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The influence of ranitidine on the pharmacokinetics and toxicity of doxorubicin in rabbits*

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Summary. The influence of ranitidine on the pharmacokinetics and toxicity of doxorubicin was studied in six female New Zealand white rabbits. Plasma pharmacokinetic data were first obtained from rabbits given 3 mg/kg doxorubicin. After 1 month, the same rabbits were treated with ranitidine, 2.5 mg/kg or 25 mg/kg, before and during doxorubicin administration. The plasma doxorubicin assays to determine pharmacokinetic parameters were repeated. Drug toxicity was evaluated using complete blood counts, and hepatic function was measured using a ^{14}C-aminopyrine breath test. High-dose ranitidine increased the total exposure to doxorubicin (area under the curve of doxorubicin alone = 1.44 ± 0.88 $\mu M \cdot$h/ml vs 4.49 ± 2.35 $\mu M \cdot$hr/ml for doxorubicin given with high-dose ranitidine; $P = 0.06$). Low-dose ranitidine did not alter doxorubicin pharmacokinetics. Exposure to doxorubicinol was altered by either high-dose or low-dose ranitidine. ^{14}C-Aminopyrine half-life was altered by a raniditine dose of 25 mg/kg (aminopyrine half-life after placebo control = 97 ± 6 min as against aminopyrine half-life after ranitidine = 121 ± 7 min; mean ± SEM; $P < 0.02$). Low-dose ranitidine did not exacerbate doxorubicin-induced myelosuppression. High-dose ranitidine enhanced doxorubicin-induced erythroid suppression while sparing the myeloid series. At cytochrome P-450-inhibitory doses, ranitidine's effects upon doxorubicin plasma pharmacokinetics are similar to those previously seen with cimetidine. These changes did not appear to alter drug detoxification and are not related to microsomal inhibition of doxorubicin detoxification. Low doses of ranitidine do not alter doxorubicin plasma pharmacokinetics or toxicity in rabbits.

Introduction

Treatment of cancer patients with antineoplastic agents in conjunction with a variety of other drugs may result in the occurrence of drug-drug interactions that can potentially alter the therapeutic index of the antineoplastic drug [29]. Many cancer patients receiving antineoplastic drug therapy are concurrently treated with histamine-2 (H_2) blockers, known cytochrome P-450 inhibitors, for prevention of or therapy for peptic or duodenal ulceration, gastritis, or reflux esophagitis. Based upon the hypothesis that pharmacologic cytochrome P-450 inhibitors should inhibit the metabolism of doxorubicin and doxorubicinol to their respective aglycone metabolites, we previously investigated the effect of cimetidine on doxorubicin pharmacokinetics in a controlled setting in rabbits [5]. We found increased doxorubicin concentrations in rabbits pretreated with cimetidine compared with paired controls. The plasma concentrations of metabolites were unchanged. Had cimetidine effectively blocked microsomal doxorubicin metabolism, we should have seen increased doxorubicinol concentrations and some increase in doxorubicin concentrations. We have seen such patterns with enhanced drug toxicity after sublethal hepatocellular necrosis induced with allyl alcohol [6].

Ranitidine differs chemically from cimetidine in that it possesses a furan ring in place of the imidazole nucleus of cimetidine. It is 5–10 times more potent as an inhibitor of gastric acid secretion than cimetidine [9]. This enhanced potency does not extend to hepatic microsomal inhibition [3, 16, 21], as ranitidine possesses less affinity for hepatic cytochrome P-450 enzymes [3, 21].

This study was designed to investigate the influence of two different doses of ranitidine on the pharmacokinetics and toxicity of doxorubicin. We hypothesized that ranitidine at therapeutic doses would not alter hepatic oxidative function or the metabolism of doxorubicin in a rabbit model. At very high doses, we hypothesized that ranitidine would produce changes in doxorubicin pharmacokinetics and metabolism similar to those found with cimetidine.

