JPPT | Clinical Investigation

Tolerability of Aerosolized Versus Intravenous Pentamidine for *Pneumocystis jirovecii* Pneumonia Prophylaxis in Immunosuppressed Pediatric, Adolescent, and Young Adult Patients

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OBJECTIVES Pentamidine is an antifungal that is used alternatively to sulfamethoxazole-trimethoprim for the prophylaxis and treatment of *Pneumocystis jirovecii* pneumonia (PJP). The primary objective of this study was to assess the tolerability of aerosolized versus intravenous pentamidine for PJP prophylaxis in pediatric, adolescent, and young adult immunosuppressed patients. Secondary objectives included comparing pentamidine formulation reaction to dosing frequency and diagnosis.

METHODS This retrospective chart review used electronic medical record (EMR) data from patients at a tertiary care pediatric teaching institution from January 1, 2014, to January 1, 2017. Information used from the EMR included pentamidine dosing, ordering, and laboratory values. Inclusion criteria consisted of patients with a cancer diagnosis, hematopoietic stem cell transplant (HSCT) recipients, and renal transplant recipients who received pentamidine for PJP prophylaxis.

RESULTS Ninety-six patients met inclusion criteria, of which 31 received aerosolized pentamidine. Ten of the 96 patients experienced a drug-related reaction to either aerosolized or intravenous pentamidine ($p = 0.134$). Nine of 10 patients who experienced a reaction received intravenous pentamidine versus 1 patient who received aerosolized pentamidine ($p = 0.132$). In those patients who reacted to pentamidine there was a higher incidence of reactions after subsequent administration ($p = 0.039$) and in patients with a blood cancer diagnosis ($p = 0.042$).

CONCLUSIONS Data suggest that patients who receive aerosolized pentamidine may tolerate therapy better compared to intravenous administration. Additional studies involving larger numbers of pediatric, adolescent, and young adult patients are needed for stronger statistically significant clinical differences in tolerability of aerosolized versus intravenous pentamidine.

ABBREVIATIONS EMR, electronic medical record; HIV/AIDS, human immunodeficiency virus infection and acquired immune deficiency syndrome; HSCT, hematopoietic stem cell transplant; IV, intravenous; PJP, *Pneumocystis jirovecii* pneumonia; SMZ-TMP, sulfamethoxazole-trimethoprim

KEYWORDS aerosol vs intravenous; drug tolerability; immunosuppressed; pentamidine; PJP

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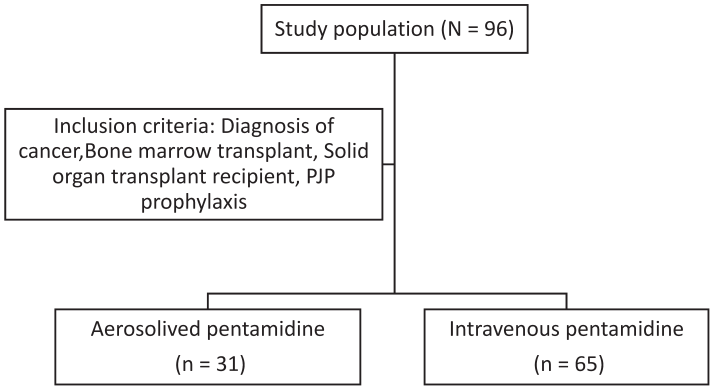
Introduction

Pneumocystis jirovecii pneumonia (PJP) was initially described in the middle of the last century in premature neonates and malnourished infants.[1] The causative organism, *Pneumocystis jirovecii*, is an ascomycetes fungus, which is a common cause of opportunistic infection in severely immunosuppressed patients. In the immunosuppressed population, PJP has high rates of transmission (person-to-person contact) and is associated with high mortality. In children, PJP is most common in patients with lymphoid malignancies, hematopoietic stem cell transplant (HSCT) recipients, patients treated with long-term corticosteroids, patients with HIV/AIDS, and patients with severe lymphocytopenia due to treatment with fludarabine, temozolomide, or alemtuzumab.[2] Owing to the high mortality and transmission rate of PJP, it is standard practice to initiate prophylaxis with either antibiotic or antifungal agents in patients with expected prolonged neutropenia.[3] Without prophylaxis the incidence of PJP infection is 5% to 15% in HSCT, 22% to 45% in lymphoid malignancies, and 25% in severe immunodeficiency.[1–3]

The gold standard for PJP prophylaxis is sulfamethoxazole-trimethoprim (SMZ-TMP).[1] While this medication is commonly used in the immunosuppressed population, alternative prophylactic agents may be necessary owing to allergic reactions and/or SMZ-TMP-associated bone marrow suppression.[1] Alternative agents for PJP

Figure 1. Study population.



