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Pretreatment H_2 receptor antagonists that differ in P450 modulation activity: comparative effects on paclitaxel clearance rates and neutropenia

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Abstract Histamine-2 receptor antagonists (H_2RAs) are principal components of the premedication regimen used to prevent major hypersensitivity reactions in patients receiving paclitaxel. Several different H_2RAs, including cimetidine, ranitidine and famotidine, have been used in clinical trials of paclitaxel, as well as by clinicians in different geographic regions and hospitals primarily because of differences in the availability of the various H_2RAs. However, H_2RAs have highly variable cytochrome P450-modulating capabilities, and the P450 system appears to play a major role in paclitaxel metabolism and disposition. Therefore, the use of different H_2RAs may result in different pharmacologic, toxicologic and antitumor profiles due to differential effects on paclitaxel metabolism. This study evaluated whether cimetidine and famotidine, which possess disparate P450-modulating capabilities, differentially affect paclitaxel clearance rates and the agent's principal toxicity, neutropenia. Women with advanced, platinum-refractory ovarian carcinoma received two courses of treatment with 135 mg/m^2 paclitaxel over 24 h while participating in the National Cancer Institute's Treatment Referral Center Protocol. A crossover design was employed in which consecutive patients received either 300 mg cimetidine i.v. or 20 mg famotidine i.v. before their first course of paclitaxel and the alternate H_2RA before their second course. In order to evaluate the differential effects of cimetidine and famotidine on pertinent pharmacologic and toxicologic parameters in the same individual, paclitaxel concentrations at steady-state (Css), paclitaxel clearance rates, and absolute neutrophil counts (ANCs) were obtained during both courses. Paclitaxel Css values were not significantly different in individual patients when either cimetidine or famotidine preceded paclitaxel ($p = 0.16$). Mean paclitaxel clearance rates were 271 and 243 ml/min per m^2 following cimetidine and famotidine, respectively. These clearance rates were not significantly different in paired analysis ($p = 0.30$). The likelihood of subsequently requiring granulocyte-colony stimulating factor (G-CSF) for severe neutropenia during course 1 did not differ significantly between the two H_2RAs ($p = 0.9$). Among patients who did not require G-CSF, mean percentage decreases in ANC were 87.7% and 84.2% after paclitaxel cycles preceded by cimetidine and famotidine, respectively. These measures of neutropenia did not differ significantly in paired analysis ($p = 0.13$). These results show that the H_2RAs cimetidine and famotidine do not differentially affect the pharmacologic and toxicity profiles of paclitaxel when used in the premedication regimen to prevent major hypersensitivity reactions, and may be interchanged.

Key words Paclitaxel · H_2 antagonists · Cytochromes P450

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Introduction

Major hypersensitivity reactions (HSRs) were a major obstacle during the early development of the prototypic taxane antimicrotubule agent paclitaxel [20,29]. Although it is not clear whether paclitaxel itself or the major constituent of its excipient, Cremophor EL (polyoxyethylated castor oil), is responsible for HSRs, Cremophor EL, by inducing the direct release of histamine from circulating cells, is generally believed to be the cause [13,15,29]. The incidence of HSRs was subsequently reduced after the simultaneous institution of two empiric measures. The first of these is the use of a prolonged (24-h) infusion schedule and the second

is the use of a premedication regimen consisting of steroids, H_1-histamine receptor antagonists, and H_2-histamine receptor antagonists (H_2RA) since similar premedication regimens are successful in permitting retreatment of patients who previously had major HSRs after receiving iodinated radiocontrast agents [4]. The institution of these measures resulted in a substantial reduction in the incidence of major HSRs [20,29], permitting broad evaluations of paclitaxel and eventually leading to drug approval worldwide. However, the relative merits of each measure in reducing the incidence of HSRs were not entirely known until a study performed by the National Cancer Institute of Canada Clinical Trials Group demonstrated similar incidences of major HSRs in patients randomized to receive paclitaxel on either 3-or 24-h infusion schedules along with premedications, indicating that the premedication regimen was the more important prophylactic measure [26].

