

Gentamicin- and Cephalothin-Associated Rises in Blood Urea Nitrogen

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Standardized rates of drug-attributed rises in blood urea nitrogen were 8.6%, 2.9%, and 9.3%, respectively, in patients receiving gentamicin alone, cephalothin alone, and both drugs together. These results provide evidence against a substantial synergism between the two drugs in the production of impaired renal function.

Recently, case reports have appeared describing the development of impaired renal function in patients receiving both gentamicin and cephalothin, and it has been suggested that they may be synergistic in producing this effect (1, 3, 8, 12). To evaluate this possibility, the data collected by the Boston Collaborative Drug Surveillance Program (BCDSP) were examined.

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PATIENTS AND METHODS

The BCDSP has to date collected data on over 22,000 consecutive admissions to selected wards in nine hospitals. All patients were admitted to medical services, none had undergone surgery, and none had received anesthetic agents. The data routinely collected include detailed information on demographic characteristics, all drugs administered, and a record of any adverse events deemed by the attending physician to be related to the administration of any drug or combination of drugs. Thus, the event, rising blood urea nitrogen (BUN) attributed to a drug, was based on the attending physician's discovery and notation of this event during the clinical course of his patient. Further details of the program and its methods have been presented elsewhere (10).

As a first step in the evaluation of the effect of the combination of gentamicin and cephalothin in producing impaired renal function, all patients receiving these drugs alone or in combination were identified. From this group, patients receiving other nephrotoxic agents (i.e., kanamycin, colistin sulfate, polymixin B, amphotericin B, cephaloridine, or tetracycline) were excluded from further study. For all of the remaining patients who had developed a drug-attributed rising BUN, the records were studied in detail. For the purposes of the present evaluation,

rising BUN was ascribed to the relevant antibiotic under study in those instances where it occurred at least 24 h after treatment was begun and not more than 24 h after it was stopped.

The following were evaluated as possible confounding factors: age, sex, hospital, admission BUN level, first discharge diagnosis, survival, drug dosage, route of drug administration, duration of antibiotic therapy, and concomitant administration of diuretics.

A total of 1,073 patients met the criteria for inclusion. Among these, 18% were 40 years of age or less, 26% were between 41 and 60 years, and 56% were over 60 years of age. Fifty-six percent were male. The admission BUN was less than 25 mg/100 ml in 63% of the group, between 25 and 50 mg/100 ml in 22%, and over 50 mg/100 ml in 15%. The overall mortality rate was 25%. The first recorded discharge diagnosis was neoplasm in 246 patients (23%), respiratory disease in 237 patients (22%), cardiovascular disease in 188 patients (18%), genitourinary disease in 82 patients (7%) and other diseases in 320 patients (30%).

The number of patients receiving gentamicin alone (group G) was 334, the number receiving cephalothin alone (group C) was 492, and the number receiving both together (group GC) was 247. The distributions of these groups by age, sex, hospital, and admission BUN were similar and, therefore, these factors were not controlled in further analyses. In addition, the distributions of patients with rising BUN and those without were similar with respect to discharge diagnosis and the concomitant administration of diuretics. There were, however, differences between the comparison groups with regard to survival and this factor was taken into account in evaluating the relationship. The mortality rate for groups G and C was 20%, whereas for group GC it was 40%. The frequency of BUN rise was 3.9% in those who lived and 8.8% in those who died.

RESULTS

The crude rate of drug-attributed rising BUN was 6.6% for group G, 2.0% for group C, and 9.3% for group GC (Table 1). Standardized (9)

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TABLE 1. Frequency of rises in BUN among the compared groups

Group	Frequency of rise in BUN					
	Gentamicin		Cephalothin		Both antibiotics	
Survivors	13/268	(4.9%)	5/392	(1.3%)	13/141	(9.2%)
Nonsurvivors	9/66	(13.6%)	5/100	(5.0%)	10/106	(9.4%)
All						
Crude	22/334	(6.6%)	10/492	(2.0%)	23/247	(9.3%)
Standardized ^a		8.6%		2.9%		9.3%

^a Using the "both antibiotics" group as the standard.

for the survival distribution of group GC, the rates of rising BUN were 8.6, 2.9, and 9.3% for groups G, C, and GC, respectively.

The maximum rise of BUN averaged 59 (range 10 to 330), 76 (range 20 to 100), and 46 (range 10 to 120) mg/100 ml for groups G, C, and GC, respectively. In 17 cases data on changes in the plasma creatinine were available, and in each instance the plasma creatinine rose in proportion to the rise in BUN.

