Cimetidine-Drug Interactions

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The use of cimetidine, the histamine H_2 receptor antagonist, is associated with a relatively low incidence of adverse reactions. However, its liberal use has led to the identification of several clinically significant cimetidine-drug interactions that can lead to drug accumulation, toxicity, and life-threatening sequelae. A review of the literature and the clinical significance and physiologic basis of these interactions are presented. Recommended management of cimetidine-drug interactions is discussed.

Cimetidine, the histamine H_2 receptor antagonist, now the seventh most frequently prescribed drug in the United States [1], is used for the treatment of peptic ulcer disease, Zollinger-Ellison syndrome, systemic mastocytosis, multiple endocrine adenoma syndrome, reflux esophagitis, and prophylaxis of stress ulceration [2,3]. Although the use of cimetidine is associated with a relatively low incidence of side effects including mental confusion, bone marrow depression, gynecomastia, bradycardia, interstitial nephritis, and hepatotoxicity [4,5], its inhibition of drug metabolism frequently leads to accumulation and toxicity of other drugs. In addition, cimetidine interferes with gastrointestinal absorption and renal excretion of other pharmacologic agents and, thereby, may markedly influence their biologic effect. Since the extent of these pharmacokinetic drug interactions is not well appreciated [6–9], a review of the literature and the clinical significance of these interactions are presented.

EFFECTS OF CIMETIDINE ON THE ABSORPTION OF OTHER DRUGS

Cimetidine inhibits gastric acid secretion by virtue of its H_2 receptor blocking activity, which increases the pH of the stomach contents and proximal small bowel. An increased pH could lead to differences in the rate and extent of absorption of drugs that are destroyed at low pH or require low pH for disintegration or dissolution, and provides the theoretic basis for the following drug interactions.

Ketoconazole. Adequate absorption of ketoconazole, an orally administered, poorly water-soluble antifungal agent, occurs only at low gastric pH [10]. The concomitant use of cimetidine and antacids with ketoconazole in one patient with disseminated Cryptococcus neoformans resulted in subtherapeutic ketoconazole plasma concentrations and persistent fungal infection [10]. Control of infection was achieved after cimetidine was discontinued, and further studies [10] in normal volunteers demonstrated that cimetidine given with ketoconazole resulted in a 65 percent reduction in ketoconazole systemic availability and a fivefold decrease in peak plasma level. Cimetidine presumably interfered with the acid milieu required for dissolution and

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subsequent absorption of this drug, since the administration of ketoconazole in acidic solution to patients receiving cimetidine resulted in excellent ketoconazole availability and peak plasma concentrations. Therefore, the concomitant use of ketoconazole and cimetidine should be avoided because of the potential for inadequate gastrointestinal absorption, or ketoconazole should be administered in an acidic solution if both drugs must be given together.

Penicillin. An eightfold increase in penicillin absorption was noted in one patient after sodium benzylpenicillin was given with cimetidine [11]. Although significant increases in penicillin absorption were not observed in four other subjects [11], these data suggest that cimetidine may lead to the increased absorption of acid labile drugs. Additional support for this theory is derived from the use of cimetidine to protect the activity of orally ingested enzymes in patients with severe pancreatic insufficiency, whose condition has failed to respond to pancreatic enzyme replacement alone [12].

Other Drugs. Surprisingly, cimetidine has been reported to have little effect on the absorption of other drugs. The absorption of digoxin [13], ampicillin [14], cotrimoxazole [14], and prednisolone [15] is unaffected. Inconclusive results have been reported regarding the effect of cimetidine on the absorption of tetracycline [16–18] and aspirin [19], but it appears that cimetidine has no clinically significant impact on the gastrointestinal absorption of these drugs.