Although H_2RAs have been demonstrated to be partially responsible for the success of the premedication regimen in patients who are allergic to radiocontrast agents [8] and may confer a similar benefit in preventing HSRs associated with paclitaxel, different H_2RAs may inhibit many cytochrome P450-dependent hepatic metabolic processes to different extents, including hydroxylation reactions which are responsible for the bulk of paclitaxel's pharmacologic disposition in both rats and humans [6,10,17]. Unlike the H_2RAs ranitidine and famotidine that possess little or no P450-modulating activity, cimetidine is a potent inhibitor of cytochrome P450 systems [22,23,25]. By this mechanism, cimetidine decreases the clearance of many agents that are metabolized by P450-dependent processes, such as phenytoin and theophylline, which may lead to increased drug accumulation and toxicity [23]. Although cimetidine has been the most commonly used H_2RA for the prophylaxis of HSRs associated with paclitaxel, ranitidine and famotidine have also been used [16,21]. These agents are often not uniformly available between different geographic regions and even among hospitals in similar regions [1,24]. A potential source of drug interactions, different pharmacologic and toxicity profiles, and possibly different antitumor effects may be due to the differential effects of H_2RA premedications on the hepatic metabolism and biliary excretion of paclitaxel.

The purpose of this study was to evaluate the differential effects of the H_2RAs cimetidine and famotidine on the pharmacologic and toxicologic profiles of paclitaxel in women with advanced ovarian cancer using a prospective crossover design.

Patients and methods

Participation in this pharmacologic study was offered to consecutive women with advanced ovarian carcinoma who had previously consented to receive paclitaxel therapy through the National Cancer Institute Treatment Referral Center (TRC) protocol at The Johns Hopkins Oncology Center. This pharmacologic study enrolled patients from 1, July 1992 to 10, February 1993. Eligibility requirements and early results of the TRC protocol have been reported [27]. The TRC program required that patients had ovarian carcinoma which had progressed after at least three prior regimens of systemic therapy, including at least one platinum-based regimen. The protocol was later amended to allow entry of patients after only two prior regimens. Each patient provided written informed consent according to Federal and institutional guidelines before participating in both the TRC protocol and this pharmacologic study.

All patients were treated with 135 mg/m^2 paclitaxel as a 24-h continuous infusion, repeated every 21 days. The TRC protocol recommended a prophylactic regimen of 10 mg dexamethasone given orally 12 and 6 h prior to the start of the paclitaxel infusion, 50 mg diphenhydramine i.v. given 30 min prior to the start of paclitaxel and 300 mg cimetidine i.v. 30 min prior to paclitaxel. For patients on this study, 20 mg famotidine i.v. was substituted for cimetidine prior to one of the paclitaxel treatments. As required by the TRC protocol, patients who developed significant myelosuppression (white blood cell count (WBC) $< 1000/\mu l$ for > 7 days or failure to recover to WBC $> 4000/\mu l$ or absolute neutrophil count (ANC) $> 2000/\mu l$ by day 22 or occurrence of neutropenia with fever or sepsis) were treated with 5 μg/kg granulocyte-colony-stimulating factor (G-CS) subcutaneously daily until resolution of myelosuppression during subsequent courses of treatment. Clinical assessments were performed in accordance with the TRC recommendations. These included pretreatment and at least weekly measurement of total WBC and ANC.

The study was designed as a prospective crossover trial. Consecutive patients were assigned to alternate between treatment group A and group B. Group A patients received premedication for the first paclitaxel course according to the TRC recommendations; famotidine was substituted for cimetidine during the second course. Group B patients received the same treatments but in reverse order, i.e. famotidine preceded cimetidine.

Venous blood was sampled twice before the end of the 24-h infusion and the mean concentration was used to calculate total drug clearance. Plasma concentrations achieved at the end of 24-h infusions (C24h) have been calculated to be nearly equivalent to the steady-state concentrations (Css) (C24h = 0.97 Css) using the mean kinetic parameter values for drug disposition and elimination derived from early pharmacologic studies at the Johns Hopkins Oncology Center [14]. This Css value was then used to compute the plasma clearance rate of paclitaxel according to the expression, clearance rate = paclitaxel infusion rate/Css [21]. Paclitaxel concentrations were measured by a high performance liquid chromatography assay as described previously [14].

A target sample size of 30 patients was estimated to provide type I and II error rates of 0.05 and 0.2, respectively, based on an expected difference in paclitaxel concentrations of 0.1 μ*M* and an expected standard deviation 0.2 [12]. Data analyses were performed with SAS software for the PC version 6.0. The effects of H_2RA premedication and sequence were compared using the paired *t*-test (two tailed). The Chi-squared test was used to compare the number of patients in each group who required the use of hematopoietic growth factor support.

Results

Patient characteristics.