Materials and methods

Materials. Doxorubicin hydrochloride was purchased from Adria Laboratories, Inc. (Columbus, Ohio). HPLC-grade tetrahydrofuran (THF) was obtained from Fisher Laboratories of Allied Industries (Pittsburgh, Pa). A 0.1% (w/v) ammonium formate buffer was prepared daily, adjusting the pH to 4.0 with formic acid (Fisher certified), and filtered and degassed using a 0.45 μm Millipore filter (Milford, Mass). Chemical extraction of doxorubicin and its metabolites from plasma was accomplished using Fisher certified chloroform, 2-propanol, and ammonium sulfate. ^{14}C-Aminopyrine was obtained from Research Products International (Mt Prospect, Ill). Aquasol was obtain-

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ed from New England Nuclear (Boston, Mass). Ranitidine (25 mg/ml) and placebo consisting of carrier solution for ranitidine (phenol 5 mg/ml, 0.96 mg/ml monobasic potassium phosphate and 2.4 mg/ml dibasic potassium phosphate buffers) were supplied by Glaxo, Inc (Research Triangle Park, NC).

Synthesis of doxorubicin metabolites. Doxorubicinol, doxorubicin aglycone, doxorubicinol aglycone, 7-deoxydoxorubicin aglycone, and 7-deoxydoxorubicinol aglycone were synthesized according to the published work of Takanashi and Bachur [27]. Identity of the standards was confirmed by mass spectroscopy. Purity was confirmed by the presence of a single peak on HPLC at published retention times [4], indicating at least 98% purity at this sensitivity.

Rabbits. Female white New Zealand rabbits weighing 3–4 kg were obtained locally and housed in clean individual cages in the animal care facility at the Nashville Veterans Administration Medical Center. The quarters are supervised by an Animal Care Committee as required under U. S. Federal regulations. Procedures for the study were reviewed and approved by a veterinarian and the local Research and Development Committee prior to the study. Rabbits were allowed unlimited food and water.

^{14}C-Aminopyrine breath test. This test, used as an indicator of hepatic cytochrome P-450 activity, was adapted from the rat model (Fig. 1) [11]. Rabbits were given 0.5 μCi ^{14}C-aminopyrine i.v. and secured in a restrainer. A ventilated glass hood covered the head and was connected to suction to provide one-way flow of expired $^{14}CO_2$ from the hood into the collection apparatus. The collection apparatus consisted of a sulfuric acid trap for breath dehydration and 20 ml scintillation vials containing 10 ml methanol-ethanolamine (2:1 v/v) for $^{14}CO_2$ collection. The expired $^{14}CO_2$ was collected over nine 20-min fractions (total 3 h). Then 5 ml scintillation fluid and 5 ml methanol were added to each collection vial. The samples were counted in an Isocap/300 liquid scintillation system (Searle Analytic, Des Plains, Ill).

The elimination rate constant, k_{el}, was obtained from the slope of a logarithmic linear regression of counts per minute against time. The half-life was calculated by the equation $t_{½} = 0.693/k_{el}$. The variability between days in the calculated half-life for an individual animal was minimal. Variability between individual rabbits was substantial and required paired controls for normalization. Statistical differences in half-lives and elimination rate constants were analyzed using the Wilcoxon signed rank test [14].

Study protocol. The protocol for study is shown in Table 1. All studies were performed in groups of paired New Zealand white rabbits. Treatment ^{14}C-aminopyrine breath test results were compared with those recorded in paired controls. The first paired group of six doxorubicin-treated rabbits received a low ranitidine dose, 2.5 mg/kg every 12 h. This dose was chosen as equivalent to a standard intravenous human dose. A standard i.v. human dose ranitidine is 200 mg/day [20]. Assuming a '70-kg' man, this is a dose of 2.86 mg/kg per day. We estimated the scale-down dosing factor from humans to rabbits to be a factor of 3 on the basis of the work of Freireich et al. [18]. The equivalent rabbit dose would be 8.57 mg/kg per day. The low-dose group of rabbits received a total of 5 mg/kg per day. The second group received the high ranitidine dose, 25 mg/kg every 12 h. This dose was chosen after studies described above had demonstrated inhibition of cytochrome P-450 function as documented by ^{14}C-aminopyrine breath test (Fig. 2).

Doxorubicin assay. Blood specimens 3 ml in volume were obtained in heparinized (green top) tubes as outlined in Table 1. Blood samples were immediately centrifuged at 4° C. The plasma supernatant was removed and frozen at −20° C until assayed. All samples were assayed within 3 weeks of their collection. The specimens were extracted in chloroform:isopropanol (1:1 v/v) and assayed by high-performance liquid chromatography and fluorescence detection according to a previously published procedure [4]. This procedure was altered by the use of a 15-cm μBondapak phenyl column (Waters Associates, Milford, Mass) in place of a 30-cm μBondapak phenyl column.