EFFECTS OF CIMETIDINE ON THE METABOLISM OF OTHER DRUGS

Most significant drug interactions that have been reported during cimetidine therapy result from its inhibition of hepatic drug metabolism [9]. The interaction of cimetidine with liver microsomal enzymes, specifically cytochrome P-450, often has resulted in decreased hepatic clearance of poorly extracted drugs, whereas a reduction in hepatic blood flow [20], attributed to a blockade of vascular H_2 receptors, is predominantly responsible for decreased metabolism of drugs that are highly extracted by the liver. These two mechanisms of metabolic inhibition provide the basis for the following cimetidine-drug interactions.

Low-Clearance Drugs. Oral anticoagulants: Several authors [21–29] have demonstrated a doubling of serum warfarin concentration and a marked increase, 20 to 200 percent, in prothrombin time in patients given cimetidine who had previously received long-term anticoagulant therapy with warfarin alone. Clinical manifestations of excessive anticoagulation included soft tissue and urinary tract hemorrhage [21,24,25], which occasionally required hospitalization, and because of the narrow therapeutic index for oral anticoagulants, it is recommended that coagulation parameters be closely monitored in patients receiving these agents when cimetidine therapy is initiated or discontinued.

Enzymatic conversion of the cimetidine side chain thioether moiety to the sulfoxide metabolite [4,30] by the hepatic mixed function oxidase system is responsible for about 30 percent of total cimetidine plasma clearance. Warfarin apparently is metabolized by this same microsomal enzyme system, and a number of studies [31–35] have demonstrated that excessive anticoagulation results from competitive inhibition of warfarin metabolism by cimetidine. This action does not appear to be a function of H_2 receptor blockade, since ranitidine, a structurally dissimilar H_2 antagonist, has no effect on drug metabolism when given in equipotent doses [36,37]. It appears that the unique cimetidine structure facilitates binding to cytochrome P-450-dependent microsomal enzymes and thereby inhibits drug metabolism [36,37].

Benzodiazepines: Patients treated with cimetidine for peptic ulcer disease often receive benzodiazepines at the same time, and a potentiation of the sedative effects of these compounds has often been observed when cimetidine was added. Cimetidine was shown to impair the hepatic metabolism of diazepam [38–44], desmethyldiazepam [45], and chlordiazepoxide [46,47], which provided an explanation of the prolonged sedation seen in these patients. A 15 to 63 percent reduction in plasma clearance and a 1.2- to 2.0-fold increase in steady-state serum concentration were noted when these compounds were given with cimetidine. Moreover, altered drug disposition was closely associated with a change in drug pharmacodynamics; i.e., diazepam and desmethyldiazepam given to subjects without cimetidine resulted in mild sedation, whereas the concomitant administration of cimetidine produced marked sedation in these same patients [38,45]. Impaired formation of the N-dealkylated chlordiazepoxide metabolite was demonstrated [46], and this again suggested that the cytochrome P-450 microsomal enzyme system was responsible for these drug biotransformations. This proposed mechanism of metabolic inhibition also has been supported by the work of other authors [32–35]. Changes in plasma clearance or blood concentration have not been reported following the administration of oxazepam or lorazepam along with cimetidine to human subjects [45,48]. These drugs are eliminated exclusively from human serum after conjugation with glucuronic acid. Glucuronidation appears to be independent of cytochrome P-450, and this led to the hypothesis that cimetidine selectively impairs cytochrome P-450-dependent microsomal biotransformations while sparing cytochrome P-450-independent

conjugation reactions. An analogous sparing of glucuronidation also has been reported [49,50] in patients with liver disease, and it has been suggested that oxazepam or lorazepam rather than diazepam or chlordiazepoxide be used in patients receiving cimetidine or in those with liver disease, especially elderly patients or those with other diseases who may be more sensitive to the sedative effects of benzodiazepines. Based on theoretic considerations, benzodiazepines, which have not been studied but which undergo cytochrome P-450-dependent microsomal metabolism, such as prazepam and chlorazepate, also may be contraindicated in these same patients [43].

Patients who must be given cimetidine and benzodiazepines should be treated with oxazepam, lorazepam, or may require reduced amounts of diazepam, desmethyldiazepam, or chlordiazepoxide.

