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ORIGINAL ARTICLE / ÖZGÜN ARAŞTIRMA

Efficacy of N-acetylcysteine in preventing amphotericin B induced acute kidney injury

Amfoterisin-B ilişkili akut böbrek hasarını önlemede N-asetilsistein'in etkisi

Buket ERTURK SENGEL, Elif TUKENMEZ TIGEN, Tayfur TOPTAS, Isik ATAGUNDUZ, Ayse Tulin TUGLULAR, Mehmet Onder ERGÖNÜL, Zekaver ODABASI

ABSTRACT

Objectives: Previously, in an animal study we showed that N-acetylcysteine (NAC) could decrease deoxycholate amphotericin B (DAmB) induced renal tubular apoptosis. In this clinical study, we aimed to evaluate the efficacy of NAC in preventing acute kidney injury (AKI) in febrile neutropenic patients with invasive pulmonary aspergillosis treated with DAmB.

Patients and Methods: Thirty-three patients were included in the study. 17 patients were randomly placed into the DAmB group and 16 were randomly placed into the DAmB plus NAC group.

Results: The characteristics of patients, durations and cumulative doses of DAmB, concurrent nephrotoxic drugs and basal serum creatinine (SCr) levels of patients were similar. Occurrence of a 1.5 fold or greater increase in the concentration of basal SCr and serum electrolytes were observed prospectively. The overall AKI was found in 13 patients (76.4%) in DAmB group and 6 patients (37.5%) in combination group (P = 0.024). No significant difference was observed in hypokalemia incidence between the groups (87.5 % in combination vs. 94.1 % in DAmB only groups).

Conclusion: This clinical pilot study showed that NAC may be a promising anti-oxidant agent to decrease DAmB-induced AKI in febrile neutropenic patients.

Keywords: Amphotericin B, Acute kindey injury, N-acetyl cysteine, Febrile neutropenia

ÖZ

Amaç: Daha önceki bir hayvan çalışmasında, N-asetilsistein (NAC)'in amfoterisin B (DAmB) ilişkili renal tubuler hasarı azalttığını gösterdik. Bu çalışmada, DAmB ile tedavi edilen invaziv pulmoner aspergillozlu febril nötropenik hastalarda NAC'in akut böbrek hasarı (ABH)'nı önlemedeki etkisini göstermeyi amaçladık.

Hastalar ve Yöntem: Otuz üç hasta çalışmaya dahil edildi. Randomize olarak 17 hasta DAmB grubuna ve 16 hasta DAmB ve NAC grubuna alındı.

Bulgular: Hastaların karakteristik özellikleri, DAmB tedavi süreleri ve kümülatif dozları, ek olarak aldıkları nefrotoksik ilaç ve bazal serum kreatinin (SCr) değerleri benzer bulundu. Bazal SCr değerlerinde 1.5 kat veya daha fazla artış ve serum elektrolitleri prospektif olarak gözlemlendi. ABH, DAmB grubunda 13 hastada (%76,4), kombine grupta 6 hastada (%37,5) görüldü (P = 0,024). İki grup arasında hipokalemi insidansında anlamlı fark saptanmadı (Kombine grupta % 87,5, DAmB grubunda % 94,1).

Sonuç: Bu klinik pilot çalışma, NAC'in febril nötropenik hastalarda, DAmB ilişkili ABH'nı azaltmada umut vaad eden bir antioksidan ajan olduğunu göstermektedir.

Anahtar kelimeler: Amfoterisin B, Akut böbrek hasarı, N-asetilsistein, Febril nötropeni

Introduction

Invasive aspergillosis is frequently seen in febrile neutropenic patients, and immediate treatment such as; widely used antifungal, amphotericin B (AmB), has shown to decrease its mortality [1]. Due to the high incidence of nephrotoxicity with its deoxycholate form (DAmB), lipid formulations are increasingly preferred in developed countries [2]. The mechanism of DAmB nephrotoxicity has not been fully elucidated, however, Varlam et al. has demonstrated that AmB has a dose-dependent apoptotic effect in renal tubular cells of rats [3].

Buket Erturk Sengel (✉), Elif Tukenmez Tigen, Zekaver Odabasi
Department of Infectious Diseases and Clinical Microbiology, School of Medicine, Marmara University, Istanbul, Turkey
e-mail: buket.sengel@marmara.edu.tr
Tayfur Topbas, Isik Atagunduz, Ayse Tulin Tuglular
Sub-department of Hematology, Department of Internal Medicine, School of Medicine, Marmara University, Istanbul, Turkey
Mehmet Onder ERGÖNÜL
Sub-department of Hematology, Department of Internal Medicine, School of Medicine, Koc University, Istanbul, Turkey

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The antioxidant N-acetylcysteine (NAC), a pharmaceutical primarily used as a mucolytic agent, has also been used to prevent radio - contrast nephrotoxicity in patients who have undergone coronary angioplasty procedures due to its possible anti-apoptotic effect [4-6]. We have previously demonstrated in an animal study that renal tubular apoptosis caused by DAmB, is significantly reduced by the concomitant use of NAC [7]. These encouraging findings prompted us to perform this clinical study, in which we aimed to demonstrate NAC's possible beneficial effect in DAmB induced acute kidney injury (AKI), in patients who are under treatment of DAmB for invasive pulmonary aspergillosis.