PJP, Pneumocystis jirovecii pneumonia

prophylaxis include pentamidine, dapsone, and atovaquone. Of these agents, pentamidine is the most commonly used medication at our institution.

Pentamidine is an antifungal medication that is administered either aerosolized or intravenously for PJP prophylaxis. The adverse reaction profile of these 2 administration routes varies, based on localized versus systemic exposure. Aerosolized pentamidine has been associated with local respiratory symptoms including bronchospasm and increased work of breathing.[4] In addition to the adverse reaction profile of aerosolized pentamidine, the route of administration can pose challenges. Aerosolized pentamidine requires special nebulization equipment that may be difficult for younger children to use. Also, hospital policies and procedures may address specific logistics with regard to the location of administration of the aerosolized route of administration owing to the teratogenicity of pentamidine. In contrast, intravenous pentamidine has been associated with systemic symptoms such as lip tingling, neuropathy, and increased work of breathing.[2] Current evidence has shown that both administration routes are comparably efficacious for PJP prophylaxis.[4,5] Additionally, supporting evidence suggests the safety of aerosolized and intravenous pentamidine individually, but there is a lack of literature comparing the tolerability between the 2 administration routes. The primary objective of this study was to determine the tolerability of aerosolized versus intravenous pentamidine for PJP prophylaxis in immunosuppressed pediatric, adolescent, and young adult patients.

Methods

This study was a retrospective chart review that used electronic medical record (EMR) data from immunosuppressed patients at a tertiary care pediatric teaching institution from January 1, 2014, to January 1, 2017. All aspects of this study were approved by the University Hospitals Health System Institutional Review Board. Inclusion criteria consisted of patients treated at Rainbow Babies and Children's Hospital (both pediatric, adolescent, and young adult patients) with a diagnosis of cancer, those who had undergone or are currently undergoing HSCT, and solid organ transplant recipients who received pentamidine for PJP prophylaxis. Exclusion criteria for this study were limited to those receiving pentamidine for PJP treatment. Study variables were retrieved from the electronic medical record and stored in a protected data database (REDCap; Vanderbilt University, Nashville, TN).

Patients were categorized into either the aerosolized or intravenous administration groups on the basis of the formulation received (Figure 1). Data collected included patient sex, ethnicity, age, body weight, allergy history, primary diagnosis, concomitant medications (if applicable), cycle of chemotherapy (if applicable), days from transplant (if applicable), pentamidine dose, dosage form, administration frequency, infusion duration, premedications, immunosuppressive therapy, type of reaction, history of SMZ-TMP use, number of pentamidine doses administered, and absolute neutrophil count. The information was gathered during the initial pentamidine administration and during subsequent administrations categorized for both administration routes and compared relative to the collected variables focusing on dosage, route, and the reaction(s). Intravenous pentamidine was dosed at 4 mg/kg with a maximum dose of 300 mg. The intravenous pentamidine solutions were administered via intravenous infusion over 60 minutes and were extended to 120 minutes if not tolerated. Aerosolized pentamidine was dosed at a flat dose of 300 mg and was administered via nebulization in a negative pressure room with albuterol as a premedication.

Summary data are shown as mean, standard deviation, percentage, frequency, non-parametric statistics,

Table. Population Demographics

Variable	Aerosolized	Intravenous
Number of patients	31	65
Age, yr, mean ± SD	17 ± 5.8	9 ± 8.02
Sex, %		
Male	55	50.7
Female	45	49.3
Race, %		
Caucasian	68	66
African American	26	17
Asian	3	2
Other	3	15

and frequency analysis, which were used to assess for any differences between the 2 routes of pentamidine administration. Linear regression was also used to evaluate the variable(s) to determine if there was any association with a greater likelihood of route-induced reaction. The data and statistics were analyzed by using SPSS statistical analysis software (IBM, Armonk, NY).

