Cimetidine Drug Interactions

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Cimetidine is a widely used antiulcer medication that is also a potent inhibitor of the mixed-function oxidase enzymes in the liver. This effect results in a number of clinically important interactions with other drugs, which are now being appreciated. Other effects of cimetidine, such as raising of gastric pH, alteration of liver blood flow, or alterations in renal secretory mechanisms, may also contribute to or result in clinically significant interactions. Current data document appreciable alterations in the metabolism or excretion of warfarin, theophylline, phenytoin, lidocaine, certain β-adrenoceptor antagonists, certain benzodiazepines, and probably narcotic analgesics and procainamide. Thus, effects of these drugs and serum levels, where available, should be more closely followed when used in combination with cimetidine. Cimetidine appears to exacerbate the myelosuppressive effects of the nitrosoureas, and may also significantly alter the absorption of ketoconazole. Though other drugs may affect the absorption or elimination of cimetidine, the clinical implication of these effects is uncertain.

Cimetidine (Tagamet, Smith Kline & French) is a widely prescribed histamine H_2-receptor antagonist with demonstrated efficacy in a number of disorders related to gastrointestinal acid output.[1] Numerous literature reports and trials describe a widespread use of cimetidine for FDA-approved and other indications.[2-4] Recent estimations place cimetidine as the ninth most widely prescribed drug in the United States in terms of retail sales.[5] Because of this common use and its long-term administration in many patients, there is a great potential for the interaction of cimetidine with other drugs that may be concomitantly administered. A recent survey of cimetidine use on the surgical-care areas of one large hospital indicated that 25 percent of 101 patients on cimetidine received other drugs that have been documented to interact adversely (unpublished data, W.L. Greene). The purpose of this review is to bring attention to the potential for unsuspected adverse effects of other drugs due to cimetidine interaction.

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Metabolic Effects of Cimetidine

Following oral absorption or parenteral administration of the drug, approximately 50 to 70 percent is excreted unchanged in the urine.[1] A significant amount of hepatic handling of cimetidine occurs, and it has been demonstrated that binding to liver microsomal enzymes takes place, specifically involving cytochrome P-450 and P-448.[6,7] Mixed-function oxidase enzymes located in hepatic smooth endoplasmic reticulum[8] are involved in the degradation of many drugs; therefore, the potential exists for cimetidine to inhibit the clearance of other drugs metabolized by these mixed-function oxidase enzymes. The inhibition that results is competitive[9] and is thought to be secondary to an increased affinity of cimetidine for the enzyme complexes.

A number of factors determine the extent of drug metabolism and, hence, the significance of interaction. Increased lipid solubility promotes penetration of the drug into the smooth endoplasmic reticulum, thus facilitating the interaction of enzyme and drug substrate.[8] Other factors directly relating to hepatic drug metabolism include the concentration of the cytochrome complexes and their affinity for the specific drugs, patient sex,[10,11] age,[11-13] smoking history,[13] nutritional status,[14] environmental exposure,[15] and other drug use.[16] Thus, each of these factors may affect the interaction of the enzyme system with cimetidine and other drugs. It is prudent to recall these factors when evaluating any potential drug-drug interaction mediated through metabolic effects.

Documented Cimetidine Interactions

Cimetidine and Warfarin

Data suggesting an interaction between cimetidine and warfarin first appeared in the literature in 1978. At that time, Smith Kline & French Laboratories reported evidence that the addition of a cimetidine dose of 1 g/d to patients receiving a stable dose of warfarin might result in an approximate 20 percent increase in both the prothrombin time and ratio.[17] Other reports soon followed. For example, Serlin and his cohorts[18] observed the effect of cimetidine on warfarin concentration and prothrombin time in seven normal volunteers. These subjects received warfarin in doses to prolong their prothrombin time three to five seconds above baseline for two weeks. Addition of 1,000 mg/d of cimetidine for three weeks significantly prolonged the prothrombin time (mean increase from 19.4 to 22.9 seconds) and plasma warfarin concentration by the end of the first week. Discontinuation of cimetidine resulted in return of prothrombin time and warfarin concentration to pretreatment levels within ten days. The authors suggested inhibition of metabolism as the mechanism of interaction and recommended caution in the use of warfarin in the presence of cimetidine.

It has been noted that the inhibition of warfarin metabolism may be related to the dose of cimetidine used. Administration of 800 to 1,000 mg/d was found to increase the prothrombin-time ratio by 40 to 50 percent in the presence of warfarin; however, 400 mg daily at bedtime resulted in only a 10 percent increase, as noted by Hetzel et al.[19]

The evidence indicates a clinically appreciable adverse interaction between cimetidine and warfarin that is due to the narrow therapeutic index seen with warfarin. If warfarin is to be used at all in the presence of cimetidine, a significant dose reduction of as much as 50 percent is recommended. The dose can then be titrated to the desired effect. Any patient receiving the two agents should not be discharged from close observation and monitoring of the prothrombin time until it is documented that consecutive clotting times are stable and within the desired range while on both agents. Likewise, a similar upward warfarin dosage revision may be necessary to continue adequate anticoagulation following discontinuation of cimetidine. Interestingly, another oral anticoagulant agent, phenprocoumon, is not adversely affected by cimetidine.[20] This drug, little used in the United States, is eliminated by glucuronidation, thus bypassing the potential adverse effects of cimetidine.