Theophylline: Patients with asthma and chronic obstructive pulmonary disease are frequently treated with the bronchodilator theophylline and/or corticosteroids. Because both drugs may result in exacerbations of peptic ulcer disease, these same patients often are given cimetidine for amelioration of symptoms. Decreases in theophylline clearance, and a two- to threefold increase of theophylline serum concentration have been reported [51–60] after cimetidine was given to patients along with theophylline, when compared with those given theophylline alone. Since theophylline has a narrow therapeutic range and excessive levels may result in seizures [55] and death, a 50 percent reduction in theophylline dosage should be considered when both drugs are to be given together. Serum theophylline concentrations may serve as a guide for further dosage adjustment.

Anticonvulsants: Several authors [61–65] have shown that plasma phenytoin levels increase by 13 to 60 percent after administration of cimetidine. Mild symptoms of phenytoin intoxication developed in one patient [63], and resolved when cimetidine was discontinued. The mechanism of drug interaction remains unknown, but Hetzel et al [63] demonstrated that inhibition of the metabolic conversion of phenytoin to its major metabolite, 5-(p-hydroxyphenyl)-5-phenylhydantoin, was unlikely.

A 50 percent increase in carbamazepine serum concentration has been reported [66] in one patient treated with cimetidine in addition to carbamazepine. Elevated drug concentration and toxicity manifested by dizziness, somnolence, nystagmus, and vomiting resolved after cimetidine was discontinued. Although cimetidine alone may have been responsible for the neurologic changes, increased carbamazepine concentration may have been a contributing factor.

Patients who receive phenytoin or carbamazepine with cimetidine should be closely observed for symptoms of drug toxicity. Anticonvulsant serum concentrations should be monitored for several days following the initiation of cimetidine therapy and used to guide therapy.

Other drugs: Interaction of cimetidine with caffeine [67–69], phenacetin [68], and quinidine/digitoxin [70] has been described but needs to be further investigated to determine the clinical significance.

High-Clearance Drugs. Lidocaine: Cimetidine reduced the systemic clearance of lidocaine by 25 percent in one study [71], and other authors [72,73] reported a statistically significant 46 to 75 percent increase in steady-state lidocaine serum levels after administration of cimetidine, 300 mg orally every six hours. Increased lidocaine toxicity was noted during cimetidine administration [71,73] and, in view of this drug's low therapeutic index, these authors [71–73] have recommended that patients receiving lidocaine with cimetidine be given reduced doses of lidocaine and have serum lidocaine levels monitored frequently to prevent toxicity. Initially, a standard lidocaine loading dose followed by a 50 percent reduction of maintenance infusion rate is recommended.

Beta-blocking agents: A 33 percent reduction of liver blood flow and direct inhibition of microsomal enzymes have been demonstrated to produce a 27 percent reduction in propranolol clearance [20]. Decreased clearance of propranolol after administration of cimetidine resulted in a two- to threefold higher propranolol blood concentration than after administration of propranolol alone [74–76], and in one study [20] these increased blood levels were manifested clinically by significant reduction in resting heart rate. However, Warburton et al [77] have reported no alteration of heart rate or blood pressure response to treadmill exercise after cimetidine was given with propranolol.

Although one study [20] demonstrated no change in the availability of propranolol after cimetidine therapy, other authors [74,75,78] suggested that cimetidine may markedly increase the bioavailability of propranolol and metoprolol. Another study [79] has documented a doubling of the bioavailability of labetalol, a similar beta-blocking agent.

Therefore, it appears that cimetidine not only inhibits metabolism of beta-blocking agents after entry into the circulation but also may increase bioavailability of these drugs by decreasing first pass hepatic extraction. Both phenomena would lead to increased blood concentration and presumably greater therapeutic effect, but further studies are needed to determine the clinical significance of these changes.

