EFFECTS OF RENAL FAILURE ON BLOOD LEVELS OF CIMETIDINE

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Serial blood samples for determination of drug levels were obtained after intravenous administration of 300 mg of cimetidine. Sixteen patients with varying degrees of renal failure were studied. There was a prolongation of drug half-life in patients with renal insufficiency compared with that in normal controls (P < 0.001). A significant inverse relationship between the half-life and the creatinine clearance was noted (r = 0.69; P < 0.01). The effect of hemodialysis was studied in 12 patients. Cimetidine was found to be dialyzable. This was demonstrated both by a shortening of the half-life of the drug during dialysis and by measurement of dialysance. This suggests that the dose schedule should be modified for patients with renal insufficiency and for those on hemodialysis. A single intravenous dose of cimetidine was well tolerated by the patients. One patient developed an urticarial skin rash, believed to be allergic in nature. There was a transient, mild (but significant) rise in blood urea nitrogen and serum creatinine concentration in 5 patients with moderate renal failure.

Peptic ulceration has been reported to have a higher incidence in patients with chronic renal failure than in control subjects.1 Gastric hypersecretion occurs in patients on chronic hemodialysis.2 Renal failure is also noted to be associated with a high incidence of stress ulceration and bleeding of the upper gastrointestinal tract in which the presence of gastric acid appears to be important pathophysiologically.3,4 Cimetidine, an H2-receptor antagonist, has been shown to be a potent inhibitor of gastric acid secretion6 and, hence, may be of value in the management of these conditions. Because the kidney is the major route of excretion of cimetidine,6 the dosage regimen may have to be modified in patients with renal failure. The current study was done to determine: (1) the effect of varying degrees of renal insufficiency on the blood levels of cimetidine after intravenous administration, and (2) the rate of removal of cimetidine by hemodialysis.

Patients and Methods

Part 1: study of patients with chronic renal failure. Sixteen male patients with varying degrees of renal insufficiency were admitted to the study. Their mean age was 52.9 years, with a range of 34 to 66. They did not have other significant medical problems unrelated to their kidney disease, and their renal function had been stable for a minimum of 3 months.

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Prior approval of the Human Study Subcommittee and informed consent were obtained in each case. The patients were divided into three groups according to the degree of their renal insufficiency as estimated by measurement of the endogenous creatinine clearance (Cr Cl). Their distribution was as follows: group A, 5 patients with mild renal failure (Cr Cl from 49.3 to 86.9 ml per min); group B, 5 patients with moderate renal failure (Cr Cl from 19.1 to 34.1 ml per min); and group C, 6 patients with severe renal failure (Cr Cl from 0 to 9.1 ml per min). Group C patients were being maintained on chronic hemodialysis, but the study was done on a nondialysis day.

A complete physical examination was performed upon admission to the metabolic ward. Complete blood cell count and blood chemistries including creatinine, urea nitrogen, total protein, albumin, bilirubin, alkaline phosphatase, and serum glutamic oxaloacetic transaminase (SGOT) were done. Urinalysis and a 24-hr collection for Cr Cl were obtained. Cimetidine, 300 mg diluted to 20 ml with normal saline, was given intravenously over a 2-min period. Blood pressure and pulse were monitored, and any subjective symptoms were noted. Blood sampling for cimetidine levels was done before and at 0.25, 0.50, 1, 2, 4, 8, 16, and 24 hr after injection. Hemogram, blood chemistries, and urinalysis were repeated at 24 to 48 hr and again at 5 to 7 days after the administration of cimetidine.

Part 2: study of patients during hemodialysis. Twelve male patients with a mean age of 51.2 years (range from 36 to 69) and on chronic hemodialysis for a minimum of 3 months were studied. Patient selection and initial evaluation were identical with those described in part 1. Follow-up blood tests and urinalysis (where possible) were also obtained at 24 to 48 hr and 5 to 7 days after cimetidine was given. In 6 patients (group D), 300 mg of cimetidine were given intravenously at the beginning of dialysis. Dialysis was performed with a Cordis Dow, hollow-fiber dialyzer (model 4; Cordis Corp., Miami, Fla.) with a blood flow of 200 to 250 ml per min, a single pass dialysate flow of 500 ml per min, and minimal transmembrane pressure. The duration of dialysis was 4 hr. Blood sampling for cimetidine levels was done before and at 0.25, 0.50, 1, 2, and 4 hr during dialysis, hourly after dialysis.
for 6 hr, and on the following morning 24 hr after drug administration.