Cimetidine and β-Adrenergic Receptor Blocking Agents

Following the observation that profound sinus bradycardia had occurred in a patient taking cimetidine and propranolol, Donovan and associates[21] examined the effects of the combination in a 54-year-old man with an ulcer. They found that the

area under the plasma propranolol concentration-time curve increased by 340 percent in the presence of cimetidine. Later another study was undertaken to investigate the effect of 1 g of cimetidine per day on the oral disposition of 80 mg of propranolol in six peptic ulcer patients.[22] These investigators noted an elevated peak concentration as well as a significantly increased (by 61 percent) area under the propranolol plasma concentration-time curve (AUC) in the presence of cimetidine. No half-life was estimated, and the data were interpreted to reflect a decrease in first-pass extraction of propranolol by cimetidine.

The most comprehensive investigation of the effect of cimetidine on propranolol disposition was undertaken by Feely and associates.[9] Eight healthy subjects were given 80 mg of propranolol before and after one week of treatment with 1,200 mg of cimetidine per day. A significant decrease in the clearances of oral and parenteral propranolol was noted, the extent of which was dependent on plasma cimetidine concentration. Resting pulse rates were also significantly lower during concomitant treatment. Hepatic blood flow was noted by these authors to be decreased by approximately 25 percent in the presence of cimetidine.

Kirch and cohorts[23] investigated the effect of cimetidine on the pharmacokinetics of metoprolol and atenolol as well as propranolol. Six healthy volunteers were treated for seven days with one of these drugs before addition of 1 g of cimetidine per day for seven days. Combined therapy resulted in significantly elevated ($P < .05$) peak concentrations and AUCs for metoprolol and propranolol. No effect was noticed with atenolol. There was also no noticed effect of the combination on inhibition of exercise-induced tachycardia in either of the groups. In contrast to this report, Houtzagers and colleagues[24] found no effect of cimetidine upon metoprolol kinetics, but they found a slight prolongation of atenolol elimination half-life for patients treated concomitantly with these agents and cimetidine. Further delineation of the effect of cimetidine on these drugs is warranted.

It is well demonstrated that clearance of propranolol is decreased by concomitant cimetidine use. Further studies are needed to clarify the effect of cimetidine on the disposition of metoprolol and atenolol. However, clinical effects have been noted, and it is therefore prudent to monitor appropriately patients on combined therapy.

Cimetidine and Theophylline

The possibility that theophylline elimination may be impaired by cimetidine is not surprising since theophylline is eliminated substantially by hepatic metabolism.[25,26]

Jackson and co-workers[27] investigated the change in theophylline elimination half-life produced by two days' treatment with 1,200 mg of cimetidine per day. Five healthy nonsmoking adults were given 6 mg/kg of theophylline before and after cimetidine treatment. Elimination half-life increased by a mean of 60 percent (range from 23 to 104 percent). A follow-up study using the same protocol found that theophylline clearance was significantly decreased (mean, 39 percent), with no change in the volume of distribution.[28] Elimination half-life was elevated from a mean of 7.6 hours to 13.1 hours. All subjects experienced a change in clearance.

Three patients observed by Wood et al[29] receiving chronic theophylline therapy also demonstrated a decrease in theophylline clearance from a mean of 42.9 to 30.2 mL/min after five days' treatment with cimetidine. Other patients have been observed with a noted similar interaction, as reported by Campbell et al[30] and Weinberger et al.[31]

Recommendations concerning the use of cimetidine-theophylline combination should include the use of caution, with frequent patient assessment and theophylline plasma concentration monitoring and appropriate dose adjustment.

Cimetidine and Benzodiazepines

A number of studies and reports have addressed the effects of cimetidine on the various benzodiazepines. Klotz and associates[32,33] determined in two separate reports that cimetidine significantly decreased clearance and increased elimination half-life of diazepam in healthy volunteers by an average of 47 and 63 percent, respectively. Likewise, the same effects were observed with desmethyldiazepam, the primary metabolite of diazepam.[34]

Chlordiazepoxide has also been found to be affected by cimetidine. Desmond and associates[35] determined that 1,200 mg of cimetidine per day increased elimination half-life (from 10 to 24 hours) and decreased clearance (from 0.38 to

0.14 mL/min/kg) of chlordiazepoxide in eight healthy volunteers. The mechanism involved was thought to be decreased demethylation of the drug. Oxazepam and lorazepam, which only undergo glucuronidation, seem to be spared the effect of cimetidine. Patwardhan et al[36] examined the combination of lorazepam or oxazepam plus 1,200 mg of cimetidine per day in eight normal subjects. Their results show that there were no significant changes in elimination half-life or any other kinetic parameters for either drug in combination. The lack of effect of cimetidine on oxazepam has been confirmed by Klotz and Reimann,[34] who also found no significant changes in elimination half-life and clearance of oxazepam in combination.