Of 28 consecutive patients who provided informed consent and participated in the TRC protocol also asked to participate in this study, 27 agreed to participate. Table 1 summarizes the ages, sites of disease, performance status and prior therapy of the participating patients. The median age was 56 (range 34–71)

Table 1 Patient characteristics

	N
Age (years)	
< 50	4
50–59	12
60–69	9
70 +	2
ECOG performance status	
0	7
1	9
2	6
3	5
Sites of tumor	
Intraabdominal Only	16
Intraabdominal + pleura	2
Intraabdominal + liver	2
Intraabdominal + subcutaneous	2
Intraabdominal + distant nodes	3
Intraabdominal + nodes + pleura	1
Intraabdominal + liver + pleura	1
Prior therapy	
Chemo only	15
Chemo + hormonal	9
Chemo + radiation	3

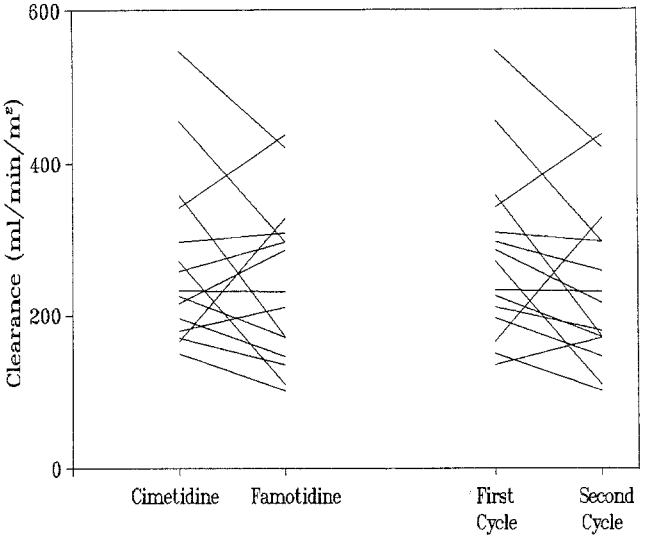

Fig. 1 Effects of H_2 antagonists and sequence on clearance rates of paclitaxel. Clearance rates were estimated from concentrations of paclitaxel measured at the end of infusion. Paired clearance rates for each of 15 patients are shown. The H_2 antagonists and sequence had no statistically significant effect on clearance rates

years. Of the 27 patients, 16 had intraabdominal disease only (stage III), and 11 had metastatic spread to other sites that included pleura, liver, lymph nodes and subcutaneous sites. All patients had had prior platinum-based therapy, with 12 having had two prior platinum-containing regimens. In addition, 11 patients had received at least two additional non-platinum-containing cytotoxic treatment regimens. Five patients had also received intraperitoneal chemotherapy, two patients had undergone high-dose chemotherapy with autologous marrow or stem cell support, nine patients had been previously treated with at least one hormonal treatment regimen and three patients had received radiation therapy to the abdomen or pelvis. The accrual target of 30 patients was not reached because paclitaxel was approved for general use by the Food and Drug Administration, and the TRC protocol was terminated.

Paclitaxel clearance

Of the 27 patients who participated in this study, 15 had complete plasma sampling performed for paclitaxel courses following both cimetidine and famotidine. A complete series of plasma samples was not obtained from the remaining 12 patients due to referral for treatment in the community following approval of the drug (4), failure to receive a second course due to progressive disease and/or a decline in overall clinical status (2), inappropriate sample collection or storage (3), interruption of a treatment course due to cardiac dysrhythmias (2), and dose reduction during the second course (1).

Paclitaxel Css values ranged from 0.20 to 1.07 μM. The mean and 95% confidence intervals for paclitaxel Css values after cimetidine and famotidine were 0.46 (0.37–0.55) μM and 0.55 (0.40–0.69) μM, respectively. These paclitaxel Css values did not differ for the two H_2RAs (paired $t = 1.48$, $p = 0.16$). Mean paclitaxel clearance rates and 95% confidence intervals were calculated to be 271 (208–334) ml/min per m^2 when paclitaxel followed cimetidine and 243 (184–301) ml/min per m^2 when paclitaxel followed famotidine.

Figure 1 shows the paired clearance rates as a function of the specific H_2RA that preceded paclitaxel. Differences in clearance rates between courses in which paclitaxel followed cimetidine and famotidine ($Cl_{cimetidine}$ - $Cl_{famotidine}$) had a mean of 28, a 95% confidence interval of − 28–83 and a range of − 161–186 ml/min per m^2. Analysis of paired clearance rates showed no significant differences for the different H_2RA ($t = 1.1$, $p = 0.30$). The data do not support the hypothesis that cimetidine and famotidine have differential effects on the clearance rates of paclitaxel.