In the remaining 6 patients (group E), dialysance of cimetidine was determined using a Cordis Dow hollow-fiber dialyzer (model 4). Dialysance is defined as the volume of blood in milliliters cleared of the drug per minute and is calculated according to the formula: \( Q_d = Q_b \times \frac{(B_i - B_o)}{(B_i - D)} \), where \( Q_d \) = dialysance in ml per min; \( B_i \) and \( B_o \) = drug concentrations in blood going into (Bi) and coming out from (Bo) the dialyzer; \( D \) = drug concentration in the dialysate going to the dialyzer (zero in this case); and \( Q_b \) = blood flow in ml per min, measured by a variation of the bubble flow method of Kramer et al. Serum and urine creatinine, BUN, total protein, albumin, bilirubin, alkaline phosphatase, and SGOT were measured by the Technicon SMA-12 Autoanalyzer (Technicon Corp., Tarrytown, N. Y.).

Calculations. Drug half-life (\( t_{1/2} \)) was calculated using a linear regression program for the Monroe 1775. In the calculation, data from samples through and including the 16th hr were used for groups A, B, and C. For group D, determinations through the 10th hr were used. Where trace amounts of cimetidine were found at 16 hr (2 patients in group A, 1 group B), a value of 0.025 \( \mu \)g per ml, half the lowest detectable level, was arbitrarily assigned. Student's t-test for unpaired samples was used for comparing \( t_{1/2} \) between groups, and the test for paired samples was used for comparing BUN and serum creatinine changes within groups. \( P < 0.05 \) was considered significant.

Results

Figure 1 shows mean drug concentration plotted in relation to time and mean \( t_{1/2} \pm 1 \) SD for each group. A curve describing the result obtained from a different study on subjects with normal renal function (group N) is also included for comparison. The study was done on 12 normal male volunteers (age range, 23 to 32 years) given the medication in an identical manner, with blood drug levels assayed by the same laboratory. Data on normal subjects was supplied by Smith Kline & French Laboratories. There is a significant difference between the normal controls (group N) and each group with renal insufficiency (\( P < 0.001 \)). Within the group of patients with impaired renal function, there is a significant difference between those with mild renal failure (group A) and those with severe renal failure (group C) (\( P < 0.01 \)). Hemodialysis significantly shortened the \( t_{1/2} \), as is shown by comparing the group of patients with severe renal failure studied between dialyses (group C) and those studied during dialysis (group D) (\( P < 0.005 \)).

Figure 2 shows the \( t_{1/2} \) plotted in relation to Cr Cl in patients with mild, moderate, and severe renal failure. The \( t_{1/2} \) of the normal subjects (group N) is shown for comparison. There is a significant inverse relationship between the \( t_{1/2} \) and the Cr Cl which is described by the equation: \( y = 0.01x + 3.67 \) (\( r = 0.69; P < 0.01 \)). Figure 3 shows the dialysance of cimetidine plotted in relation to blood flow through the dialyzer. Simultaneously determined dialysances of BUN and creatinine are shown for comparison. Each substance has a line drawn to represent a linear regression equation. Cimetidine was removed by hemodialysis at a rate less than that of BUN or creatinine. There is a direct linear relation-
ship between the dialysance and blood flow rate when the latter was varied from 150 to 250 ml per min \( (r = 0.72) \).

Cimetidine was well tolerated by all but 1 patient. This patient developed an urticarial, pruritic rash 15 min after injection. There was no hypotension or bronchospasm. Diphenhydramine hydrochloride was given, and signs and symptoms subsided within the next 3 hr.

Table 1 shows the values of serum creatinine and BUN in patients with mild (group A) and moderate (group B) renal failure before, 1 to 2 days after, and 5 to 7 days after cimetidine administration. In group B the increase in BUN and serum creatinine between preinjection and 24 to 48 hr postinjection is significant \( (P < 0.005\) and \( P < 0.025\), respectively). There is no significant difference between preinjection and 5 to 7 days postinjection in values of BUN \( (P > 0.40)\) or creatinine \( (P > 0.20)\).

