Cyclosporin A and Imipenem Associated Seizure Activity in Allogeneic Bone Marrow Transplantation Patients

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Summary

Imipenem is an antibiotic used with cilastatin in the bone marrow transplant (BMT) setting. Cyclosporin A (CsA) is an immunosuppressive agent. Seizures can be seen with both imipenem/cilastatin and CsA. Our hypothesis for study was that CNS toxicity and seizures are increased by the concomitant administration of CsA and imipenem/cilastatin. Between December of 1989 and 1996, all of the 166 stem cell BMTs performed at Mount Sinai Hospital in New York were evaluated for this study. Three groups were studied: 77 patients received CsA alone (Group 1); 89 patients received imipenem/cilastatin, and of these, 45 received concomitant CsA (Group 2); and 44 patients who underwent autologous BMT received imipenem/cilastatin only (Group 3). We observed a total of 5 seizure episodes. There were no statistical differences in frequency between the groups. Adverse effects may be difficult to relate to a particular drug, especially for patients on multidrug regimens but the use of imipenem/cilastatin and CsA did not cause a significant rise in the frequency of seizures when compared to CsA alone.

Key words: Cyclosporin A, imipenem, seizure, allogeneic bone marrow transplantation, BMT.

INTRODUCTION

Carbapenems (imipenem and meropenem) are a new class of beta-lactam antibiotics that were introduced in the 1980s. They are derivatives of thienamycin (N-formimidoyl thienamycin) and are bactericidal by inhibition of cell wall synthesis. Imipenem is administered together with cilastatin, which inhibits the enzymatic breakdown of imipenem in the kidney [1]. The predominant concern regarding the use of imipenem/cilastatin is the increased tendency to induce seizures [2]. The risk of seizure is highly associated with inadequate dose adjustment

in relation to kidney function. If appropriate care is taken, seizures occur in less than 1% of patients treated. However, it is possible that concomitant administration of other drugs with neurotoxic profiles (i.e. theophylline), may increase the risk of seizures if overdosed. The interaction with gamma-amino butyric acid (GABA) receptor inhibition may pave the way for seizures. The risk of seizures in patients treated with imipenem/cilastatin is convincingly summed up by Pestotnik et al [3]. They prospectively followed 1,951 patients treated in hospital during a 4-year period. Only 4 sezures (0.2%) were recorded during treatment, and these occurred in patients prescribed doses above those recommended if adjusted in relation to renal function. In a second series of 927 new patients, 90% of whom received imipenem/cilastatin doses according to recommendations, no seizures were observed. Therefore, if dosages of imipenem/cilastatin are kept within suggested guidelines, the risk of seizures seems to be well below 1% [4].

Cyclosporin A (CsA) is a lipophilic, cyclic decapeptide (MW 1202) produced by the fungus *Tolypocladium inflatum gams*. It has demonstrated potent, selected, immunosuppressive T-cell lymphocyte activity with lack of myelotoxicity. The mechanisms by which CsA inhibits T-cell activation and proliferation are complex, but an important initial step appears to be the inhibition of synthesis of several lymphokines, particularly interleukin-2, which are formed in response to antigen stimulation. It has been associated with many side effects, nephrotoxicity and hypertension being the most common [5]. These neurotoxic side effects are primarily seen in patients with high levels of CsA and mainly in solid organ or bone marrow transplant (BMT) recipients [6-8]. In renal allograft recipients, seizures seem to be associated with aluminum overload, whereas low cholesterol levels seems to play a causal role in liver allograft patients [9,10].

PATIENTS AND METHODS

Between December 1989 and December 1996, all of the 166 patients who underwent stem cell transplant performed in our institution (122 allogeneic BMT, 44 autologous BMT) who were given imipenem/cilastatin were studied.

All allogeneic BMT patients received CsA 1.5 mg/kg b.i.d. as part of their immunosuppressive regimen, starting 1 day before infusion of stem cells, initially intravenously and later orally. Sixteen patients received prophylactic phenytoin (Dilantin) when busulfan was used as part of their conditioning regimen. Thus, three groups were studied: 77 patients received CsA alone without imipenem/cilastatin (Group 1); 89 patients received imipenem/cilastatin, 45 of whom were administered CsA concomitantly (Group 2); and 44 patients who underwent autologous BMT received imipenem/cilastatin only and no CsA (Group 3). Patient classification according to drug exposure and seizure activity is shown in *Table 1*.