Quantitation. A standard curve for each assay was prepared from pooled rabbit plasma. The ratio of known doxorubicin peak areas to a 0.05 nmol/ml daunorubicin internal standard was calculated, and a linear regression analysis of this ratio against known doxorubicin concentrations was calculated. Concentrations of doxorubicin and its metabolites were calculated from the standard curve using their ratios of peak area to daunorubicin internal standards.

Table 1. Study schema: doxorubicin and ranitidine in rabbits

	Day										
	1	2	3	4	5	28	29	30	31	32	33
Doxorubicin	3 mg/kg						3 mg/kg				
Ranitidine							×	×	×	×	
Pharmacokinetic study	|——	——	——	——|			|——	——	——	——|	
^{14}C-Aminopyrinebreath test	×	×	×	×	×	×	×	×	×	×	

Ranitidine administered i.v. 1 h prior to doxorubicin and every 12 h for 72 h, 25 mg/kg in six rabbits, 2.5 mg/kg in six rabbits
Pharmacokinetic study: 3-ml blood specimens drawn after doxorubicin administration at 5 and 15 min, 1, 2, 4, 8, 12, 24, 36, 48 and 72 h
CBC Obtained on days 1, 5, 6, 7, 8, 9, and 28, 33, 34, 35, 36, 37

Pharmacokinetics. Doxorubicin concentrations were fit by means of the nonlinear curve-fitting program MLAB to the equation:

$$C(t) = Ae^{-\alpha t} + Be^{-\beta t},$$

where C(t) is the plasma concentration over time, t; A and B are constants; and α and β are linear elimination rate constants. A 1/(concentration)^2 weighting function was used for curve fitting. The area under the curve (AUC) was calculated for doxorubicin by the log-trapezoidal rule to infinity. Clearance, Cl, was calculated by:

$$Cl = D_0/AUC,$$

where D_0 is the administered dose. Volume of distribution at steady state, Vd_{ss}, was calculated by a noncompartmental method:

$$Vd_{ss} = D_0\,(AUMC)/AUC^2,$$

where AUMC is the area under the moment curve [2]. Areas under the curve for metabolites were calculated by the log-trapezoidal rule. The Wilcoxon signed rank test was used to test for statistical significance [14].

CBC Assay. Complete blood count (CBC), including white blood cell count, hemoglobin, hematocrit, and platelet count was assayed on an ELT-800 (Ortho Diagnostics, Raritan, NJ) system used in the clinical laboratories.

Results

^{14}C-Aminopyrine breath test – Ranitidine dose response relationship

The effect of ranitidine dose upon ^{14}C-aminopyrine half-life was evaluated in four previously untreated rabbits. The results shown in Fig. 2 reveal inhibition of cytochrome P-450 aminopyrine demethylation activity at high ranitidine doses. A dose of 6 mg/kg suggests a trend towards inhibition ($P < 0.09$); however, inhibition was statistically significant at 25 mg/kg.

^{14}C-Aminopyrine breath test associated with the administration of doxorubicin with and without ranitidine

Aminopyrine half-life was not altered by administration of 3 mg/kg doxorubicin (Fig. 4). During concomitant high-dose ranitidine and doxorubicin treatment, ^{14}C-aminopyrine excretion was delayed compared with that in paired controls given doxorubicin alone. During low-dose ranitidine pretreatment and doxorubicin, ^{14}C-aminopyrine excretion was unchanged compared with paired controls of doxorubicin alone (Fig. 4B). ^{14}C-Aminopyrine excretion on day 3 of high-dose ranitidine and doxorubicin dropped from 60% to 20% of control. This suggests some evidence of enzyme induction after repeated high ranitidine doses.

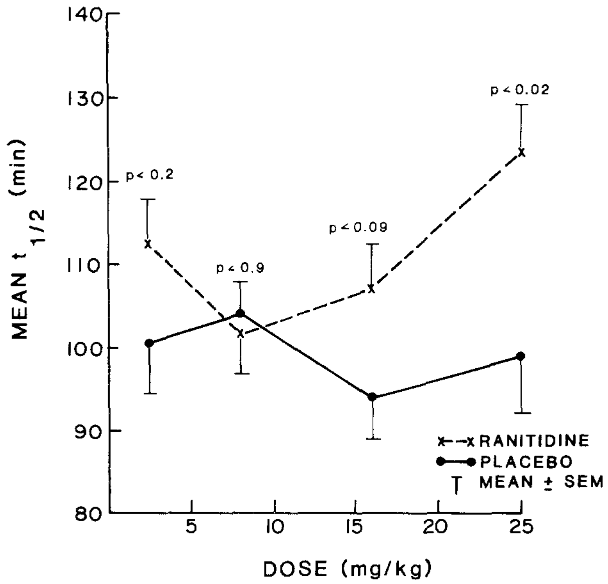

Fig. 2. Cytochrome P-450 activity as measured by ^{14}C-aminopyrine breath test for increasing dose of ranitidine pretreatment

