)	1045 (324)	2.4 (0.5)
Adults (22-32 yr)	447 (NA)	3.2 (NA)	2400 (NA)	2.6 (NA)
Steady State				
Pediatrics (7mo-14yr)	320 (199)	1.66 (0.82)	1428 (578)	2.7 (0.5)

Conclusions

1. There were no statistically significant differences found between C_{max} and $AUC_{12\ hr}$ after single dose and at steady state. Therefore, accumulation of ranitidine in pediatric patients after 4 days of bid dosing does not occur.

2. The values for half-life and t_{max} are similar in pediatric patients and adults. However, mean C_{max} and AUC values are only about 50% of those in adults. This might suggest that the extent of absorption of the ranitidine syrup was less in the pediatric patients.

3. Two adverse events were reported during the study, neither of which was considered related to the study medication.

Reviewer Comments	1. Half-life values could only be determined in 3 patients. 2. The actual evaluable patient sample size was small. Insufficient blood samples were obtained from 4/8 patients after the single dose study and the steady-state study as this procedure was considered traumatic. 3. Blood sampling deviations over the 12 hour sampling time ranged from 23 min early to 44 min late. 4. No pharmacodynamic studies included. 5. Inconsistencies in PK parameters noted; i.e., tmax is reported to be 1.6 hr, however, the methodology states that the first blood sample was drawn at 3 hours. 6. Based on the variability, small sample size, and sampling deficiencies, there are inadequate reliable data to recommend a dosing regimen in pediatric patients.

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Study 3:

Title	Use of ranitidine in young infants with gastro-oesophageal reflux.
Reference	Mallet E, et al. Eur J Clin Pharmac, 1989;36:641-642.
Objective	To assess the pharmacokinetics and pharmacodynamics of ranitidine in infants.
Study Population	1.Single dose - Eleven hospitalized infants, ages 6 wk-6 mo, with GERD. 2.Chronic administration - Twenty infants, ages 1-6 mo.
Study Design	Open-label, nonrandomized, one center. 1.Single dose (n=11) - 5 mg/kg po using the iv formulation. Plasma ranitidine concentrations determined for at least 9 hr. Gastric pH measured for 24 hours. 2.Chronic administration (n=20) - 5 mg/kg po ranitidine q12 hr for 1-3 mo. Intermittent plasma ranitidine levels and gastric pH determinations were assessed. Tolerance to ranitidine studied.
Analytical Method	Plasma ranitidine concentrations determined by (b)(4) with (b)(4) PK parameters based on a single compartment model.
Results: means±(not stated)	**Single-dose study**

Pharmacokinetic parameters

Cmax (ng/ml)	tmax (hr)	Half-life (hr)	Clearance (ml/min*m²)
476 (164)	1.2 (0.4)	2.8 (0.8)	664 (NA)

Pharmacodynamic results

Gastric pH<4 when plasma ranitidine <100 ng/ml which occurred around 9 hr post-dose.

Chronic study

1. "Spot checks" of gastric pH and serum levels reveal values consistent with the single-dose study.

2. No adverse effects noted with respect to laboratory values, ECGs, side effects, etc.

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Conclusions	1. Pharmacokinetic results consistent with those seen in adults. 2. Oral ranitidine at a dose of 5 mg/kg is safe to use in infants. 3. A dose of 5 mg/kg is necessary to maintain gastric pH>4.0 for ~9 hr, a length of time necessary for successful treatment of GERD. 4. A dose of 5 mg/kg may be used in conjuction with milk feedings to increase gastric pH>4.0 over 24 hr (milk by itself will increase pH>4.0 for about 2 hr).
Reviewer Comments	1. Very limited information was available in this paper; e.g., no PK/PD results from the chronic study, no PK calculations, etc. 2. Authors used a 1-compartment model to describe ranitidine PK, whereas, a 2-compartment model is typically used. This could introduce errors into calculations for both clearance and half-life. 3. No formal PK/PD modeling done, however, there appears to be a serum concentration/gastric pH relationship. 4. Although the study population is small and data is sparse, this study provides useful information in a population that is rarely examined.

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Study 4:

