DRUG INTERACTIONS INVOLVING CIMETIDINE – MECHANISMS, DOCUMENTATION, IMPLICATIONS –

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CONTENTS

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Cimetidine (Tagamet®, Smith Kline and French) is a histamine H_2-receptor antagonist widely used in treatment of peptic ulcer disease. This drug has demonstrated efficacy in a number of disorders related to gastrointestinal acid output /1/. A recent survey has placed cimetidine as the sixth most widely prescribed drug in the United States, in terms of retail sales /2/. Several literature reports and trials have described the widespread use of the drug, and suggest a significant degree of inappropriate indication for use /3-5/. Such widespread and potentially inappropriate drug use highlights the potential for and significance of interaction of cimetidine with other administered medications. This review will address the mechanisms and reported interactions of cimetidine when given in cmbination with other agents, and attempt to determine potential clinical significance of these interactions.

I. MECHANISMS OF INTERACTION

The most obvious and apparent mechanism by which cimetidine interacts with other drugs is through inhibition of *metabolism* by liver microsomal enzymes. Structurally, cimetidine is a substituted imidazole derivative. Drugs of this class have been previously implicated as potent inhibitors of cytochrome P-450 enzymes because of their propensity to bind to both oxygen and substrate binding sites of the enzyme /6/. Indeed, reversible binding of cimetidine to cytochrome P-450 and P-448 has been identified /7, 8/. Thus, a competitive inhibition of Phase I reactions (e.g. dealkylation, oxidation, and hydroxylation) results in decreased elimination of drugs dependent on this metabolic pathway /9-11/. In addition, recent evidence suggests that nitroreduction may also be affected by cimetidine /12/.

Multiple trials have evaluated the effect of cimetidine on hepatic microsomal enzymes /9-14/, but only recently has the time course of onset and diminution of this effect been described. Current data indicates that the inhibitory effect of cimetidine lasts essentially only while the drug is being administered /15/. As determined by the aminopyrine breath test and antipyrine saliva test, onset of this phenomenon is within 24 hours of initiation of therapy /15/. Following discontinuation, cimetidine-induced enzyme inhibition subsides within two days.

A number of factors have been demonstrated to influence the degree of enzyme inhibition secondary to cimetidine. Such factors include

baseline liver enzyme activity /16/, patient sex /17, 18/, age /18, 20/, smoking history /20/, nutritional status /21/, environmental exposure /22/, and other drug use /23/. Recent evidence also reveals a good correlation between blood levels of cimetidine and resulting enzyme inhibition in a small number of subjects /15/. This finding supports that of others who suggest a dose-related influence of cimetidine on microsomal enzyme activity /24-26/.

In addition to inhibitory effects on microsomal enzymes, cimetidine has been postulated to decrease hepatic blood flow /9/. This effect would lead to reduced hepatic clearance of drugs that are highly extracted by the liver (e.g. propranolol, lidocaine, and morphine) /27/. Results of the trial demonstrating this effect have been vigorously questioned /28, 29/. Data demonstrating an inhibited clearance of the highly extracted drugs morphine /30/, propranolol /9/, and lidocaine /31, 32/ all support the contention that cimetidine does affect hepatic blood flow (HBF). In contrast, significant data is appearing to suggest that this effect is transient or non-existent /33-35/. Indeed, a recent trial evaluating effect of cimetidine on indocyanine green clearance has been reported /36/. This trial demonstrated no effect of cimetidine on hepatic blood flow, as determined by ICG clearance. Instead, a significant effect of posture on HBF was demonstrated. Thus, the significance of cimetidine related inhibition of hepatic blood flow is not fully elucidated, but is probably less important than inhibition of enzyme activity.

A third potential effect of cimetidine on disposition of other drugs occurs via elevation of gastric pH. Thus, bioavailability of various drugs may be affected, with a resultant increase or decrease in *absorption.* Indeed, as will be discussed, absorption or effect of various drugs has been significantly altered through concurrent administration of cimetidine /37-40/.

The final interactive potential of cimetidine involves an extension or addition of adverse effects when combined with other drugs which may suppress the bone marrow /41-44/. Thus, anticipated myelosuppression from chemotherapeutic or other agents may be exacerbated.