Chlormethiazole: The clearance of chlormethia-

TABLE I Management of Drug Interactions with Cimetidine

Drug	Management
Ketoconazole	Use antacids instead of cimetidine and administer ketoconazole two hours prior to doses of antacids. If cimetidine is required, give ketoconazole in an acidic solution and monitor antifungal serum concentration.
Warfarin	Monitor prothrombin times for two weeks after cimetidine administration is begun and adjust warfarin dose accordingly.
Diazepam, desmethyldiazepam, and chlordiazepoxide	Titrate dosage based on degree of sedation, or substitute oxazepam or lorazepam.
Theophylline	Initially halve theophylline maintenance dose and use serum concentration and clinical parameters as guides to therapy. No loading dose adjustment is required.
Phenytoin and carbamazepine	Reduce maintenance dosage by 33 percent. Observe patients for toxicity and monitor serum concentrations for 10 days after cimetidine administration is begun. Loading doses remain unchanged.
Lidocaine	Use standard loading dose followed by a 50 percent reduction of maintenance infusion rate. Adjust dosage according to clinical parameters and serum lidocaine concentration.
Propranolol, metoprolol, and labetalol	Reduce dosage based on clinical parameters, or avoid interaction by use of nadolol or atenolol.
Chlormethiazole	Reduce dosage based on degree of sedation.

zole, a sedative-anticonvulsant agent, was reduced to 69 percent of pretreatment values by the co-administration of cimetidine [80,81]. Moreover, cimetidine-induced alterations in the disposition of chlormethiazole resulted in increased pharmacologic effect. Subjects slept for 30 to 60 minutes following the administration of chlormethiazole alone, whereas sleep persisted for two hours or more after chlormethiazole was given with cimetidine. Therefore, the use of cimetidine with chlormethiazole may lead to excessive sedation and respiratory depression.

Morphine: A potentially lethal adverse reaction manifested by apnea, confusion, and disorientation was described in a single patient [82] following the administration of morphine with cimetidine. Symptoms remitted with nalaxone and did not occur with the use of morphine alone. Although the mechanism of morphine potentiation remains unknown [82–86], several authors have suggested that cimetidine may interfere with the hepatic extraction of this highly cleared drug and, thereby, produces excessive morphine serum concentration.

EFFECTS OF CIMETIDINE ON THE RENAL EXCRETION OF OTHER DRUGS

Sixty percent of cimetidine is excreted unchanged in the urine [4,30] and a renal clearance in excess of 400 ml per minute [30] suggests the presence of extensive renal tubular secretion in addition to glomerular filtration. Tubular secretion provides a theoretic site for drug-drug interaction and may explain small increases in serum creatinine concentrations that have been reported [3,4] in patients treated with cimetidine. Decreased renal blood flow or glomerular filtration rate apparently is not responsible for increased serum creatinine concentration, since cimetidine therapy has no effect on inulin or para-aminohippuric acid clearance [87]. However, creatinine clearance was decreased after administration of cimetidine in these same subjects [87]. In normal humans, glomerular filtration rate measured by creatinine clearance is greater than that measured by inulin clearance, presumably due to the tubular secretion of creatinine. Therefore, decreased creatinine clearance, in conjunction with a normal inulin clearance, suggests that increased serum creatinine concentrations observed in patients treated with cimetidine may be the result of cimetidine-creatinine interaction at the tubular secretion site. In addition, another study [88] indicated that cimetidine may interact with a variety of basic drugs at the level of the renal tubule.

Renal insufficiency resulting from cimetidine-induced interstitial nephritis has been reported [89,90], and could lead to increased serum concentrations of renally excreted drugs.

SUMMARY

Cimetidine is a widely used H_2 receptor antagonist and, although not highly toxic by itself, its effects on hepatic microsomal enzymes and liver blood flow appear to predispose it to interactions with drugs that are inactivated by the liver. These interactions can lead to drug accumulation, toxicity, and may be responsible for life-threatening sequelae. Patients who receive cimetidine with other medications known to interact with cimetidine may require close observation for signs of toxicity, and/or monitoring of serum drug concentrations. Dosage reduction or use of alternative drugs may minimize adverse reactions in these patients. Several management recommendations are summarized in **Table I.**

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