Title	Efficacy, duration, and absorption of a paediatric oral liquid preparation of ranitidine hydrochloride.
Reference	Goresky, GV, et al. Can J Anaesth 1992;39(8):791-798.
Objective	To assess the efficacy of a new oral ranitidine liquid preparation in reducing gastric acidity and volume, to determine the degree of absorption, and to determine the duration of the drug effect.
Study Population	240 children, ages 1-6 yr, elective surgical patients without gastrointestinal disease.
Study Design	Three-center, randomized, double-blind comparative trial. Subjects were randomly allocated to one of 4 groups: Group A- apple jc (5ml/kg) plus placebo liquid Group B- apple jc (5ml/kg) plus ranitidine liquid (2mg/kg) Group C- 5 ml water plus placebo liquid Group D- 5 ml water plus ranitidine liquid (2mg/kg). Patients anesthetized and given the study agent 2 hr prior to surgery. Gastric contents aspirated and blood drawn. Gastric volume and pH determined.
Analytical Method	Serum ranitidine concentration determined by (b)(4)
Results	1. Ranitidine significantly decreased gastric acidity and volume when compared to placebo. 2. Administration of apple juice did not affect intragastric pH or volume. 3. 33% of patients receiving ranitidine had a gastric pH<2.5 with serum ranitidine concentrations ranging from 18-331 ng/ml. All but 4 of these patients had serum concentrations >60 ng/ml which is the concentration of ranitidine thought to supress gastric acid secretion by ≥90% (see Study 2 review, Blumer, et al). 4. There were no differences in serum ranitidine concentration between subjects receiving apple juice or water. 5. Ten minor adverse events were reported.
Conclusions	1. A single dose of 2mg/kg liquid ranitidine was effective in reducing gastric volume and acidity in about 67% of patients. No measurable response to ranitidine was observed in the remaining 33%. 2. The liquid formulation of ranitidine was adequately absorbed as evidenced by therapeutic serum levels in 28 of 32 patients who had a lack of pharmacologic response to the drug. 3. The expected duration of 2mg/kg ranitidine would be 3-4 hrs after administration. 4. Ranitidine is reasonably safe to use in children.

Reviewer Comments	1. Gastric contents examined in majority of patients at only 2 hours after drug administration. Later measurements may have demonstrated further increases in gastric pH. 2. Pharmacodynamic parameters measured in anesthetized patients which could affect gastric volume and pH. 3. No pharmacokinetic parameters provided. 4. No formal PK/PD modeling completed. 5. Inadequate PK/PD sampling. 6. Patients with gastrointestinal diagnoses excluded from the study. 7. Ranitidine formulation used was not standard. 8. No serum ranitidine levels were provided for subjects with gastric pH>2.5.

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Study 5:

Title	Pharmacokinetics of ranitidine in pediatric patients.
Reference	Leeder JS, et al. Acta Pharm Tox, 1986;59(suppl5):79.
Objective	To establish appropriate dosing guidelines for children based on pharmacokinetic data.
Study Population	23 pediatric patients with suspected peptic ulcer disease and 6 disease-free adults. The pediatric patients included 12 ICU and 11 ambulatory (AMB) patients divided into 3 groups on the basis of age: <6 yr(n=6), 6-11.9 yr(n=11) and ≥12 yr(n=6).
Study Design	Serum samples obtained over 6 hr after a single iv bolus of 2.5 mg/kg (AMB, adults) or after first iv dose of 1.25 mg/kg q6 hr (ICU).
Analytical Method	(b)(4) [redacted]

Results (means±SD)

	Half-life (hr)	Clearance (ml/min*kg)	Vdss (L/kg)
<6 yr	2.15 (2.12)	11.41 (6.86)	1.29 (0.83)
6-11.9 yr	2.11 (0.96)	8.96 (3.36)	1.14 (0.52)
≥12 yr	1.65 (0.46)	9.89 (3.00)	0.98 (0.26)
Adults	1.87 (0.33)	8.77 (0.72)	1.04 (0.10)

Conclusions

1. There were no statistically significant differences in PK parameters between the 4 age groups.

2. There were no statistically significant differences in PK parameters between the ICU and AMB patients.

3. A dose of 2.0-2.5 mg/kg bid should provide concentrations comparable to those achieved with the recommended adult dose of 150 mg bid.

[redacted]

Study 6:

Title	Ranitidine pharmacokinetics in children.			
Reference	Leeder, JS, et al. Clin Pharmacol Ther. 1985;37:201 (abstract A23).			
Objective	To determine the pharmacokinetics of ranitidine in pediatric patients and establish appropriate dosage guidelines.			
Study Population	Pediatric patients with suspected peptic ulcer disease aged 6-10 yr (n=4), 11-16 yr (n=4), and disease-free adults (n=6).			
Study Design	Single iv bolus dose of 2.5 mg/kg. Serial serum samples obtained for 6 hr.			
Analytical Method	(b)(4)			
Results (means±SD)		**6-10 yr**	**11-16 yr**	**Adults**
	$t_{1/2}$ (hr)	1.97 (0.66)	1.58 0.24	1.87 (0.33)
	V_c (L/kg)	0.43 (0.11)	0.27 (0.07)	0.21 (0.03)
	V_β (L/kg)	1.50 (0.33)	1.43 (0.45)	1.43 (0.30)
	Cl (ml/min/kg)	9.5 (3.2)	10.7 (2.8)	8.8 (0.7)
Conclusions	1. V_c in the 6-10 yr group was significantly larger than the older groups ($p<0.01$). 2. There were no statistically significant differences in the remaining pharmacokinetic parameters between any of the groups. Therefore, the pharmacokinetics of ranitidine are similar in this population and adults.			