In summary, four effects of cimetidine result which may alter concentration, pharmacologic effects, and/or toxic effects of other concurrently administered medications. These include: 1) Inhibition of hepatic microsomal enzyme activity; 2) Depression of hepatic blood flow; 3) Elevation of gastric pH, resulting in altered absorption; 4) Additive or synergistic myelosuppressive effects.

II. CIMETIDINE AND ABSORPTION OF OTHER DRUGS

A. Antibiotics and Antifungals

Because cimetidine reliably elevates gastric pH, absorption of acid-labile antibiotics may be increased. Indeed, one study has demonstrated such an effect in one of five patients taking oral penicillin G /38/. In addition, absorption of the acid-stable drug ketoconazole seems to be reliably decreased when the two drugs are taken together /40/. However, other reports demonstrate no effect of cimetidine on absorption of ampicillin and cotrimoxazole /45/. Cimetidine may inhibit absorption of tetracycline, but evidence is conflicting /46-50/, perhaps due to differences in food intake. One must therefore conclude no significant effect of cimetidine on tetracycline.

B. Aspirin

It has been demonstrated that although the optimum pH range for gastric absorption of the salicylates is from 2.5 to 4.0 /51/, the major proportion of absorption occurs in the small intestine, because of its much larger surface area /52/. Thus, cimetidine-induced elevation of gastric pH may present a larger amount of drug in solution to the intestine, causing a more rapid and complete absorption of drug. Indeed, a small report by Khoury *et al.* suggests that in three patients in whom gastric pH was elevated above 3.5, the average area under the curve for salicylate was greater in the presence of cimetidine /53/. In addition, examination of the effect of cimetidine on absorption of enteric-coated aspirin has been conducted. This small trial demonstrated a more rapid and complete absorption of salicylate in the presence of cimetidine as compared to salicylate alone /54/. These results were, however, not statistically significant.

C. Elemental Iron

Since the absorption of elemental iron may be affected by changes in gastric pH /55/, one would expect a drug which elevates pH to decrease iron absorption. At least two reports have addressed this possibility. Skikne and cohorts report that administration of iron with cimetidine may indeed significantly decrease its availability /39/. This finding was demonstrated by a dose-related effect of cimetidine on

absorption of dietary iron in their small trial. In addition, Esposito has reported on three peptic-ulcer patients treated with 1 gm cimetidine per day plus $FeSO_4$ supplement, who developed iron-deficiency anemias in spite of ulcer healing /56/. These patients all responded to a simple decrease in cimetidine dose and continued iron supplementation.

D. Vitamin B12

Although it has been concluded that the use of cimetidine would not significantly affect vitamin B_{12} absorption /57/, other data demonstrates an appreciable effect. Fielding *et al.* have found that cimetidine reduces the output and concentration of intrinsic factor in gastric secretions under basal and pentagastrin-stimulated conditions /58/. Other data indicate that cimetidine inhibits absorption of protein-bound, or dietary, cobalamin /59, 60/. It may be postulated that this effect would be significant in patients on long-term cimetidine therapy, or those with already-depleted body stores.

E. Prednisolone

It has been postulated that, by elevating gastric pH, cimetidine may enhance dissolution of enteric coated prednisolone, leading to increased absorption /61/. However, upon evaluation of this postulated effect, the investigators found no statistically significant difference in mean AUC, peak concentration, or elimination half-life. Close analysis of these results demonstrates a large interpatient variability and apparently significant order of treatment effect. Thus, further investigation must be performed in order to determine the true impact of cimetidine on prednisolone kinetics, whether involving absorption or hepatic metabolism.

F. Digoxin

Further analysis of the effect of cimetidine on absorption of other drugs has examined digoxin, a drug which exhibits absorption potentially influenced by a number of variables /62/. Fraley and cohorts evaluated the effect of cimetidine on digoxin concentrations maintained at steady-state in 11 hospitalized patients with congestive heart failure /63/. Treatment with therapeutic doses of cimetidine lowered digoxin concentrations by at least 10% in nine patients. This

effect was attributed to impairment of digoxin absorption by the authors. In contrast to this study, Jordaens *et al.* found no changes in peak concentration, time to peak, or area under the digoxin plasma concentration versus time curve in eight healthy volunteers studied with and without concurrent cimetidine /64/. Thus, the true impact of cimetidine on digoxin absorption is not clear, although there seems to be a significant potential for interaction. Future study will further elucidate and clarify this question.