Results

A total of 96 patients between the ages of 4 months and 30 years were identified as having received prophylactic pentamidine over the 3-year study period. Thirty-one patients (33%) received aerosolized pentamidine, whereas 65 (67%) received the intravenous formulation. Sex distribution was equal among both formulation groups, whereas most patients were identified as Caucasian in both groups (Table). Owing to limitations related to the nebulization procedure, the average age in each group differed by 8 years with the aerosolized pentamidine group having a mean age of 17 years and the intravenous pentamidine group having a mean age of 9 years (Table).

The primary objective of this study was to compare the tolerability of aerosolized versus intravenous pentamidine. Ten of 96 patients (10%) who had received pentamidine for PJP prophylaxis experienced a reaction to either the intravenous or aerosolized pentamidine formulation. Of the 10 patients who reacted to pentamidine, 1 (10%) received aerosolized pentamidine while 9 (90%) received the intravenous formulation ($p = 0.134$) (Figure 2).

The secondary study objectives that were included in the comparative assessment of reaction(s) to pentamidine relative to diagnosis, dosing frequency, and pentamidine administration route were assessed within 3 diagnoses groups categorized as blood cancer, solid tumor, and non-oncologic diagnosis. Forty-eight patients (50%) had a diagnosis of blood cancer, and 8 (19%) of these patients reacted to pentamidine ($p = 0.042$). The 2 (7%) remaining patients in the reaction group had a solid tumor diagnosis and there were no reactions in the non-oncologic group. We further evaluated for any relationship between route of administration and frequency of administration. Seven of the 10 patients (70%) who had reacted to pentamidine received pentamidine 2 times per month ($p = 0.047$). Nine of the 10 patients (90%) reacted after subsequent doses ranging from the second dose to repeated reactions throughout their prophylactic course ($p = 0.039$) (Figure 3). Specifically, in the intravenous pentamidine group, 8 of the 9 patients (89%) had reacted after receiving 2 or more doses ($p = 0.009$). Also, within the intravenous group, 2 of the 9 patients required desensitization owing to severity of allergic reaction. Lastly, only 2 of the 10 patients (20%) were receiving active chemotherapy when they experienced a pentamidine reaction, compared with those not receiving chemotherapy ($p = 0.193$). The chemotherapy group consisted of medications including but not limited to vincristine, methotrexate, cyclophosphamide, and cytarabine. The non-chemotherapy group included patients who received medications including but not limited to dexamethasone, prednisone, cyclosporine, and tacrolimus.

Reactions to pentamidine described in this study consisted of a wide variety of symptoms, thus preventing their categorization into one particular reaction(s) classification. Within the population of patients that reacted to pentamidine, intravenous pentamidine was associ-

Figure 2. Percentage of population that reacted to pentamidine compared with total study population.

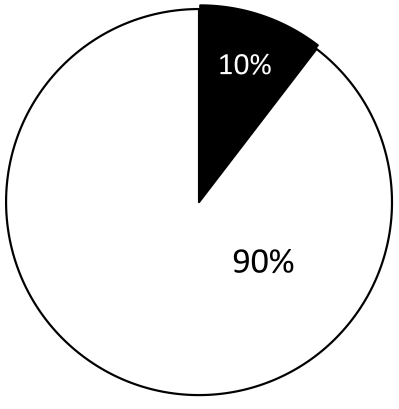
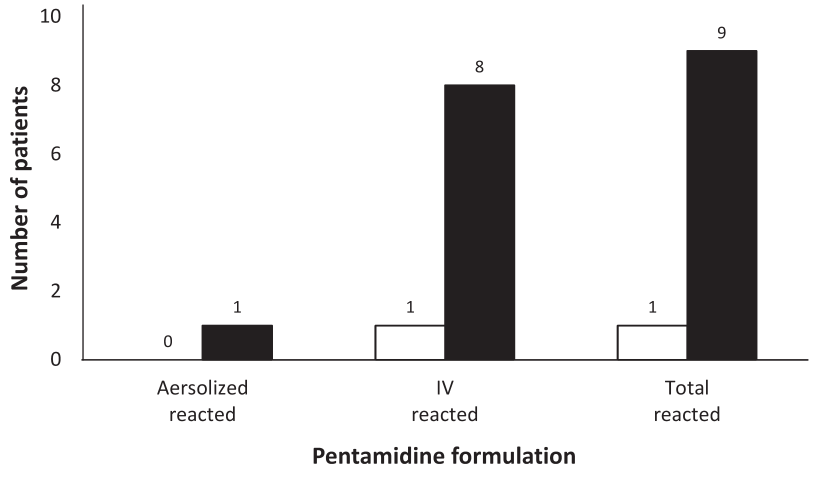