Doxorubicin and metabolite pharmacokinetic studies

Doxorubicin pharmacokinetic parameters after high- and low-dose ranitidine treatment and paired controls are listed in Table 2. Doxorubicin plasma concentration-versus-time plots are shown in Fig. 4. No significant changes in doxorubicin or doxorubicinol pharmacokinetics were found with low-dose ranitidine treatment. A trend suggesting a significant increase in doxorubicin AUC with a decrease in volume of distribution is observed after high-dose ranitidine treatment. Doxorubicinol and 7-deoxydoxorubicinol aglycone areas under the curve were not affected by high-dose ranitidine. We co-chromatographed a 7-deoxydoxorubicin aglycone standard [4] but did not find this metabolite in our analysis of rabbit plasma.

Toxicity

Neither dose of ranitidine significantly altered WBC or platelet count nadirs when compared with control (Table 3). Small but statistically significant decreases in hemoglobin and hematocrit nadirs after high-dose ranitidine treatment were observed.

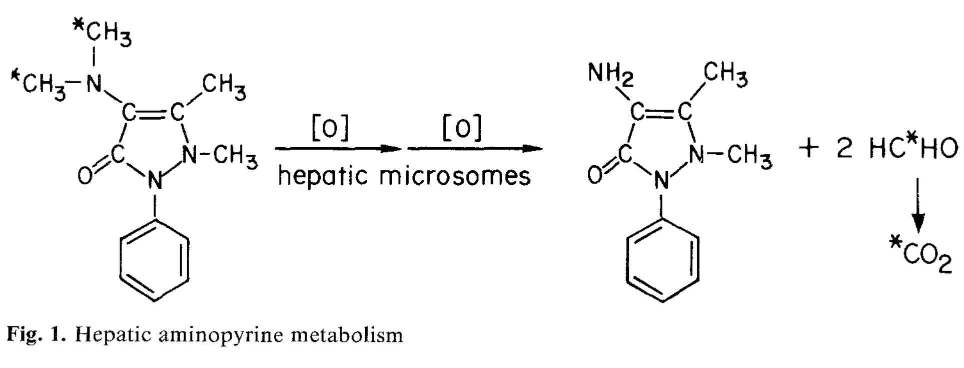

Fig. 1. Hepatic aminopyrine metabolism

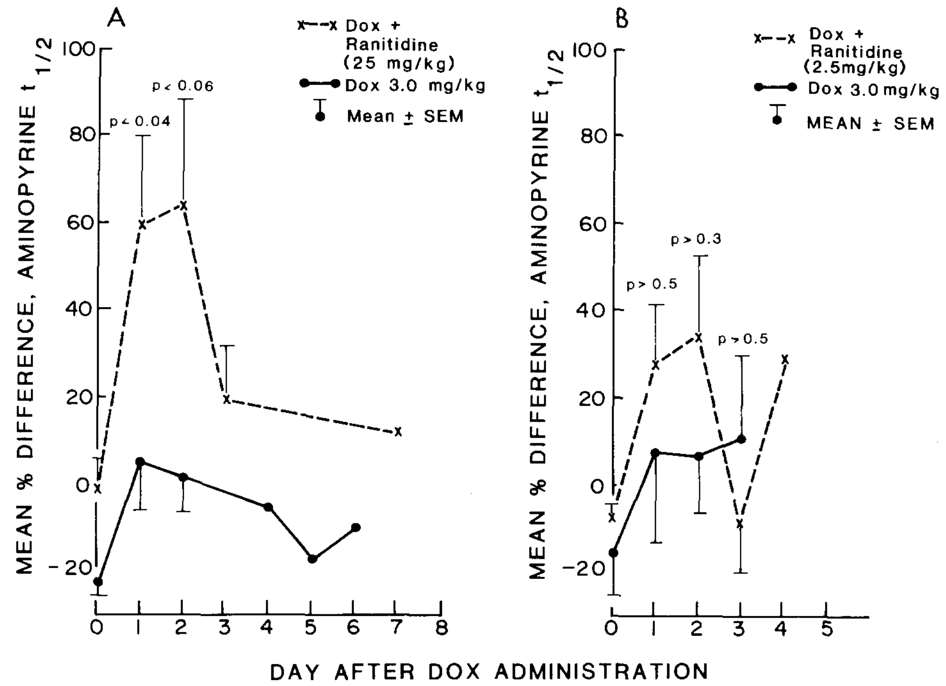

Fig. 3A, B. ^{14}C-Aminopyrine breath test in rabbits treated with ranitidine and doxorubicin. All groups of animals served as their own breath test controls. On the 3 days immediately before administration of ranitidine or doxorubicin or both, ^{14}C-aminopyrine breath tests were performed as baselines. On each day of and following drug treatment, the breath test was repeated. Excreted $^{14}CO_2$ half-life for a day was divided by the baseline value from each of six rabbits in the group. The percentage difference from baseline was then calculated over six animals. **A** Mean percentage differences from baseline in six rabbits receiving doxorubicin ± high-dose ranitidine pretreatment; **B** mean percentage differences from baseline in six rabbits receiving doxorubicin ± low-dose ranitidine pretreatment

Discussion