G. Pancreatic Enzyme Supplements

Pancreatic enzyme supplements are often found to be ineffective at reducing steatorrhea because of irreversible inactivation by acid in the stomach, or reduction of activity in the face of an acidic pH in the duodenum. Although enteric coating has not been successful in protecting enzyme activity /65/, antacids have demonstrated efficacy /66/.

The use of cimetidine in this setting provides a therapeutic interaction. When given before meals, cimetidine has improved efficacy and reduced requirements of enzyme therapy /65-68/. These findings suggest that, when given in sufficient dosage, cimetidine is as beneficial and often better tolerated than antacids in this role.

III. CIMETIDINE-INHIBITED DRUG METABOLISM

A. Cimetidine and Oral Anticoagulants

Data suggesting a significant interaction between cimetidine and warfarin first appeared in the literature in 1978. At that time, a representative of Smith, Kline and French Laboratories reported that addition of cimetidine 1 gm/d to a stabilized regimen of warfarin had caused a 20 percent increase in prothrombin time and ratio /69/. Multiple other reports have since followed. Serlin and cohorts observed the effect of cimetidine in seven volunteers treated with warfarin /70/. These subjects were stabilized over two weeks on doses of warfarin which prolonged their prothrombin time three to five seconds above normal. Upon addition of cimetidine 1 gm/d for three weeks, a significant additional prolongation of prothrombin time (mean increase from 19.4 to 22.9 sec) and elevation of plasma warfarin concentration resulted by the end of the first week. Discontinuation of cimetidine

resulted in gradual return of these parameters to pre-treatment levels over a period of 10 days. These authors suggested inhibition of metabolism as the mechanism of interaction.

Reports verifying the interaction of cimetidine and warfarin have appeared as letters as well as published trials /25, 71-75/. As suggested /70/, mechanism of interaction appears to be inhibition of metabolism /71/. These reports also document severe complications which may result from the addition of cimetidine to a warfarin regimen /72, 73/. Thus, because of the narrow therapeutic index of warfarin and the significant potential for severe adverse effects, extreme caution must be exercised if cimetidine and warfarin are to be used concurrently. No patient should be discharged on this combination until consecutive clotting times are documented as stable. In addition, when discontinuing cimetidine in a patient stabilized on warfarin, one must be aware of a possible increased anticoagulant requirement to maintain therapeutic efficacy.

One trial has examined the effect of cimetidine on an alternative oral anticoagulant. Harenberg and cohorts evaluated the interaction between cimetidine and phenprocoumon in 10 stabilized patients /76/. This anticoagulant, rarely used in the United States, is eliminated via glucoronidation /77/. As expected, no effect of cimetidine on clotting tests or plasma phenprocoumon concentrations was detected.

B. Cimetidine and Beta-Adrenergic Receptor Antagonists

Donovan and associates first described an apparent interaction of cimetidine with propranolol in a patient who experienced profound bradycardia upon taking both drugs concurrently /78/. These same authors then investigated the effects of the combination in a 54 year old ulcer patient, and found a 340 percent increase in the area under the propranolol plasma concentration-time curve in the presence of cimetidine. Further work by this group evaluated the effect of 1 gm cimetidine per day on the disposition of 80 mg propranolol given orally to six ulcer patients /79/. Once again, a significant increase (61 percent) in the area under the curve resulted in the presence of cimetidine. No half-life was estimated. However, the data were interpreted to reflect a decrease in first-pass extraction of propranolol secondary to the histamine H_2-receptor antagonist.