The effect of order (first vs. second treatment course) on paclitaxel clearance was also examined. Paired analysis of paclitaxel clearance rates by order found no significant difference ($t = 1.8$, $p = 0.10$). Additionally, analysis of variance on unpaired clearances found no evidence of interaction between H_2RA and order. These findings do not support the hypothesis that sequence affects clearance rates.

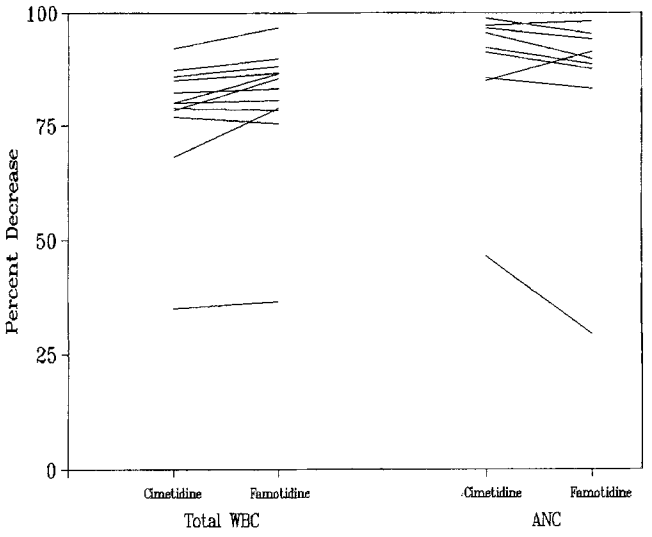

Fig. 2 Effect of H_2 antagonists on myclosuppression induced by paclitaxel. Percent decrease is the proportional change in total white blood count (WBC) or neutrophil count (ANC) from the start of each cycle of paclitaxel until the nadir. The H_2 antagonists had no statistically significant differential effect. Patients who received G-CSF are not shown

Myelosuppression

Of the 27 patients, 12 required support with G-CSF during the second treatment cycle and therefore paired samples were not comparable for quantitation of myelotoxicity. Paired pretreatment and nadir WBCs and ANCs were available for both courses administered to 12 and 9 patients, respectively, as shown in Fig. 2.

There was no association between the H_2RA administered during the first course and the likelihood of developing myelosuppression of sufficient severity to require G-CSF with the second course. Of 14 patients receiving famotidine with the first treatment cycle, 6 required growth factor, versus 6 of 13 with cimetidine ($s^2 = 0.02$, $p = 0.9$).

Among patients who did not require growth factor during course two, there was no significant difference in the percentage fall in absolute neutrophil count (100 − (100 × nadir ANC/pretreatment ANC)). The mean percentage decreases when paclitaxel followed cimetidine or famotidine were 87.7% and 84.2%, respectively. For the pairwise comparison in individual patients (%change $ANC_{cimetidine}$ -%change $ANC_{famotidine}$), the mean difference and 95% confidence interval were 3.5 (-1.3–8.3)%, a nonsignificant finding ($t = 1.7$, $p = 0.13$).

Discussion

This prospective crossover study addressed the concern that the administration of paclitaxel with different H_2RAs that have different P450-modulating capabilities may result in different degrees of drug interaction since hepatic cytochrome P450 enzymes appear to be involved in critical steps in the metabolism of paclitaxel. The study demonstrated that the pharmacologic and toxicity profiles of paclitaxel are similar following pretreatment with either of the H_2RAs cimetidine or famotidine which possess vastly different cytochrome P450-modulating capabilities.

The concern that significant interactions may occur between paclitaxel and H_2RAs, especially cimetidine, is based on the identification of hepatic P450 metabolism as a principal means of paclitaxel disposition in both humans and rodents [17,18]. Monsarrat et al. have reported that approximately 20% and 40% of a dose of paclitaxel administered to humans and rats, respectively, is excreted into the bile as both parent compound and metabolites during treatment and in the 24-h post-treatment period [17,18]. It is also possible that other as yet unidentified metabolites are similarly metabolized and excreted into the bile. More recently, Walle et al. and Gauer et al. reported the recovery of 75 ± 3% and 95% of total radioactivity in the feces of patients and rodents, respectively, collected 5–7 days after the administration of ^{3}H-paclitaxel [3,28]. To date, all human biliary metabolites identified have been hydroxylated derivatives, which initially suggests that hepatic P450 mixed function oxidases, which are generally involved in hepatic hydroxylation reactions, may play a major role in the metabolism of paclitaxel [17]. In recent studies with human liver microsomes, the cytochrome P450 enzyme family CYP3A has been shown to be responsible for detoxification of paclitaxel to its major metabolite, 6α-hydroxytaxol; the CYP2C and possibly other subfamilies contribute to the formation of minor hydroxylated metabolites [2,6,11]. Cimetidine may selectively inhibit CYP3A4 [5], an isoform which does not contribute to the hydroxylation of paclitaxel [11].