Discussion

Renal insufficiency, as indicated by a decrease in endogenous Cr Cl, results in a prolongation of the \( t_{1/2} \) of cimetidine in the blood after a single intravenous injection. We divided our patients into those with mild, moderate, and severe renal failure, approximately as recommended by Bennett et al., and found that the drug \( t_{1/2} \) was significantly longer than it was in normal subjects, even in the mild group. There was no overlap of \( t_{1/2} \) between patients with renal disease and normal subjects. The \( t_{1/2} \) tended to be more prolonged as renal failure worsened, as evidenced by its inverse correlation with Cr Cl (fig. 2).

Patients getting cimetidine at the start of a dialysis treatment had significantly shorter \( t_{1/2} \) values than patients with the same degree of renal failure who were studied between dialysis treatments. The patients studied while on dialysis had \( t_{1/2} \) values similar to those of patients with both mild and moderate renal failure. This change in \( t_{1/2} \) associated with dialysis suggests that the drug is partially removed by dialysis. This removal was in fact demonstrated in dialysance studies.

![Table 1. Values of BUN and serum creatinine in patients with mild and moderate renal failure before and after cimetidine administration.](image)

<table>
<thead>
<tr>
<th>Group</th>
<th>Patient</th>
<th>Predrug</th>
<th>1 to 2 days postd rug</th>
<th>5 to 7 days postd rug</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (mild renal failure)</td>
<td>L. V.</td>
<td>23/1.4</td>
<td>23/1.5</td>
<td>19/1.4</td>
</tr>
<tr>
<td></td>
<td>F. W.</td>
<td>29/2.2</td>
<td>28/2.3</td>
<td>30/2.1</td>
</tr>
<tr>
<td></td>
<td>C. H.</td>
<td>35/2.0</td>
<td>38/2.3</td>
<td>34/2.2</td>
</tr>
<tr>
<td></td>
<td>F. S.</td>
<td>36/2.5</td>
<td>29/2.4</td>
<td>27/2.2</td>
</tr>
<tr>
<td></td>
<td>E. B.</td>
<td>41/2.8</td>
<td>39/2.8</td>
<td>34/2.7</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>33/2.2</td>
<td>31/2.3</td>
<td>29/2.1</td>
</tr>
<tr>
<td>B (moderate renal failure)</td>
<td>B. J.</td>
<td>40/2.2</td>
<td>46/2.7</td>
<td>39/1.9</td>
</tr>
<tr>
<td></td>
<td>H. G.</td>
<td>37/3.2</td>
<td>51/4.0</td>
<td>35/3.8</td>
</tr>
<tr>
<td></td>
<td>C. H.</td>
<td>46/3.3</td>
<td>54/3.5</td>
<td>44/3.2</td>
</tr>
<tr>
<td></td>
<td>B. S.</td>
<td>43/4.9</td>
<td>54/5.1</td>
<td>45/5.2</td>
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<tr>
<td></td>
<td>W. M.</td>
<td>55/6.1</td>
<td>61/7.0</td>
<td>55/7.3</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>44/5.9</td>
<td>50/4.5</td>
<td>44/4.3</td>
</tr>
</tbody>
</table>

These studies showed that cimetidine was removed at a rate somewhat less than that of BUN or creatinine. This removal rate is not unexpected for cimetidine, a compound with a molecular weight of 252.35 and only 15 to 20% protein binding. Canavan and Briggs have also demonstrated that cimetidine is dialyzable.

We can at present draw no conclusions regarding the transient but statistically significant rise in BUN and serum creatinine that occurred in one group, moderate renal failure (after a single intravenous injection of cimetidine). It is possible that these changes were drug-related. Mild but statistically significant increases in mean serum creatinine have been reported in patients receiving cimetidine. We have also shown that cimetidine or its metabolites do not interfere with the measurement of serum or urine creatinine.

Cimetidine can be given intravenously in doses of 300 mg every 6 hr in subjects with normal renal function (Smith Kline & French Laboratories, personal communication). A blood level of 0.5 \( \mu g \) per ml is associated with a 50% inhibition of maximal gastric acid output.

We have not given repeated doses of cimetidine and measured blood levels. However, we tentatively suggest that, to maintain the blood drug concentration above 0.5 \( \mu g \) per ml in patients with chronic renal insufficiency, a dose of 300 mg can be given intravenously every 6 hr in patients with mild renal failure, every 8 hr in patients with moderate renal failure, and every 12 hr in patients with severe renal failure. In patients on hemodialysis, we recommend an extra 300-mg dose at the end of dialysis.