Other reports have demonstrated similar changes in pharmacokinetic

and/or clinical parameters measured when cimetidine is administered concurrently with propranolol /9, 80-82/. The most comprehensive evaluation of this interaction was undertaken by Feely and associates /9/. These investigators evaluated eight healthy subjects who were given 80 mg of propranolol before and after one week of treatment with cimetidine 1.2 gm/d. A significant decrease in the clearance of both intravenous and oral propranolol was detected. The extent of this decrease was found to be proportional to plasma cimetidine concentration. In addition, resting pulse rates were significantly lower during cimetidine therapy.

As previously discussed, one controversial finding of this trial was the detection of a significant (25%) reduction of hepatic blood flow in the presence of cimetidine. Though currently debated /28, 29/, this effect of cimetidine is generally accepted at this time. However, further trials will more clearly elucidate the true significance of cimetidine's effect on hepatic blood flow.

The potential of cimetidine to inhibit clearance and/or alter clinical effects of other beta blockers has been evaluated on a small scale. A brief report by Daneshmend and Roberts has indicated an elevation of labetalol blood concentrations when given in the presence of cimetidine (83). Other data deal with metoprolol and atenolol /84, 85/.

The initial report evaluating the interaction of cimetidine with metoprolol and atenolol found a significant interaction with metoprolol, but none with atenolol /84/. Six healthy volunteers were treated for seven days with either atenolol or metoprolol, followed by addition of cimetidine 1 gm/d for seven days. Combined therapy resulted in significant elevations of peak concentration and AUC for metoprolol, but no change in atenolol concentrations. In addition, no change in effect on pulse rate was noted for either group.

This latter finding was noted to be of importance by Houtzagers *et al.* /85/. These investigators found no effect of cimetidine on metoprolol kinetics, but detected a slight prolongation of atenolol elimination half-life when cimetidine was administered concurrently. Comparison of their findings with those of Kirch *et al.* /84/ led these authors to suggest that the lack of detection of effect on heart rate signified laboratory error in measurement of metoprolol blood levels in the earlier report /85/. Thus, they suggested no important interaction between cimetidine and metoprolol, with a slight effect of cimetidine on atenolol elimination (apparently secondary to decreased renal secretion). Certainly, further investigations must address these considerations.

C. Cimetidine and Theophylline

The potential for interaction of cimetidine and theophylline is quite logical, in that theophylline is substantially eliminated via hepatic transformation /86, 87/. Multiple trials and individual reports have now substantiated this suspicion.

There are now at least 15 separate reports or studies in the literature which evaluate the effect of cimetidine on theophylline /13, 26, 88-100/. In general, this interaction can be quite significant, with increases in elimination half-life of 50 percent or greater resulting from addition of 1.2 gm cimetidine per day to a theophylline regimen /88, 89/. It should be noted that not all patients treated with such combination therapy will experience a significant interaction /90, 91/. This finding may be consistent with a lesser susceptibility of some patients with lower baseline clearances to the effects of cimetidine. Further data indicates that some individuals taking theophylline may exhibit a significant interaction even with low-dose cimetidine /26/. The interaction resulting from combination of these drugs has resulted in severe toxicity, even death /92/. Thus, in the situation where both agents are used concomitantly, frequent monitoring of theophylline serum concentrations should be performed in order to avoid adverse effects.

D. Cimetidine and Phenytoin

Cimetidine has been reported to interact with phenytoin in two different fashions. Both drugs have, individually, rarely been implicated as causative etiologies of granulocytopenia and agranulocytosis /101, 102/. Two cases have been reported in which severe granulocytopenia /103/ or agranulocytosis /104/ occurred while the patients were taking cimetidine and phenytoin concurrently. The authors of these reports attributed the reactions to idosyncratic hypersensitivity /103/, or to synergistic myelosuppression in the face of the combination /104/.

Far more literature has addressed the inhibition of metabolism of phenytoin which results from concurrent administration of cimetidine. Hetzel *et al.* reported on four epileptic patients stabilized on phenytoin and other anticonvulsants /105/. Treatment with cimetidine 1 gm/d for six days resulted in elevation of mean plasma phenytoin concentration from 13 to 33 percent above baseline. Following cessation of cimetidine, levels in all patients dropped to near baseline within six

days. One patient experienced symptoms of mild phenytoin intoxication during cimetidine treatment, which resolved following its discontinuation.