Patients and Methods

This study is a prospective, unblinded and randomized controlled study performed in Marmara University Hospital, between April 2010 and December 2012. Febrile neutropenic patients (> 18 years old), with hematological malignancies who were candidates for treatment with DAmB due to suspected or proven invasive fungal infections [8] were randomly assigned to either a group receiving DAmB, or to a group receiving a combination of DAmB and NAC. Any patient with a history of DAmB or NAC allergy, or who had received DAmB in the three months prior to recruitment, or with any of the confounding comorbidities including renal disease or basal SCr above 1.1 mg/dL (upper limits of normal laboratory value), cardiac disease, chronic liver disease, was excluded. All participating patients were required to sign an informed consent form prior to enrollment. This study has been approved by the Marmara University Ethics Committee.

Drug doses were: 1 mg/kg/day of DAmB administered by intravenous infusion over 2 hours; and oral NAC 600 mg given three times a day. Before the first dose of DAmB, all patients were premedicated with 500 mg oral paracetamol, 45.5mg/2 mL intravenous pheniramine and 20 mg oral prednisolone to avoid possible infusion-related reactions such as fever and rigor. Renal function tests, SCr, blood urea nitrogen (BUN), complete blood count and electrolytes (sodium, potassium) were measured before the onset of DAmB therapy and then repeated everyday throughout the therapy. Liver function as well as calcium and magnesium levels were measured before the therapy and then two times a week. A serum galactomannan antigen test was performed two times a week through the neutropenic period, and computerized tomography (CT) imaging was performed when the patient tested positive for galactomannan antigen or in the case of clinical suspicion of invasive fungal infections. We recorded the concomitant usage of any potential nephrotoxic drug (e.g., aminoglycosides, vancomycin, ganciclovir or cyclophosphamide), and also recorded other side effects such as fever, chills, coughing and infusion reactions.

DAmB induced acute kidney injury (AKI) was defined as an increase of SCr concentration during the therapy to greater than or equal to 1.5 times of basal SCr, according to the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline for acute kidney injury [9]. The primary outcome of the study was the AKI while receiving DAmB therapy. The antifungal therapy was discontinued if a patient develops AKI, in such cases an alternative antifungal agent was prescribed. Patients who developed hypokalemia with serum potassium levels below or equal to 3.0 mEq/L, or those who developed symptoms, were also given supplemental intravenous potassium. DAmB therapy was discontinued in patients with refractory hypokalemia.

Statistical analysis

Chi squared tests were used for comparison of categorical variables, and nonparametric Kruskal-Wallis tests were used for comparison of continuous variables. A multivariate analysis was performed for the prediction of nephrotoxicity. In the logistic regression model, age, body mass index, gender, nephrotoxic drug use, and DAmB usage with or without NAC were included as independent variables. The statistical analysis was performed using STATA, version 11 (Texas, USA). Statistical significance was set as $P < 0.05$.

Results

Thirty-three patients were included in the study: 17 patients were randomly placed into the DAmB group and 16 were randomly placed into the DAmB plus NAC (combination) group. Table I shows the details of the patients' characteristics and the results of the study. No significant differences were noted between the study groups with respect to age, underlying diseases, cumulative dose of DAmB, concurrent nephrotoxic agent usage, and basal SCr values. The DAmB group received treatment for a mean of 9.3 days, in comparison to 9.6 days for the combination group ($P = 0.82$).

The overall AKI was found in 13 (76.4%) of 17 patients in DAmB group and 6 (37.5%) of 16 patients in combination

group (P = 0.024). These results indicate that addition of NAC significantly decreased DAmB-induced AKI. A multivariate analysis revealed that DAmB usage without NAC was associated with a 9.77 fold rise in AKI (P = 0.011). Note that hypokalemia was seen in 16 (94%) patients in the DAmB group and in 14 (87.3%) patients in the combination group (P = 0.509).

The treatment in the study was stopped in 4 patients in the combination group due to refractory hypokalemia depending DAmB, skin reaction, refractory cough and gastrointestinal intolerance due to NAC. The refractory cough, which caused hemoptysis secondary to thrombocytopenia, was probably related to the administration of NAC; the coughing diminished after NAC was ceased. One patient in the combination group and two patients in the DAmB group were switched to another antifungal agent due to progression according to CT findings and worsening clinical conditions. In the DAmB group, therapy was stopped in one patient because of nephrotoxicity and refractory hypokalemia.