Figure 3. Comparison of pentamidine formulation and number of administrations to incidence of reaction.



ated with tingling lips and tongue, tingling extremities, increased work of breathing, and chest tightness, while aerosolized pentamidine was associated with increased work of breathing and chest tightness. All of these reactions were experienced during the pentamidine infusion or aerosolization and resulted in discontinuation of the medication. Since these reactions lessened or resolved with diphenhydramine it would appear that these reactions were anaphylactoid in nature. A few cases resulted in patients requiring desensitization to continue pentamidine therapy.

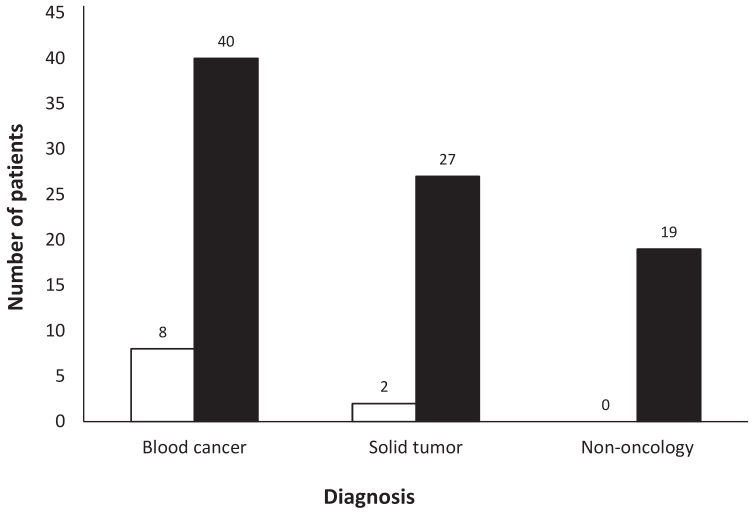
Discussion

A lack of information exists regarding the tolerability of aerosolized versus intravenous pentamidine. Numerous trials have described the efficacy of pentamidine when administered via the aerosolized or intravenous routes.[4–7] Our study focused on comparing the tolerability of the 2 administration routes in patients in a pediatric hospital, including both pediatric and adolescent and young adult patients. The primary objective of our study evaluating for any differences in tolerability between the 2 routes of administration proved to be statistically non-significant, which led to failure of rejecting the null hypothesis. Nevertheless, 9 of the 10 identified patients who experienced a reaction to pentamidine received the intravenous formulation, suggesting possible better tolerability with the aerosolized formulation. While the primary objective was not proven to be statistically significant, several secondary objectives were identified as significant and present an opportunity for further investigation.

Of the 96 patients studied, 10 patients (10%) had experienced a pentamidine-associated reaction during the 3-year study period. Of the subset of patients that had a reaction, only 1 patient reacted to aerosolized pentamidine, whereas 9 patients reacted to the intravenous formulation ($p = 1.00$). The reactions were classified as allergic reactions or anaphylaxis and included symptoms such as numbness of the lips and tongue and increased work of breathing. Two of the 10 patients (20%) did require desensitization to pentamidine during the study period owing to the individual severity of the reaction. Though not statistically significant, reactions experienced by those patients who received intravenous pentamidine were greater than for those who received aerosolized pentamidine (Figure 3). When the study population was examined, those of Caucasian race made up a majority of those who reacted ($p = 0.028$). While this outcome was statistically significant, data may be skewed owing to the majority of our population being of Caucasian race. In addition to race, several other factors were evaluated as secondary objectives, including incidence of reaction compared with dose, number of doses received, and diagnosis.