The hepatic microsomal enzyme system is of central importance in drug metabolism and detoxification. Histamine-2 (H_2) blockers such as cimetidine and ranitidine in certain situations are known inhibitors of this enzyme system. Clinically, ranitidine at therapeutic doses not alter the disposition of propanolol [15, 24, 25], lidocaine, phenytoin, diazepam and atenolol [25]. Changes in the pharmacokinetics of theophylline, fentanyl, midazolam, warfarin, metaprolol and niefedipine have been caused by ranitidine's inhibition of cytochrome P-450 [25]. The clinical significance of altered pharmacokinetics for most of these drugs has not been demonstrated. Midazolam [21] and cobalamin [21] interact with ranitidine via inhibition of absorption. Procainamide [21] interacts with rantidine via inhibition of renal secretion.

One aim of this study was to determine whether or, if so at what dose ranitidine inhibits cytochrome P-450 activity in rabbits. We employed the ^{14}C-aminopyrine breath test as a useful means of assessing hepatic cytochrome P-450 enzyme function in vivo. The choice of this test was based upon several considerations. First, standard biochemical hepatic function tests, such as aspartate transferase (AST), alkaline phosphatase, or bilirubin, are often nonspecific indicators of hepatic damage which do not reliably test function [8, 24]. Second, tests using nontoxic compounds that are biotransformed and hepatically excreted improve our ability to measure hepatic function

Table 2. Doxorubicin and doxorubicinol pharmacokinetic parameters

	DOX AUC (µM · h/ml)	t½ (h)	K_{el} (h^{-1})	Cl_{TB} (l/min per kg)	V_{dss} (l/kg)	Doxorubicinol AUC (µ*M* · h/ml)
Low-dose ranitidine						
DOX 3.0 mg/kg	1.50±0.80	30.0±10.8	0.025±0.007	0.076±0.035	131±42	1.16±1.04
DOX 3.0 mg/kg + RAN 2.5 mg/kg	2.74±2.34	40.3±31.9	0.023±0.009	0.048±0.022	99±25	2.73±1.62
P	>0.25	>0.25	>0.25	0.16	0.22	0.22
High-dose ranitidine						
DOX 3.0 mg/kg	1.44±0.88	37.1±13.9	0.021±0.008	0.058±0.049	200±89	1.47±1.16
DOX 3.0 mg/kg + RAN 25 mg/kg	4.49±2.35	31.8±12.7	0.025±0.011	0.014±0.005	56±21	1.91±0.59
P	0.06	>0.25	0.5	0.06	0.031	0.22