The interaction with diazepam and chlordiazepoxide results in clinically appreciable increased sedation, and there appears to be no interaction with oxazepam or lorazepam. On this basis it is recommended that when a benzodiazepine is needed in combination with cimetidine, oxazepam or lorazepam should be considered as agents of first choice.[37]

Cimetidine and Anticonvulsants

Another drug with a narrow therapeutic index that has been found to be affected by cimetidine is phenytoin. In four epileptic patients stabilized on phenytoin and other anticonvulsants, treatment with 1 g of cimetidine per day for six days resulted in an elevation of serum phenytoin concentration from 13 to 33 percent over pretreatment values.[38] All these levels dropped to near baseline after cessation of cimetidine. One patient experienced symptoms consistent with mild phenytoin toxicity during cimetidine therapy; these symptoms resolved upon removal of cimetidine.

The most comprehensive investigation of the effect of cimetidine on phenytoin pharmacokinetics was conducted in nine patients receiving phenytoin for reasons not related to seizure disorders.[39] The authors of this study examined anticonvulsant concentrations before and after three weeks of therapy with 1 g of cimetidine per day. Results of this study showed that mean steady-state phenytoin concentration increased significantly by 57 percent (from 5.7 to 9.0 mg/L) after two weeks' therapy with cimetidine. Two weeks following cessation of cimetidine, anticonvulsant concentration returned to baseline. In addition, while the antipyrine elimination rate was increased by phenytoin alone, coadministration of cimetidine decreased its clearance significantly ($P < .01$) in all patients. Based on these results, the authors concluded that cimetidine exerts a significant effect on phenytoin concentrations, most likely through inhibition of metabolism.

Carbamazepine is another anticonvulsant that has been reported to be affected by cimetidine. A case report by Telerman-Toppet et al[40] describes an elderly woman with trigeminal neuralgia well controlled by carbamazepine. Following addition of 1.6 g of cimetidine per day, the patient developed symptoms consistent with carbamazepine toxicity, with a plasma carbamazepine concentration of 10.5 μg/mL. Withdrawal of cimetidine resulted in serum concentrations between 5.7 and 6.8 μg/mL, with resolution of the patient's clinical status.

Thus there is strong evidence to implicate cimetidine as an interacting agent with phenytoin and probably with carbamazepine. Further studies are needed to adequately describe the dynamics, but because of the narrow therapeutic index of these drugs, cimetidine is best used with phenytoin and carbamazepine only under close monitoring.

Cimetidine and Lidocaine

Since the metabolism of lidocaine is dependent on hepatic blood flow as well as enzyme activity, and cimetidine appears to affect these parameters, it is logical to assume a high potential for an interaction. Recent evidence has been published that verifies this assumption. Knapp and cohorts[41] have documented a significant elevation (mean increase of 29 to 46 percent) of lidocaine serum concentration in six patients following administration of 1,200 mg of cimetidine divided into four doses. Other work by Feely et al[42] has further documented the significance of this interaction. Elimination half-life, peak serum concentration, free drug concentration, and adverse effects were all significantly increased when cimetidine was combined with lidocaine. These results definitely implicate the multifactorial interaction of cimetidine with lidocaine. Obviously, caution must be used if

lidocaine is to be used in the presence of cimetidine, even on a short-term basis.

Cimetidine and Narcotic Analgesics

The first report of an apparently significant interaction between cimetidine and narcotic analgesics concerned the use of morphine. Fine and Churchill[43] described a 46-year-old patient with chronic renal failure who was intermittently receiving "large amounts" of parenteral narcotics for hip and leg pain control: up to nine doses of 10 mg of morphine intramuscularly every three hours with no adverse effects noted. Following development of a bleeding gastric ulcer, treatment with 300 mg of cimetidine three times daily was begun. Shortly thereafter, 15 mg of morphine given intramuscularly every four hours was begun, and after the sixth dose of morphine the patient became apneic and had a grand mal seizure. Administration of naloxone and withdrawal of cimetidine resulted in eventual resolution for this patient. Later in the same hospital admission the patient required surgical revision of a leg stump, and cimetidine was reinstated at 150 mg twice daily. Postoperative pain required administration of seven doses of opium alkaloid mixture, which resulted in apnea, confusion, disorientation, and diffuse muscle twitching after the final dose. Administration of naloxone again resulted in resolution and eventual full recovery of the patient.