Anaphylaxis is defined as a rapid, generalized, and often unanticipated immunologically mediated event that can occur after exposure to certain foreign substances.[8] In many instances, reactions can recur or intensify after a second exposure to the agent owing to a more sensitized immune system. The 10 patients who reacted were stratified on the basis of the number of pentamidine administrations prior to the reaction in an attempt to identify whether the reactions were more common after the first or subsequent administrations. Upon patient reaction to pentamidine the infusion was extended from 60 minutes to 120 minutes and symptoms were treated on an individual basis; if reaction persisted pentamidine was discontinued. Overall, 9 of 10 (90%) patients who reacted did so after subsequent

Figure 4. Comparison of clinical diagnosis to incidence of reaction.



☐ Reacted; ■ Did not react

administrations of pentamidine regardless of the formulation. This increased incidence of reaction following subsequent doses could suggest that pentamidine reactions are immunomodulated and related to a type of anaphylactoid reaction. Another area examined was the incidence of reaction related to the patient diagnosis. The list of diagnoses was extensive and divided into 3 different categories by the type of diagnosis. These categories included blood cancer, solid tumor, and non-oncologic (Figure 4). Overall there was an increase in reactions noted in the blood cancer diagnosis group. However, patients with a blood cancer diagnosis may more commonly receive pentamidine prophylaxis owing to prolonged myelosuppression in which SMZ-TMP may cause additive toxicity.

Treatment of the disease states of those patients included in this study require medications that can alter how the body's immune system functions. It is possible that these therapies alter a patient's immune response and affect their tolerance to pentamidine and thus the increased incidence of reactions. Treatments were divided into chemotherapy and non-chemotherapy (i.e., other immunosuppressant medications) and assessed by incidence of reaction. This objective did not prove to be statistically significant, though patients who received chemotherapy had a higher incidence of reactions than those who did not receive chemotherapy.

Limitations of Study

Pentamidine tolerability differences between aerosolized and intravenous routes were not established in our study, supporting that both administration routes are equally safe and tolerated among pediatric and adolescent and young adult immunosuppressed patients. One strength of this study was that it included both pediatric and adolescent and young adult patients, which broadened the population analysis. Adolescent and young adult patients (n = 23) were not excluded because these patients were being treated per pediatric protocols. That being said, aerosolized pentamidine is less likely to be administered to younger patients owing to the required nebulization. The inclusion of patients older than 18 years may have skewed the total population in favor of aerosolized pentamidine.

Another strength of this study was that it adds to the current body of literature by comparing pentamidine administration routes. This study provides a basis for further investigation into the safety of aerosolized versus intravenous pentamidine, given data that suggest a possible association of increased reactions with intravenous pentamidine. Weaknesses of this study include a small sample size, retrospective chart review, and the potential interference of other concomitant medications. Despite expanding the study period to 3 years, a total of 96 patients were identified as having received pentamidine. It may have benefited to increase the time frame over which data were gathered to increase the sample size of the study. Owing to the retrospective and single center design of this study it is difficult to extrapolate the results across other institutions. Lastly, concomitant medications including diphenhydramine, albuterol, and steroids were used during the course of this study period. The concomitant use of these medications may have contributed to the tolerability of pentamidine but are difficult to control for in this complex patient population.

Conclusions

Though the primary objective of this study was not statistically significant, this study identified several areas of interest for further investigation that could prove to be of clinical importance. The first of these being the association between race and incidence of reaction. Though most of the population was of Caucasian race, the statistical value for the correlation of reaction cannot be ruled out as inconsequential. A second opportunity for further investigation would be to assess the correlation between blood cancer and reaction to pentamidine. Limiting the patient population to this diagnosis could establish a more clinically significant relationship. Further investigation comparing the safety of the administration routes of pentamidine is warranted. Since the performance of our study and submission of our manuscript, we have been made aware of a pending publication of a much larger trial assessing similar study targets as our own. Our study results are supported by this publication.[9]

ARTICLE INFORMATION

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Ethical Approval and Informed Consent Given the nature of this study, the institution review board/ethics committee at Rainbow Babies and Children's Hospital did not require HIPAA Authorization, Assent, and Parental Permission under Expedited criterion.

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