Several previous in vitro and clinical studies have also failed to demonstrate that cimetidine significantly affects the metabolic and pharmacologic behavior of paclitaxel. In a study in which ^{3}H-paclitaxel was incubated with human liver microsomes in vitro, cimetidine was shown not to inhibit the metabolism of ^{3}H-paclitaxel, whereas other modulators of P450 enzymes, such as ketoconazole and fluconazole, were inhibitory [7]. In addition, investigators have also failed to demonstrate that cimetidine alters the metabolism and biliary excretion of ^{3}H-paclitaxel in rats [9] and that large increases in the dose of cimetidine do not alter paclitaxel clearance rates [19]. Similarly, the overall excretion of unmetabolized paclitaxel and metabolites has not been demonstrated to be affected by pretreating rats with various inducers of the cytochrome P450 enzymes, including benzopyrene, troleandomycine, and phenobarbital, but the percentage of minor metabolites increases after pretreatment with phenobarbital [17].

This study used a crossover design, which has a greater statistical power than a prospective randomized design. Four potential sources of bias exist, but none of these appeared to have influenced the results. First, selection bias was unimportant since all patients eventually received both H_2RAs before paclitaxel. Second, order or carryover effects could have influenced the outcome if paclitaxel produces cumulative pharmacologic and toxicologic effects so that the second treatment may have been inherently associated with a different outcome compared with the initial treatment. Such effects were sought but were not apparent. Third, observer bias was probably not important due to the objectivity of the outcome variables such as paclitaxel Css, clearance rates and complete blood counts. Finally, the small sample size may be somewhat restrictive, especially with respect to the limited number of patients who had complete plasma sampling. However, the use of paired analyses in the same individuals reduced the potential impact of the small sample size. The power to detect toxicologic differences between cimetidine and famotidine was higher since a larger number of patients had paired toxicologic data available. The crossover design permitted paired comparisons, removing interindividual variability, and the intraindividual variance in the percentage decrease in ANCs was small. Since neutropenia was the most clinically relevant endpoint of the study, the existence of a clinically significant type II error is unlikely.

The results of this study indicate that H_2RAs with vastly different P450-modulating capabilities, such as cimetidine and famotidine, can be interchanged in the paclitaxel premedication regimen without significantly affecting the pharmacologic and toxicologic profiles of paclitaxel. Although this study design did not address differences in antitumor response, such an evaluation would require hundreds of patients, and important differences are unlikely in view of the lack of pharmacologic and toxicologic differences between H_2RAs. This study also provides indirect evidence that the modulatory effects of cimetidine on the metabolism of paclitaxel are not clinically significant, although the effects of chronic oral cimetidine administration are still undefined. Further studies are now required to expand the scant information available about the metabolism of paclitaxel and potential drug interactions.