Six patients (35%) in the DAmB group (2 due to probable fungal pneumonia, 2 due to bacterial sepsis, and 2 due to unidentified causes) and five patients (31%) in the combination group (2 due to probable fungal pneumonia, 2 due to bacterial sepsis and one due to intracranial hemorrhage) died. Among these patients, nephrotoxicity was observed in one patient in the combination group and in 3 patients in the DAmB group, attributable fatality analysis was not performed because of the low number of the patients in this set.

Table I. Comparison of patient characteristics and study results

Characteristics and study results	DAmB alone (n = 17)	DAmB + NAC combination (n = 16)	P value
Age (yr), mean, range	43.94 (14.41), 18 - 73	42.25 (14.84), 19 - 67	0.742
Gender			0.829
Male	10	10	
Female	7	6	
Weight (kg) mean (SD), range	67.6 (11.8), 44 - 86	66.5 (11.9), 50 - 90	0.794
Body mass index mean (SD), range ± SD	24.65 (4.091), 17.58 - 30.70	24.49 (4.041), 18.94 - 30.70	0.909
Underlying hematological malignancy			
Acute lymphocytic leukemia	1	5	
Acute myelocytic leukemia	12	7	
Lymphoma	2	3	
Stem cell transplantation	1 (autologous)	2 (allogeneic)	
Myelodysplastic syndrome /other	2	1	
Baseline neutrophils < 500/mm^3	14/17	12/16	
Reason to use antifungal therapy			
Empirical	3	5	
Pre - emptive	14	11	
Amphotericin B therapy			
Cumulative dose (mg), mean ± SD	637.35 ± 235.22	622.81 ± 237.30	0.860
Duration (days), mean ± SD	9.3 ± 2.97	9.6 ± 3.91	0.823
Concurrent nephrotoxin usage	11/17	10/16	0.895
Baseline SCr value (mg/dL)	0.64 (0.3 - 1.08)	0.59 (0.2 - 1.08)	0.438
Acute kidney injury			
Increase in SCr > 1.5 x baseline SCrS	13/17	6/16	0.024
Maximum SCr (mean ± SD)	1.25 ± 0.532	0.91 ± 0.351	0.0387
Hypokalemia	16/17	14/16	0.509
Median day to acute kidney injury	7 (3 - 15)	6.5 (3 - 12)	0.915
Median cumulative dosage of DAmB when acute kidney injury developed	412 (183 - 1050)	335 (250 - 732)	0.594
Mortality	6	5	0.805

DAmB: deoxycholate amphotericin B, NAC: N-acetylcysteine, SD: standard deviation, SCr:serum creatinine

Discussion

DAmB, with its wide antifungal spectrum, is one of the agents used in the treatment and/or empiric therapy for invasive fungal infections in febrile neutropenic hematology–oncology patients. Because of the high incidence of nephrotoxicity and infusion reactions, use of this form of the drug is often limited [10]. Currently, most guidelines recommend lipid formulations of AmB instead of DAmB [8,10]. According to the Turkish Ministry of Health Directives, however, DAmB is approved as the first – line antifungal drug for febrile neutropenic patients, and only when side effects occur, health professionals in Turkey are able to use alternative antifungal agents such as voriconazole or lipid formulations of AmB. Therefore, unfortunately our patients are face to face with these possible side effects of DAmB and in this prospective study, aiming to investigate a possible preventive measure, we were able to demonstrate that the NAC therapy significantly reduces DAmB induced AKI, yet has no beneficial effect in reducing hypokalemia and infusion related side effects.

As mentioned above, infusion reactions, hypokalemia and nephrotoxicity are some of the most important side effects of DAmB. Premedications such as paracetamol, steroids and anti-histamines have usually been given to prevent infusion reactions, and potassium supplements have been given for hypokalemia. Among the side effects, however, nephrotoxicity is the most concerning as it increases the length of hospital stays and health costs, as well as increasing morbidity and mortality rates [12]. DAmB-induced nephrotoxicity has been reported at rates between 49% and 65% in different studies [13-15]. Wingard et al., evaluated the nephrotoxicity of DAmB in patients treated for proven or suspected aspergillosis and they found a doubling of the basal SCr values in 53% of the patients, 14.5% of which required hemodialysis [13]. In our study, 13 of 17 patients (76.4%) treated with DAmB experienced a 1.5 fold increase in basal SCr levels. Because of the ethical points and available more qualified antifungal agents, in case of rise of SCr 1.5 fold of the basal levels and rise above 1.1 mg/dl we switched DAmB to another non-toxic antifungal agent. So we could not be able to observe patients until 2 or more folds of SCr above basal levels. None of the patients required hemodialysis probably due to early termination of DAmB therapy immediately when AKI developed.