DOX, Doxorubicin; RAN, ranitidine. Values are means ± SD

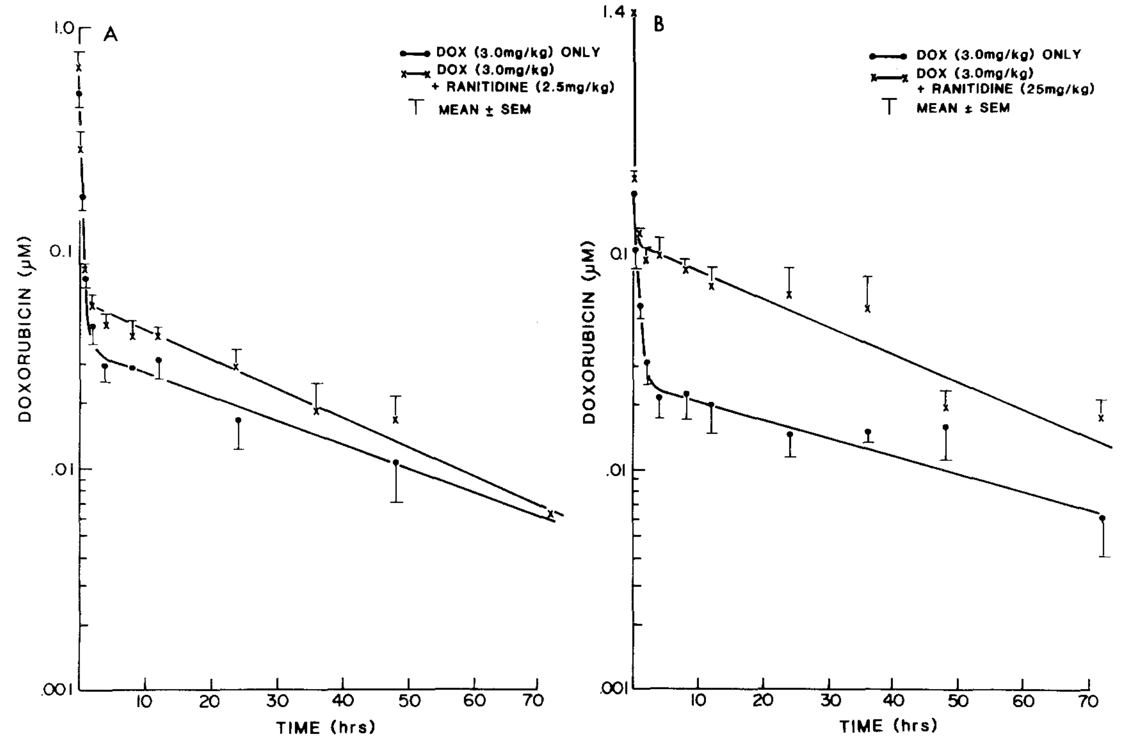

Fig. 4 A, B. A Doxorubicin plasma concentration-time curves obtained from paired studies with and without standard-dose ranitidine pretreatment (2.5 mg/kg); **B** Same as **A** except high-dose ranitidine pretreatment (25 mg/kg)

rather than cellular necrosis. Finally, ^{14}C-aminopyrine was specifically chosen from a large group of compounds used to assess hepatic function (e.g., ^{14}C-phenacetin, ^{14}C-galactose, ^{14}C-antipyrine, ^{14}C-diazepam) [25] because of the large clinical experience with ^{14}C-aminopyrine [10, 22, 23]. Even though high-performance liquid chromatographic analysis of serum antipyrine metabolites may be an improvement over breath test analyses [10, 28], our ability to obtain frequent blood specimens from rabbits was limited. The ^{14}C-aminopyrine breath test provided a precise noninvasive measurement of hepatic function while meeting the needs ofanimal care. Our data showed that ranitidine inhibits aminopyrine *N*-demethylation in the rabbit at a dose of 25 mg/kg.

While the pharmacokinetic profile of doxorubicin and its major metabolite, doxorubicinol, was unchanged by therapeutic ranitidine doses (2.5 mg/kg), high ranitidine doses (25 mg/kg) significantly increased doxorubicin AUC and decreased the steady-state volume of distribution. No changes in doxorubicinol concentrations or AUC were found with high-dose ranitidine treatment.

The doxorubicin pharmacokinetic data are consistent wih our previous work with cimetidine [5]. As with cimetidine, doxorubicin plasma exposures were increased in the animals receiving cytochrome P-450 inhibitory doses of ranitidine. Doxorubicin and 7-deoxydoxorubicinol aglycone exposures were not altered by ranitidine. We did not detect any 7-deoxydoxorubicin aglycone in the plasma. This metabolite, in our experience, is more commonly seen in humans than in rabbits.