Further evaluations have added to understanding of the interaction between cimetidine and phenytoin. A report by Algozzine *et al.* /106/, and three separate trials /107-109/ have confirmed the consistency with which cimetidine will interfere with phenytoin metabolism and elevate serum concentrations. Data recently reported by Frigo *et al.* /110/, suggests a significant variability of different subjects to the effect of cimetidine on phenytoin concentrations. These authors noted that their subject exhibiting the greatest effect in this regard demonstrated the lowest phenytoin clearance prior to addition of cimetidine. Additional data reported by Bartle and cohorts /24/ suggests a cimetidine dose-related inhibition of phenytoin metabolism. These investigators examined eight healthy volunteers who were given a 250 mg intravenous dose of phenytoin in the presence of various cimetidine dosages. Mean clearance of phenytoin was inhibited significantly by cimetidine doses of 400 mg/d, 1200 mg/d, and 2400 mg/d. Although no difference in clearance was demonstrated between patients receiving 400 mg/d and 1200 mg/d, these two groups did demonstrate significantly greater clearances than when receiving 2400 mg/d. In addition, a non-linear relationship was demonstrated between steady-state cimetidine concentrations and inhibition of clearance. This finding is at odds with that of Salem *et al.* /107/, who could determine no relationship between cimetidine concentration and change in phenytoin concentration. Future trials will resolve this question.

Thus, it is easily stated that the inhibition of phenytoin metabolism by cimetidine is potentially great in any patient. Since phenytoin exhibits Michaelis-Menton pharmacokinetic characteristics /111/, only a slight effect on enzyme activity may result in a precipitant elevation of serum concentration with attendant risk of toxicity. Thus, it is prudent when using cimetidine and phenytoin concurrently to closely monitor serum phenytoin concentrations until they have stabilized.

E. Cimetidine and Other Anticonvulsants

This author knows of no literature which demonstrates a significant effect of cimetidine on the pharmacokinetics or actions of phenobarbital. However, there is some evidence to suggest that phenobarbital may

increase nonrenal elimination and dosing requirements of cimetidine /112/. In addition, there is one report of an apparent interaction of cimetidine with carbamazepine /113/. This report demonstrated carbamazepine toxicity and elevated serum concentrations in a patient taking this anticonvulsant with cimetidine 1.6 gm/d. Withdrawal of cimetidine resulted in a 40 percent drop in carbamazepine concentration, with resulting resolution of signs of toxicity.

F. Cimetidine and Lidocaine

Two small trials have examined the effects of cimetidine on lidocaine elimination and toxicity. The first evaluated the effect of 1200 mg cimetidine administered over one day on the disposition of 1 mg/kg lidocaine given as an intravenous bolus to six healthy men in a randomized, placebo-controlled manner /31/. These investigators demonstrated a significant increase in elimination half-life, peak serum concentration, free drug concentration, and adverse effects of lidocaine in the presence of cimetidine. The mechanism of interaction was unclear, but related to reduction of hepatic blood flow, inhibition of enzyme activity and/or altered volume of distribution.

Further data reported by Knapp *et al.* involved a total of 21 patients studied in an open, non-randomized format /32/. Fifteen of these patients received cimetidine 1200 mg/d in addition to lidocaine 2-3 mg/min over a period of 26 hours. These investigators found the mean 26-hour serum lidocaine concentration to be approximately 75% greater in the cimetidine-treated group. Reduction in liver blood flow was again implied as the predominant mechanism.

Much controversy has surrounded the implications of these studies, particularly concerning the findings of the study of Knapp *et al.* Criticism of this trial has been registered in the medical literature /34, 114/. In addition, a recent trial reported in abstract form has found no evidence supporting an interaction between the two drugs /33/. Although free and total serum lidocaine concentrations increased over the 29 hour durations of infusion, this was not determined to be an effect of cimetidine. Rather, this phenomenon was attributed to accumulation normally detected with prolonged lidocaine infusion /115/.

The data reviewed are, therefore, controversial regarding the significance of the interaction between cimetidine and lidocaine. Future trials must resolve this debate. However, until such time as a better understanding of this interaction is detailed, it is wise to proceed with

caution whenever lidocaine and cimetidine must be used concurrently.