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Reviewer Comments	1. The data presented are taken from an abstract, therefore, information is sparse. For example, there is no demographic data for the subjects, no detailed methodology, no kinetic calculations, etc. 2. The authors conclude that a dose of 2.0-2.5 mg/kg bid in children should result in ranitidine concentrations comparable to those observed in adults after a dose of 150 mg bid, however, there is no information provided to support this statement. 3. Sample sizes are small, however, results seem to confirm those found in similar studies. 4. Neonates and infants were not studied. 5. No pharmacodynamic data were collected. 6. No safety information available. 7. PUD not confirmed, only suspected.

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Study 7:

Title	Pharmacokinetics of ranitidine in critically ill infants.
Reference	Wiest, DB, et al. Dev Pharmacol Ther. 1989;12:7-12.
Objective	To describe the pharmacokinetics of ranitidine after administration of a single iv dose in critically ill infants.
Study Population	Hospitalized infants ages 2-36 months (3F,6M) with a clinical indication for H_2-blocker therapy.
Study Design	Single iv dose of 1.5 mg/kg administered over 10 min. Plasma sampled at 0.25, 0.5, 1, 2, 4, and 8 hr. Computer simulations performed to evaluate steady-state serum concentration profiles using 3 dosage regimens of 0.3, 0.5, and 0.7 mg/kg q 6 hr.
Analytical Method	(b)(4) [redacted]
Results	**Patient demographic data and pharmacokinetic parameters**

Patient No.	Age (months)	Weight (kg)	Half-life (hr)	Vd_β (L/kg)	Cl_s (ml/min/kg)
1	21	(b)(4) [redacted]			
2	16				
3	2				
4*	2				
5	9				
6	4				
7	19				
8	15				
9	10				
Mean (SD)	12 (6.9)	8.2 (2.7)	2.1 (1.3)	1.6 (1.0)	13.9 (10.0)

*Pt. 4 not included in data analysis

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^Adult data taken from Garg el al (1983)	**Adults^ (n=12)**	NA	7.5 (range 4.7-8.2)	2.9 (range 2.5-4.7)	72%
	Pharmacodynamic Results (n=20): 1. 10 patients had gastric pH≥4.0 prior to and throughout 6 hr study. 2. 10 patients had gastric pH≤2.0 prior to ranitidine dosing. a. 4/10 achieved pH≥4.0 by 2 hr post-dose. b. 2/10 achieved pH≥4.0 by 3 hr post-dose. c. 2/10 achieved pH≥4.0 by 4 hr post-dose. d. 2/10 revealed no gastric acid suppression.				
Conclusions	1. There was considerable inter-subject variability in ranitidine pharmacokinetics in the pediatric population. However, PK parameters are similar in infants, children, adolescents, and adults when normalized for body weight. 2. The neonate had a much longer half-life, larger AUC, and smaller Cl_P, Cl_R, and Vd_{area} for ranitidine than the older patients. A considerable reduction in dose may be required for this age group if an H_2-blocker is considered necessary. 3. There was a large variability in pharmacodynamic data between patients. The current dosage regimen may not be sufficient to maintain a gastric pH≥4.0. 4. The use of iv ranitidine 1 mg/kg in pediatric patients appears to be safe. No adverse events were reported during the study.				
Reviewer Comments	1. All patients in the current study were admitted to the hospital for diagnoses other than gi-related. The majority of these had surgery prior to ranitidine administration. This may account for some of the varibiltiy in PK parameters. 2. The lower renal clearance for ranitidine in the neonate is probably a reflection of the lower glomerular filtration rate observed in this age group. 3. The smaller volume of distribution value in the neonate may be due to a larger total body water content inherent in this age group. This would result in a lower lean mass/total body water ratio, therefore, resulting in a lower weight-normalized Vd. 4. No formal PK/PD modeling was done nor was any attempt made to correlate gastric pH with ranitidine plasma concentration. 5. Marginal blood/urine sampling scheme.				

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Study 10:

Title	Ranitidine pharmacokinetics in newborn infants.		
Reference	Fontana M, et al. Arch Dis Child 1993;68:602.		
Objective	To explore ranitidine pharmacokinetics in the neonatal period.		
Study Population	27 term newborns, ages 18-27 hr, with bloody vomitus.		
Study Design	Multi-center, single iv dose 2.4 mg/kg. No more than 2 samples drawn from each patient (population PK) with the sampling interval ranging from 120 to 300 min.		
Analytical Method	(b)(4) [redacted]		
Results: presented as estimated means±SD	**Half-life (hr)**	**Cl_{plasma} (ml/kg/min)**	**Vd (L/kg)**
	3.45 (0.32)	5.02 (0.46)	1.5 (0.9)
Conclusions	1. Half-life is greater with a decreased clearance in newborns compared to older children. This is likely due to a low GFR in these subjects.		
Reviewer Comments	1. PK parameters assessed using a 1 COM. 2. No safety data reported. . Even though the sponsor is not seeking approval for the use of ranitidine in newborns, this study provides useful information and implications regarding the safety of this drug in this pediatric subgroup.		

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