The frequency of drug-attributed rising BUN was 10.5% among 229 patients who received a daily dose of more than 180 mg of gentamicin. By contrast, the frequency among 352 patients who received 180 mg or less was 6.0% ($P < 0.05$). The dose-response relationship was apparent both in group G and in group GC. There was no appreciable correlation between the frequency of rising BUN and route of administration of gentamicin.

The mean durations of treatment before the identification of rising BUN were 7, 8, and 6 days for groups G, C, and GC, respectively.

DISCUSSION

Both gentamicin and cephalothin have been shown to be nephrotoxic in animal studies (7, 11; O. Flandre and M. Jannon, *Gentamicin, First Int. Symp., Paris, 1967*). In rats, gentamicin causes pathological changes in the proximal tubules at a dose of 200 mg/kg per day, whereas for cephalothin a dose of 1,000 mg/kg per day is required and must be combined with glycerol or furosemide. Recent animal studies have failed to show a synergistic effect of the combination of gentamicin and cephalothin in the production of renal damage (6; W. Harrison, F. Silverblatt, and M. Turck, *Progr. Abstr. Intersci. Conf. Antimicrob. Agents Chemother., 14th, San Francisco, Calif., Abstr. 70, 1974*). Impaired renal function was attributed to gentamicin in 4.9% of 349 patients carefully monitored for antimicrobial toxicity (4) and in 6.5% of 77 courses of gentamicin after other A similar estimate for cephalothin given alone has not been reported previously, but this drug has been implicated in case reports as causing

nephrotoxicity (2, 5, 13).

In the current clinical study, each reported instance of rising BUN was attributed to either gentamicin, cephalothin, or both, if it occurred 24 h or more after the relevant treatment was begun and not more than 24 h after it was stopped. Despite the absence of patients undergoing surgery and the exclusion of patients receiving other nephrotoxic drugs, it is possible that some of these events were not caused by antibiotic treatment and would have occurred in its absence. Indeed, in four instances the rising BUN occurred after an episode of hypotension, which may have contributed to the development of impaired renal function. Nevertheless, in the absence of other apparent causes, it is quite likely that a substantial majority of these events were caused by one of the treatments being evaluated. It should be noted that the events reported here were of substantial clinical significance since the mean rise in BUN for the entire series was of the order of 60 mg%.

Whereas the standardized rates of rising BUN patients receiving gentamicin alone and cephalothin alone were 8.6% and 2.9%, respectively, the rate for the recipients of both drugs (9.3%) was lower than the sum of these. Considering the statistical stability of these estimates, the results provide evidence against a substantial synergism between gentamicin and cephalothin in the production of rising BUN.

In the current study, treatments were not randomized. Furthermore, the evaluation of individual patients for rising BUN was certainly not standard since many physicians in many hospitals were involved. It is, therefore, possible that a real synergism between gentamicin and cephalothin was missed. For this to have occurred, it would require either that patients receiving both drugs were a priori less susceptible to developing drug-induced rising BUN or that the event was less likely to have been discovered in patients receiving the combination or both. None of these seems likely. Patients receiving both drugs seemed to have more severe illness and this would tend to raise

the susceptibility to developing rising BUN. Also, it seems unlikely that patients receiving both drugs would be less carefully watched with regard to renal function as compared with patients receiving gentamicin alone. Nevertheless, such possibilities cannot be excluded entirely.

Because of the method of ascertainment, the observed rates of rising BUN reported in this study are likely to be underestimates of the true rates, as only those rises detected by the attending physicians and thought to be drug-related were recorded. However, as mentioned above, it is most unlikely that such under-reporting would be more pronounced in patients receiving both antibiotics, and therefore the failure to find an increased frequency of rising BUN in such patients cannot be reasonably explained on this basis.

Ten of 492 patients who received cephalothin alone developed a rising BUN after the drug was started and before its discontinuation. For the purposes of this study, the event was assigned to cephalothin since in each instance there was no other evident cause for the rise and cephalothin was suspected clinically to be the cause. However, in no instance could the drug be implicated with certainty, and these data therefore provide only suspicion that cephalothin alone may occasionally cause a rise in BUN.

In summary, the data indicate that no appreciable synergy exists between cephalothin and gentamicin in the production of impaired renal function. The rate with gentamicin correlates with daily dose but does not appear to correlate with route of administration or concomitant administration of diuretics.

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