REFERENCES


DISCUSSION OF PAPER PRESENTED BY DR. MA ET AL.

DR. W. BURLAND (Welwyn Garden City): In the introduction of your paper you mentioned surgically anephric patients but you only referred to severe renal failure and dialysis. Do you have any data for anephric patients?

DR. SILVIS: In the severe renal failure group the zeros in the creatinine clearance are surgically anephric. There were 3 patients that were surgically anephric and a number of other patients who had very low creatinine clearances but were not surgically anephric. Their values were not distinct from the patients who had very low creatinine clearances.

DR. K. F. SEWING (Tübingen, Los Angeles): Have you any idea whether the volume of distribution changes in renal failure patients?

DR. SILVIS: I do not have information on that. I am not sure whether it can be calculated from the data that we have.

DR. H. L. BONKOWSKI (Hannover, West Germany): I wonder whether the measurement just represented unchanged drugs or did it include metabolites.

DR. SILVIS: The technique used for measurement of the blood level does not include metabolites.

DR. BONKOWSKI: I would like to ask again whether you know anything about the accumulation of the metabolites, the sulfoxide, the hydroxymethyl, and perhaps others, in the patients with renal failure, and whether they have pharmacological or toxic effect.

DR. SILVIS: We do not have that information.

DR. M. I. GROSSMAN (Los Angeles): Is there any indication of any toxicity in patients with renal failure that is not encountered in patients without renal failure?

DR. SILVIS: As I mentioned, there was a slight but statistically significant elevation of the BUN (blood urea nitrogen) and creatinine in the moderate renal failure patients. Their means went up from 44 to 53 BUN and then back down to 44 BUN 5 days later. But I would emphasize to you that this is only 6 patients.

DR. GROSSMAN: And that was promptly reversible.

DR. SILVIS: And that was promptly reversible. And the creatinine does a similar thing.

DR. C. F. CODE (Los Angeles): My question relates to the disappearance rate from the blood of cimetidine in the anephric patients. This must represent the rate of metabolism of the drug in the body under these circumstances. Have any of the breakdown products been identified? Do you have any good idea of where the metabolism of cimetidine occurs?

DR. SILVIS: There is a second route of elimination of the drug in normal subjects, through the feces. Some of the drug is being eliminated in that manner. The half-lives are about 3-fold increased. As far as looking at metabolites of the drug, we have not done that in this study.

DR. D. M. McCARTHY (Bethesda): I wonder whether you could tell us whether the people who had transient elevations in creatinine had equivalent changes in BUN. Would similar changes in creatinine in normal subjects which have been documented on the drug carry an implication for changes in half-life?

DR. SILVIS: The changes in creatinine and BUN seem to parallel each other. Again, I would emphasize that these are 6 individuals. We could not use the severe renal failure in this comparison because of the dialysis and the constant fluctuation of the values in those cases.
Dr. Grossman: This might be an appropriate time to ask you or anyone else who wants to offer information as to whether there is any further information about the mechanism of the elevation of creatinine seen with cimetidine. Dr. Burland, would you care to comment on whether there is any new information about that?

Dr. Burland: I do not think we know yet; ask me in a few months and I hope that we may have some more information. We have done some preliminary studies to determine whether there are changes in glomerular filtration rate or tubular function and, so far, we have not been able to demonstrate this. There is apparently no relation between a rise in creatinine and the rise in BUN in patients who get the rise in creatinine.

Dr. Silvis: Is that in normal subjects or in patients with some degree of renal failure?

Dr. Burland: I am talking about normal subjects.

Dr. J. W. Dubb (Philadelphia): In evaluating the effects of cimetidine on renal function, specifically total bicarbonate reabsorption, we had the opportunity to do simultaneous creatinine and inulin clearances over a prolonged period of time and, in the middle of this, infused 300 mg of cimetidine. Usually the ratio of creatinine clearance to inulin clearance in normal man is 1.2 and this ratio did obtain in the first collection periods. However, after infusion of cimetidine the inulin clearance remained unchanged, whereas the creatinine clearance fell in all 3 of the volunteers so far studied. The ratio of creatinine to inulin clearance, then, was close to 1. Therefore, these preliminary data would indicate that there may be some effect on the secretion of creatinine by the tubule.