It is possible to interpret data from our studies in at least two ways. First, the cytochrome P-450 isozyme associated with aminopyrine demethylation [13] may be associated with those parts of the mixed function oxidase system that metabolize the more lipophilic moiety doxorubicin to the aglycone rather than the more hydrophilic me-

Table 3. Doxorubicin-induced toxicity as measured by blood count nadirs

	WBC Nadir ($\times 10^3/\mu l$)	Hemoglobin nadir (g/dl)	Hematocrit nadir (%)	Platelet nadir ($\times 10^3/\mu l$)
Low-dose				
DOX 3.0 mg/kg	5.1 ± 1.3	9.1 ± 0.5	32.3 ± 2.2	130 ± 73
DOX 3.0 mg/kg + RAN 2.5 mg/kg	4.7 ± 0.6	8.5 ± 0.3	29.6 ± 1.8	75 ± 26
High-dose				
DOX 3.0 mg/kg	4.4 ± 1.1	9.0 ± 0.7	30.4 ± 2.2	101 ± 50
DOX 3.0 mg/kg + RAN 25 mg/kg	4.4 ± 0.9	8.7 ± 0.6*	28.7 ± 2.8*	65 ± 51
Mean ± SD				

* $P < 0.05$; WBC, White blood count; DOX, doxorubicin; RAN, ranitidine

tabolite, doxorubicinol. Hence, we see evidence of alteration of doxorubicin metabolism directly to the aglycone, but no evidence of change in detoxification of doxorubicinol. Second, the cytochrome P-450 isozyme associated with aminopyrine *N*-demethylation is not involved in detoxification of doxorubicin or doxorubicinol to the aglycone. Reductive cleavage of the anthracycline glycoside bond is mediated by cytochrome P-450 reductase [1, 26]. We favor the latter explanation. The increase in circulating doxorubicin concentration could be due to (1) inhibition of tissue aldehyde-ketone reductase [17] by H_2-blockers causing a block in the formation of doxorubicinol at peripheral tissues; (2) inhibition of select cytochrome P-450 isoenzyme which could be involved in doxorubicin reduction but not reductive cleavage of the glycosidic linkage; (3) an alteration in anthracycline volume of distribution caused by the H_2 blocker; or (4) inhibition of hepatic excretion of doxorubicin by ranitidine. No data, to our knowledge, are available to favor any of these hypotheses.

Finally, we found no changes in white blood cell or platelet count nadirs in the animals treated with cytochrome P-450-inhibitory doses of ranitidine. Significant decreases in red cell parameters suggest a possible direct toxic effect on the red cell series by ranitidine or increased sensitivity of the red cell series to the combined toxic effects of high doses of ranitidine and anthracyclines. Other H_2 receptor antagonists (cimetidine, metiamide, burimamide) have been associated with myelosuppression [19]. Ranitidine rarely, if ever, causes myelosuppression. However, it is conceivable, at very high doses or in conditions of severe hepatic excretory impairment [7], with its structural similarities to other H_2-blockers, that ranitidine may cause myelotoxicity. Increased exposure (twice that of paired controls) to doxorubicin without a concomitant increase in doxorubicinol concentrations does not appear to cause increased toxicity to the myeloid series. These data suggest that increased concentrations of doxorubicin alone may not be the only or most important predictor of myelotoxicity. Evaluation of plasma doxorubicin metabolite [12] exposure may also provide important clues to the drug pharmacodynamics in individuals.