References

1. Berkowitz HS (1992) Formulary designation of cimetidine as the primary intravenous histamine H2-receptor antagonist. Am J Hosp Pharm 49:134
2. Cresteil T, Monserrat B, Alvinerie P, et al (1994) Taxol metabolism by human liver microsomes: identification of cytochrome P450 isozymes involved in its biotransformation. Cancer Res 54:386
3. Gaver RC, Deeb G, Willey T, et al (1993) The disposition of paclitaxel (taxol) in the rat. Proc Am Assoc Cancer Res 34:390
4. Greenberger PA, Patterson R, Simon R, et al (1981) Pretreatment of high risk patients requiring radiographic contrast media studies. J Allergy Clin Immunol 67:185
5. Halpert JR, Guengerich FP, Bned JR, Correia MA (1994) Selective inhibitors of cytochromes P450. Toxicol Appl Pharmacol 125:163
6. Harris JW, Rahman A, Kim B-R, Guengerich P, Collins JM (1994) Metabolism of taxel by human microsomes and liver slices: participation of cytochrome P450 3A4 and an unknown P450 enzyme. Cancer Res 54:4026
7. Jamis-Dow CA, Klecker RW, Katki AG, et al (1993) Metabolism of taxol by human liver microsomes and effect of inhibitors. Proc Am Assoc Cancer Res 34:369
8. Kaliner M, Sigler R, Summers R. (1981) Effects of infused histamine: analysis of the effects of H1 and H2 histamine receptor antagonists on cardiovascular and pulmonary responses. J Allergy Clin Immunol 68:365
9. Klecker RW, Jamis-Dow CA, Egorin MJ, et al (1993) Distribution and metabolism of ^{3}H-taxol in the rat. Proc Am Assoc Cancer Res 34:380
10. Kumar GN, Oatis JE, Thornburg KR, et al (1994) 6α-Hydroxytaxol: isolation and identification of the major metabolite of taxol in human liver microsomes. Drug Metab Distrib 22:177
11. Kumar GN, Walle UK, Walle T (1994) Cytochrome P450 3A-mediated human liver microsomal taxol 6α-hydroxylation. J Pharmacol Exp Ther 268:1160
12. Lachin JM (1981) Introduction to sample size determination and power analysis for clinical trials. Control Clin Trials 2:93
13. Lassus M, Scott D, Leyland-Jones B (1985) Allergic reactions associated with cremophor containing antineoplastics. Proc Am Soc Clin Oncol 4:268
14. Longnecker SM, Donehower RC, Cates AE, et al (1987) High-performance liquid chromatographic assay for taxol in human plasma and urine and pharmacokinetics in a phase I trial. Cancer Treat Rep 71:53
15. Lorenz W, Reimann H-J, Schmal A, et al (1977) Histamine release in dogs by Cremophor EL and its derivatives: oxethylated oleic acid is the most effective constituent. Agents Actions 7:63
16. McGuire WP, Rowinsky EK, Rosenshein NB, et al (1989) Taxol: a unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms. Ann Intern Med 111:273
17. Monserrat B, Alvinerie P, Wright M, et al (1995) Hepatic metabolism and biliary excretion of taxol in rats and human. (in press)
18. Monsarrat B, Mariel E, Cros S, et al (1990) Taxol metabolism. Isolation and identification of three major metabolites of taxol in rat bile. Drug Metab Dispos Biol Fate Chem 18:895
19. Reed E, Sarosy G, Jamis-Dow C, et al (1993) Cimetidine does not influence taxol steady-state plasma levels. Proc Am Assoc Cancer Res 34:395
20. Rowinsky EK, Cazenave LA, Donehower RC (1990) Taxol: a novel investigational antineoplastic agent. J Natl Cancer Inst 82:1247–59
21. Rowinsky EK, Gilbert MR, McGuire WP, et al (1991) Sequences of taxol and cisplatin: A phase I and pharmacologic study. J Clin Oncol 9:1692
22. Sakaue H, Akamatsu K, Hirabayashi Y, et al (1987) Effects of prolonged oral cimetidine, ranitidine and famotidine therapy on antipyrine elimination. Clin Ther 9:602
23. Somogyi A, Muirhead M (1987) Pharmacokinetic interactions of cimetidine. Clin Pharmacokinet 12:321
24. Souney PF, Stoukides CA (1989) Pharmacoeconomic aspects and formulary considerations related to histamine 2-receptor antagonists. Drug Inf Clin Pharm 23 [suppl 10]:S29
25. Staiger CH, Korodnay B, Devries JX, et al (1984) Comparative effects of famotidine and cimetidine on antipyrine kinetics in healthy volunteers. Br J Clin Pharmacol 18:105

26. Swenerton K, Eisenhauer E, ten Bokkel Huinink W, et al (1993) Taxol in relapsed ovarian cancer: high versus low dose and short versus long infusion: A European-Canadian study coordinated by the NCI Canada Clinical Trials Group. Proc Am Soc Clin Oncol 12:256
27. Trimble EL, Adams JD, Vena D, et al (1993) Paclitaxel for platinum-refractory ovarian cancer: Results from the first 1,000 patients registered to National Cancer Institute Treatment Referral Center 9103. J Clin Oncol 11:2405
28. Walle T, Bhalla KN, Walle UK et al (1994) Taxol disposition in humans after tritium-labeled drug. Proc Am Soc Clin Oncol 13:404
29. Weiss RB, Donehower RC, Wiernik PH, et al (1990) Hypersensitivity reactions from taxol. J Clin Oncology 8:1263