Other reports have confirmed the potential for significant interaction between narcotics and cimetidine. Lam,[44] for example, reported that a group of subjects in his ongoing study were more susceptible to respiratory depressive effects of morphine in the presence of cimetidine.

In the patient receiving either morphine or meperidine in the presence of cimetidine, the clinician must monitor closely for unfavorable drug interaction. This consideration is especially important in the patient likely to have relatively high serum cimetidine concentrations, ie, the patient with renal failure.

Other Antiarrhythmics

A recent report has implicated a potentially significant interaction between cimetidine and procainamide.[45] In this report, six healthy volunteers were given 1 g of procainamide before and during one day of treatment with 1 g of cimetidine per day. Area under the plasma concentration-time curve increased by 35 percent for procainamide, and by 25 percent for its metabolite, N-acetylprocainamide. A concomitant elevation in mean procainamide half-life from 2.9 to 3.8 hours occurred. These authors noted that the mechanism of interaction appeared to be a reduced renal clearance of drug, which dropped by 43 percent upon cimetidine administration. Apparently, reduced renal drug clearance was secondary to either cimetidine-induced reduction in renal blood flow, competition for active tubular secretion, or both, since cimetidine has been demonstrated to affect renal elimination of creatinine by each of these mechanisms.[46]

Because of the potential mechanisms of interaction via hepatic or renal interference, cimetidine might also be expected to interfere with the elimination of other antiarrhythmics. Quinidine, which is hepatically metabolized,[47] and disopyramide, which is primarily eliminated through renal excretion,[47] are two commonly used agents in particular that may be expected to be affected by cimetidine. However, no data exist on this possibility.

Other Interactions

Other interactions involving cimetidine have been documented and may involve various other mechanisms as well as an effect on enzyme activity or hepatic blood flow. Cimetidine has been shown to decrease the elimination of both alcohol[48] and caffeine,[49] with some slight increases in noted effects of the drugs. The significance of these findings is unknown. Of particular worry is the risk of apparent synergistic bone-marrow suppression when cimetidine is given in the presence of other suppressive agents, such as the nitrosoureas[50,51] or even chloramphenicol.[52] In addition, ketoconazole absorption is significantly decreased by cimetidine.[53]

Metoclopramide, propantheline, and antacids[54] seem to inhibit cimetidine absorption. Chronic administration of phenobarbital apparently leads to decreased absorption and increased elimination

Table 1. Effect of Cimetidine on the Elimination or Effects of Various Drugs

Drugs	Probable Mechanism	Serum Concentrations Commonly Assessable	References
Warfarin	HM	Y	18,19
Propranolol	HB,HM	N	9,21-23
Metoprolol	?HB,?HM	N	23,24
Theophylline	HM	Y	27-31
Diazepam	HM	N	32,33,37
Chlordiazepoxide	HM	N	35
Phenytoin	HM	Y	38,39
Carbamazepine	?	Y	40
Lidocaine	HM,HB	Y	41,42
Procainamide	RE	Y	45
Morphine	HB	N	43,44
Nitrosoureas	Tox	N	50,51
Chloramphenicol	Tox	N	52
Ketoconazole	ABS	N	53

Key:
RE—decreased renal excretion
HM—inhibits hepatic metabolism
HB—decreases hepatic blood flow
ABS—decreases absorption
Tox—possibly additive or synergistic direct toxicity
Y—yes
N—no

of cimetidine and may result in delayed onset of cimetidine effect.[55]

Summary

Cimetidine is a drug that affects the management of a number of agents primarily by means of competitive inhibition for hepatic metabolism (Table 1). Other mechanisms, such as the effect of cimetidine on gastric pH, alteration of liver blood flow, or alterations in renal handling, may also contribute to realized interactions. Clinically important interactions involve warfarin, bone marrow depressants, theophylline, phenytoin, lidocaine, and probably procainamide. When cimetidine is used concomitantly with these agents, serum concentrations and clinical effects should be closely monitored, and doses adjusted accordingly. Cimetidine should be avoided in the patient treated with warfarin or nitrosoureas because of the increased risk of severe side effects from the anticoagulant and the risk of bone marrow suppression with the myelotoxic agent. Combination with compounds such as the β-adrenergic receptor blocking agents, narcotic analgesics, and benzodiazepines also results in clinically detectable effects, and patients should be more closely monitored. Apparently the β-blocker atenolol, possibly metoprolol, and the benzodiazepines oxazepam and lorazepam are not affected by cimetidine. The effects of cimetidine on the absorption of other drugs is probably not important, with the exception of ketoconazole. Other drugs may decrease the absorption or increase elimina-

tion of cimetidine, but the clinical meaning of these effects is not clear.

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