G. Cimetidine and Other Antiarrhythmics

Since cimetidine inhibits microsomal enzyme activity, virtually any drug eliminated via this route may be expected to be affected. Such would be the case with a number of cardioactive drugs. Indeed, recent evidence indicates an appreciable and probably clinically significant interaction between cimetidine and the antiarrhythmic agent quinidine. Hardy and associates examined the effect of cimetidine on disposition and pharmacodynamics of quinidine /116/. Quinidine sulfate 400 mg was administered to 6 healthy volunteers before and in the midst of a seven-day course of cimetidine 1.2 gm/day. These investigators detected a significant ($p < 0.05$) difference in apparent oral clearance (mean decrease 36%), elimination half-life (meaan increase 55%), peak concentration, and time to peak when *quinidine* was given with cimetidine. Accompanying pharmacodynamic changes were consistent with these pharmacokinetic effects. Changes in Q-T interval, R-R interval, and particularly rate-corrected Q-T interval were consistent with elevation of serum quinidine concentrations. Mechanism of interaction could not be purely ascertained, but was suggested to involve hepatic enzyme activity inhibition, decreased hepatic blood flow, and/or increased absorption of orally administered quinidine. Regardless of the mechanism, the authors suggested appropriate caution and monitoring whenever the two drugs are concurrently used.

Another commonly used antiarrhythmic which is significantly hepatically metabolised and therefore potentially subject to the effects of cimetidine is *procainamide.* This drug is normally approximately 50% excreted renally, with the remaining drug metabolized primarily via acetylation /117, 118/. Recent investigations have found that the elimination of procainamide is significantly inhibited by cimetidine /119, 120/. However, this interaction apparently occurs not through inhibition of metabolism, but rather via inhibition of renal tubular secretion /119-121/. Somogyi *et al.* report that administration of 1 gm cimetidine over a 12 hour period significantly elevated the procainamide AUC and elimination half-life. In addition, measured renal clearance fell by approximately 44 percent. A similar effect was noted for N-acetyl-procainamide. Therefore, the authors attributed this interaction to the ability of cimetidine to reduce renal blood flow and/or compete for active renal tubular secretion /121/.

Based on the limited available data, it appears that there is appreciable interaction potential for cimetidine and the antiarrhythmics quinidine and procainamide. Because of this potential, and the significant concentration-related toxicities of these agents /122/, it is wise to be aware of the effects of cimetidine on these drugs. Certainly, appropriate monitoring must be undertaken. In addition, because many antiarrhythmics currently in use are eliminated via similar mechanisms as quinidine and procainamide, future data may demonstrate a risk with other agents as well.

H. Cimetidine and Acetaminophen

An intriguing possibility of a beneficial drug interaction involving acetaminophen and cimetidine has recently received due attention in the medical literature. Acetaminophen (paracetamol) is a relatively non-toxic analgesic when ingested in low to moderate dosages as recommended. However, in an overdose situation, the toxicity of acetaminophen becomes great, causing significant life-threatening hepatic injury /123/. In this situation it is postulated that the large load of drug which is presented to the liver overwhelms the normal metabolic pathways of glucuronidation and sulfation. Minor metabolic pathways then become important, resulting in metabolism via cytochrome oxidative mechanisms to highly reactive quinoneimine and semiquinone free radicals. These radicals then react to form nontoxic glutathione conjugates /124/. In the overdose situation glutathione stores are overwhelmed, resulting in binding to subcellular liver components and subsequent centrizonal liver necrosis /125/.

It has been shown that the rate of formation of toxic metabolites is directly dependent upon the activity of the cytochrome P-450 system. Thus, drugs which inhibit or induce activity of this system may have significant effects on the hepatotoxicity of acetaminophen /126/. It is with this rationale in mind that in-vivo animal studies have been initiated to determine the significance of this interaction. To date, results have been encouraging /124, 127-129/, although there is some dissent /130/. Thus, future trials and study will determine the true potential for use of cimetidine as an adjunct in the treatment of acetaminophen overdose.