TABLE 1 - *Patient classification according to drug exposure and seizure activity.*

Patients received CsA	122
Patients received prophylactic phenytoin because of busulfan exposure	16
Patients who were on prophylactic phenytoin and received CsA	7
Patients who were on prophylactic phenytoin and received CsA and imipenem/cilastatin	3
Patients received imipenem/cilastatin	86
Patients received CsA and imipenem/cilastatin	45
Patients who seized while on CsA alone	2
Patients who seized while on CsA and imipenem/cilastatin	3

Serum levels of CsA were monitored with specific fluorescence polymerization assay (Abbott) twice weekly while they were in the hospital.

Differences between proportions were evaluated using a two-tailed Fisher´s exact test, (as well as the uncorrected test for differences in proportions). A t-test was used to compare baseline values of the patients with seizures and without seizures with respect to blood chemistries. Wilcoxon´s non-parametric tests were used if the data were markedly skewed or non-normal, usually due to extreme outliers. These two-sample tests were also used to compare the values of the chemistries at seizure with baseline values of patients without

seizures. These latter results must be interpreted with caution as the lab procedures were not carried out at the same time. Changes between baseline and seizure chemistries were examined for the 5 patients on which such data were recorded.

RESULTS

We observed 3 (3.8%) seizure episodes in patients who were on CsA alone (Group 1). There were also 2 (4.4%) seizure episodes in patients who were receiving imipenem/cilastatin and CsA (Group 2). Group 3 patients had no seizures. Patients' characteristics are shown in *Table 2*.

To study whether electrolytes, liver and renal function influenced which patients would experience seizures, we compared their values at the time of seizure to those at admission. The only apparent significant difference was for bilirubin with the seizure patients having higher values (p=0.0006, based on Wilcoxon´s test). In addition all five seizure patients showed an increase over baseline values of alkaline phosphatase, but the post values were not themselves different from the baseline values of non-seizure patients.

DISCUSSION

Adverse effects may be difficult to relate to any particular drug. This is especially true for severely ill patients receiving multidrug thera-pies. Our hypothesis was that CNS toxicity would be increased by the concomitant administration of CsA and imipenem/cilastatin. At the time treatment was begun, all 5 patients with eventual seizures were in good general condition with no evidence of neurogical disturbances. They had no history of seizures and their baseline multiple blood chemistries and functional parameters, including sodium, magnesium, phosphate, calcium, bicarbonate, BUN, creatinine, bilirubin, albumin, alkaline phosphatase, gamma GTP and uric acid, were not significantly different from values at admission or those of patients who received these two drugs concomitantly and did not have any seizures.

All patients were on CsA for various time periods (7-142 days, median 37.6 days). The average number of days for patients who seized was similar (7-250 days, median 64.3 days). Patients receiving imipenem/cilastatin were administered the combination for a mean of 13.7 days and 12.3 days for patients who seized. The average number of days that patients were on both CsA and imipenem/cilastatin was the same, 13.7 days. These details are shown in *Table 3*.

The use of imipenem/cilastatin and CsA did not cause a significant increase in frequency of seizures compared to CsA alone. An antibiotic regimen including imipenem/cilastatin should be considered for neutropenic febrile allogeneic BMT patients who fail firstline therapy. In general, it is very difficult to prove significance with a sample size of 5 in one group but it appears that administration of imipenem/cilastatin and

TABLE 2 - *Characteristics of patients who seized.*

Name	Sex	Age	Preparative regimen*	Days on CsA	CsA level at seizure	Days on CsA & imipenem /cilastatin	Comments
NR	F	37	TBI	31	214	16	Did not seize while on imipenem
PM	F	23	BU/Ctx	29	233	7	
KC	M	34	TBI	250	286	14	Seizure did not occur during acute BMT period
BW	M	35	TBI	54	<25	n/a	Patient started on imipenem after seizure
DS	F	48	TBI	15	114	n/a	Patient started on imipenem after seizure

TBI= total body irradiation,   CTX= cyclophosphamide,   BU= busulfan

TABLE 3 - *Comparative characteristics of three patient groups.*

	All patients	Patient seized while on CsA	Patients seized while on CsA & imipenem/cilastatin
Age (yr)	33.7 (1-64)	36 (25-48)	31.3 (23-37)
Sex: M/F	42/54	1/2	1/1
Days on CsA	37.6	25.3	103.3
Days on imipenem	13.7	n/a	12.3
Days on CsA+imipenem/cilastatin	13.7	n/a	12.3

CsA concomitantly does not increase the incidence of seizures in patients on CsA, if imipenem/cilastatin is properly dosed and patients are monitored.

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