Several procedures aimed to decrease DAmB nephrotoxicity have been tested, such as infusion with intralipid solutions, prolonging infusion time, and the addition of low-dose dopamine or mannitol, however, none of them have provided satisfactory results [16-20]. The high rate of nephrotoxicity has led to the development of AmB formulations in three different lipid bases: lipid complex, colloidal dispersion, and liposomal [21]. While lipid formulations of AmB were found to be less nephrotoxic than other formulations of the drug, these formulations do not completely eliminate nephrotoxicity. In a randomized double-blind study of more than six hundred patients that compared liposomal AmB (AmB-L) and AmB-D for empirical treatment in persistent febrile neutropenic patients, nephrotoxicity rates were 18.7% and 33.7% respectively [15]. Although lower rates of nephrotoxicity are observed with lipid formulations than with DAmB, the cost of these agents is substantial, and access may be challenging in resource-limited settings.

DAmB-induced nephrotoxicity is secondary to renal vasoconstriction, which leads to tubular damage and a decreased glomerular filtration rate [22,23]. In an animal study, Varlam et al., demonstrated that AmB has a dose-dependent apoptotic effect in renal tubular cells of rats, with ensuing nephrotoxicity [3]. In the same study, they also showed that AmB-induced apoptosis and the resulting nephrotoxicity could be reduced by the concomitant use of recombinant human insulin-like growth factor 1 (rhIGF-1), an anti-apoptotic agent. In our previous studies, we have found that rats that received NAC concomitantly with DAmB had significantly decreased levels of AmB-induced renal tubular cell apoptosis compared to animals that only received DAmB [7].

These animal-study results are consistent with the results of the current clinical pilot study which suggest that NAC, probably with its anti-apoptotic effect, significantly decreases DAmB induced AKI. Cumulative DAmB doses and concurrent nephrotoxin use was similar between the study groups. Incidence of hypokalemia, however, was similar in both the combination and DAmB only groups (see above and Table I) suggesting that NAC has no preventive effect on hypokalemia. In a recently published randomized, double-blinded, placebo-controlled, clinical study, efficacy of the NAC in prevention of DAmB induced electrolyte imbalances was evaluated. They showed that NAC has no preventive effect against hypokalemia or hypomagnesemia as we found [24]. They also evaluated the nephrotoxicity as a secondary end point in their study and they defined the nephrotoxicity as either doubling of SCr from the baseline value or ≥50 % decrease in glomerular filtration rate. Although the rate of DAmB nephrotoxicity was higher in

the placebo than in the NAC group (60 % versus 40 %), this difference was not statistically significant (P = 0.209). In our study AKI was defined as 1.5 fold or more increase in basal SCr and also we used total 1800 mg of NAC per day while they used 1200 mg in a day. Major problem at this point is the standardization of definition of drug-induced nephrotoxicity. In 2002, the Acute Dialysis Quality Initiative (ADQI) was developed RIFLE classification system for the uniform definition of AKI in the world [25]. A few years later Acute Kidney Injury Network (AKIN group) proposed the AKIN criteria for the definition of AKI [26]. Finally in 2012 the Kidney Disease Improving Global Outcomes (KDIGO) released their clinical practice guidelines for acute kidney injury (AKI), which build off of the RIFLE criteria and the AKIN criteria [9]. KDIGO defines AKI as any of the following: an increase in serum creatinine by 0.3mg/dL or more within 48 hours or increase in SCr to 1.5 times baseline or more within the last 7 days or urine output less than 0.5 mL/kg/h for 6 hours. In our study we accepted AKI as 1.5 fold rise of basal SCr and because of available more potent and less nephrotoxic antifungal agents we changed DAmB to voriconazole, liposomal AmB or caspofungin. That is why we could not be able to observe 2 or 3 fold rise of SCr in our study.

Major limitations of our study is the open lable design of the study and the low number of patients. Given the promising results presented here, this study should be repeated with a larger number of patients. In addition, future research could expand upon the current work in several ways. For example, different NAC dosages could be tested to determine the ideal dosage. Also, whereas our study group consisted of high-risk neutropenic patients, future work could be extended to non-neutropenic candidemic patients that are given lower DAmB dosages. It may also be possible to consider blinded experiments rather than the current open study design, and to observe patients for a longer duration of time than we had. Also note that a refractory cough leading to hemoptysis was observed in one patient receiving NAC in the current study, and the safety of this treatment should be evaluated in a larger group of patients. In conclusion, in this study we demonstrated that NAC reduces AMB induced AKI, therefore, we suggest that in the case of DAmB use, addition of NAC may be beneficial, yet broader studies are needed to support this recommendation.

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