I. Cimetidine and Benzodiazepines

A number of benzodiazepine compounds are currently used as anti-anxiety or hypnotic compounds. The majority of these agents share metabolic pathways which are thought to involve the cytochrome multifunction oxidase system /131/. Thus, inhibition of metabolism and potentiation of pharmacologic effects of these agents would be logical deductions from this background. Indeed, multiple reports have dealt with this possibility. Klotz and associates 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 /132, 133/. Further data have confirmed this interactive potential for diazepam /134-136/, and demonstrated similar effects of cimetidine upon chlordiazepoxide /137/, desmethyldiazepam (active metabolite of diazepam and chlordiazepoxide) /138/, and alprazolam and triazolam /139/. These agents share similar metabolic pathways of oxidation via the cytochrome P-450 system. Other benzodiazepines which also share this pathway are prazepam, chlorazepate, and triazolam /131/. Although this author is aware of no data addressing the potential for interaction with these particular compounds, there exists at least a theoretical risk of such. In addition, recent data indicates that metabolism of the drug nitrazepam, which undergoes nitroreduction, is also inhibited by cimetidine /12/. Available data indicate that oxazepam and lorazepam are not affected by the administration of cimetidine /138, 140/. These agents are eliminated via glucuronidation, and hence are not dependent on microsomal enzyme activity.

The significance of the above noted interactions has been questioned by some representatives of industry /141/, and possibly by others. Indeed, at least one attempt at assessing the effect of cimetidine-diazepam interaction on cognitive functions demonstrated no change in these parameters despite a noted change in pharmacokinetic parameters /136/. No other trials document such clinical changes. However, it must be noted that this study, as well as most others, examined only single doses of benzodiazepine in healthy individuals. Thus, chronic dosing or use of this combination in any inpatient population likely will result in detectable effects. Indeed, clinical effects of this interaction have been documented in pre-operative patients /142/. Therefore, particularly in the hospitalized patient, the clinician should be attentive to the possibility of a significant adverse effect of this combination.

J. Cimetidine and Narcotic Analgesics

Initial reports have implicated cimetidine as an agent which may significantly alter the effects of morphine /30, 143/. These reports describe patients who exhibited an apparently increased susceptibility to the effects of the narcotic. However, this implication has been significantly challenged by a recent trial in seven volunteers. Mojaverian and cohorts evaluated the effects of cimetidine on the disposition of 10 mg morphine sulfate in a double-blind crossover format /35/. These investigators found no significant change following cimetidine in any parameters measured, including elimination half-life, clearance, steady-state volume of distribution, area-under-the-morphine-plasma-concentration-time-curve, and pupil diameters.

Other reports have discussed the effects of cimetidine on other narcotic analgesics. Knodell and cohorts have demonstrated an inhibition of meperidine metabolism by both rat and human microsomal enzymes in the presence of cimetidine /144/. In addition, at least one report has appeared in the literature implicating a potentiation of methadone effect by cimetidine /145/. Further reports are needed to verify these interactions. In light of these reports, one must be alert to the potential for extended or prolonged narcotic effects when these agents are administered in the presence of cimetidine.

K. Cimetidine and Antacids

Because antacids are often used in the clinical situation in combination with cimetidine, one may logically question the potential for interaction. Indeed, multiple reports and trials have addressed this issue. Steinberg *et al.* demonstrated that simultaneous administration of various antacid preparations significantly decreased cimetidine bioavailability, as determined by peak concentrations and AUC /146/. Administration of antacid 1 hour prior to cimetidine resulted in no effect. Other reports have supported the findings of this trial /147-152/. However, significant questions have been raised /153/. Of particular concern is the fact that all previous reports involved single-dose studies of this interaction. Thus, chronic combination therapy may result in no clinically significant interaction. In this regard, Russell and cohorts have very recently described results of their simulation of the effects of chronic dosing of cimetidine with antacids /154/. These investigators

found that, at simulated steady-state conditions, 70 percent of patients maintained therapeutic cimetidine levels. The implication of the data reviewed is that currently, simultaneous administration of antacids with cimetidine may be best avoided. Ultimately, however, further data may demonstrate no need for temporal spacing of cimetidine and antacid dosing.