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References

1. Bachur NR, Gordon SL, Gee MY, Kon H (1979) NADPH cytochrome P-450 reductase activation of quinone anticancer agents to free radicals. Proc Natl Acad Sci USA 76: 954
2. Benet LZ, Babeazzi RL (1979) Noncompartmental determination of the steady-state volume of distribution. J Pharm Sci 68: 1071
3. Breen KJ, Bury R, Desmond PV, Mashford ML, Morphett B, Westwood B, Shaw RG (1982) Effects of cimetidine and ranitidine on hepatic drug metabolism. Clin Pharmacol Ther 31: 297
4. Brenner DE, Galloway S, Cooper J, Noone R, Hande KR (1985) Improved high performance liquid chromatography assay of doxorubicin: comparison of thin-layer chromatography. Cancer Chemother Pharmacol 14: 139
5. Brenner DE, Collins JC, Hande KR (1986) The effects of cimetidine upon plasma pharmacokinetics of doxorubicin in rabbits. Cancer Chemother Pharmacol 18: 219
6. Brenner DE, Anthony LB, Halter S, Harris NL, Collins JC, Hande KR (1987) Effect of allyl alcohol-induced sublethal hepatic damage upon doxorubicin metabolism and toxicity in rabbits. Cancer Res 47: 3259
7. Brenner LO (1986) Agranulocytosis and ranitidine. Ann Intern Med 104: 896
8. Chan KK, Chlebowski RT, Tong M, Chen G, Gross JF, Bateman JR (1980) Clinical pharmacokinetics of adriamycin in hepatoma patients with cirrhosis. Cancer Res 40: 1263
9. Daly MJ, Humphray JM, Stables R (1980) Inhibition of gastric acid secretion in the dog by the H_2-receptor antagonists ranitidine, cimetidine, and metiamide. Gut 21: 408
10. Danhof M, Breimer DD (1979) Studies on the different metabolic pathways of antipyrine in man: I. Oral administration of 250, 500 and 1000 mg to healthy volunteers. Br J Clin Pharmacol 8: 529
11. Desmond PV, Branch RA, Calder I, Schenker S (1980) Comparison of [^{14}C]phenacetin and amino [^{14}C]pyrine breath tests after acute and chronic liver injury in the rat. Proc Soc Exp Biol Med 164: 173
12. Dessypris EN, Brenner DE, Hande KR (1986) Toxicology of adriamycin metabolites to human marrow erythroid and myeloid progenitors in vitro. Cancer Treat Rep 70: 487
13. DiPalma JR (1971) Drill's pharmacology in medicine, 4th edn. McGraw-Hill, New York
14. Dixon WJ, Massey FJ (1969) Introduction to statistical analyses, 3rd edn. McGraw-Hill, New York
15. Donn KH, Powell JR, Rogers JF, Eshelman FN (1984) The influence of H_2-receptor antagonists on steady-state concentrations of propanolol and 4-hydroxypropanolol. J Clin Pharmacol 24: 500
16. Douglas WW (1985) Antacoids. In: Gilman AG, Goodman LS, Kall TW, Murad F (eds) The pharmacologic basis of therapeutics. MacMillan, New York, pp 624–627
17. Felsted RL, Bachur NR (1980) Mammalian carboxyl reductase. Drug Metab Rev 11: 1
18. Freireich EJ, Gehan EA, Rall DP, Schmidt LH, Skipper HE (1966) Quantitative comparison of toxicity of anticancer agents in mouse, rat, hamster, dog, monkey and man. Cancer Chemother Rep 50: 219
19. Freston JW (1982) Cimetidine: II. Adverse reactions and problems of use. Ann Intern Med 97: 728
20. Glaxo Inc. (1984) Zantac Injection, Product Information Sheet. Glaxo, Research Triangle Park, NC
21. Henry DA, MacDonald IA, Kitchinghan G, Bill GD, Langman MJS (1980) Cimetidine and ranitidine: comparison of effects on hepatic drug metabolism. Br Med J 281: 775
22. Hepner GW, Vesell ES (1974) Assessment of aminopyrine metabolism in man after oral administration of ^{14}C-aminopyrine. N Engl J Med 291: 1384
23. Hepner GW, Uhlin SR, Lipton A, Harvey HA, Rohrer GV (1976) Abnormal aminopyrine metabolism in patients with hepatic neoplasm. Detection by breath test. JAMA 235: 1587
24. Hoyumpa AM, Schenker S (1982) Major drug interactions: effect of liver disease, alcohol and malnutrition. Annu Rev Med 33: 113
25. Kirch W, Hoensch H, Janisch HD (1984) Interactions and noninteractions with ranitidine. Clin Pharmacokinet 9: 493
26. Oki T, Komiyama T, Tone H, Inui T (1977) Reductive cleavage of anthracycline glycosides by microsomal NADPH cytochrome c reductase. J Antibiot (Tokyo) 30: 613
27. Takanashi S, Bachur NR (1976) Adriamycin metabolism in man: evidence from urinary metabolites. Drug Metab Dispos 4: 79
28. Teunissen MWF, Spoelstra P, Koch CW, Weeda B, Van Duyn W, Janssens AR, Breimer DD (1984) Antipyrine clearance and metabolite formation in patients with alcoholic cirrhosis. Br J Clin Pharmacol 18: 707
29. Warren RD, Bender RA (1977) Drug interactions with antineoplastic agents. Cancer Treat Rep 61: 1231

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