L. Miscellaneous Interactions

The disposition of a number of other drugs have been demonstrated to be affected by cimetidine. Shaw and cohorts have demonstrated a significant decrease in clearance of *chlormethiazole* when given with cimetidine /155/. An "obvious" increase in sleep time was noted as well. Howes *et al.* have documented an apparent increase in *chlorpromazine* elimination and decrease in *indomethacin* absorption when these drugs were given concurrently with cimetidine /156/. Plasma levels of both of these agents were depressed in the presence of cimetidine. A recent case report has also implicated imipramine as an affected agent. Miller *et al.* have described a patient stabilized on *imipramine* who developed elevated serum concentrations as well as adverse reactions to the drug following administration of cimetidine 1.2 gm/d /157/. This interaction was attributed to inhibited metabolism of imipramine by cimetidine. A recent report has described a significant increase in elimination half-life and decrease in total plasma clearance of *metronidazole* in the presence of cimetidine 800 mg per day. Once again, inhibition of metabolism was implicated.

Other interactions in which cimetidine has been implicated include *pentobarbital* /144/, *ethanol* /159/, and *caffeine* /160/. Measured concentrations and pharmacologic effects were increased for each of these drugs in the presence of cimetidine. Of particular note is the potential for additive or synergistic bone marrow suppression when cimetidine is used concomitantly with *chloramphenicol* /43/, *carmustine* /44/, or other potential myelosuppressants /103, 104/. Various reports have demonstrated a potentially decreased absorption of cimetidine when used concurrently with *propantheline* or *metoclopramide* /161/. However, the effects of metoclopramide administration remains controversial /149/. One study of the combination of cimetidine and *tolbutamide* has demonstrated no significant interaction /162/.

IV. SUMMARY AND CONCLUSIONS

In summary, cimetidine is a potent inhibitor of liver microsomal activity, which may also decrease hepatic blood flow. Other effects of the drug include inhibition of gastric secretion and intrinsic toxic properties. These effects, combined with the common use of cimetidine in clinical practice, make the risk of adverse drug interactions a relatively frequent risk in the clinical setting.

Although a multitude of interactions with cimetidine has been evaluated, many of these are incompletely described or understood. At the present time, a potentially significant alteration of absorption appears to exist with only ketoconazole, elemental iron, vitamin B_{12} (long-term therapy), and pancreatic enzyme supplements (increased activity). Significant metabolic inhibition or decreased excretion appears to exist with warfarin, propranolol, theophylline, phenytoin, quinidine, possibly lidocaine and procainamide, and certain benzodiazepines. Other potential, but less well ascertained interactions may involve the narcotic analgesics, caffeine, ethanol, pentobarbital, imipramine, chlormethiazole, and metronidazole. In these settings, the clinician must be aware of interaction potential, and astutely monitor the patient during combination therapy.

Other data indicate that concomitant administration of antacids may reduce the absorption of cimetidine, that the drug may protect against the toxic effects of acetaminophen overdose, and that combination with certain other myelosuppressants may carry a significant risk. Thus, in regard to these reports, cimetidine is a drug with complex effects on the absorption, elimination, and toxicity of other drugs. When used in the setting of multiple drug therapy, the clinician must be alert to potentially increased or decreased effects of the drugs mentioned in this review. In addition, one must be aware that other hepatically metabolised agents not mentioned here may be affected by the addition of cimetidine therapy. Because of the therapeutic successes demonstrated in the treatment of various disorders with cimetidine, one cannot disregard this agent. Thus, the responsibility for understanding and monitoring for the complex effects of this drug falls with the practicing physician.

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ADDENDUM

Since submission of this review, a number of references have appeared addressing cimetidine interactions. Daneshmend, et al have documented that cimetidine-induced acute reductions in liver blood flow are not maintained chronically /163/. Other reports and studies have verified a potentially significant interaction with procainamide /164/ and with tricyclic antidepressants /165, 166/, questioned the potential interaction with carbamazepine /167/, and demonstrated no effect on nadolol /168/ and digoxin /169/.

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