AerodigestiveAdverse Effects duringIntravenous Pentamidine Infusion for *Pneumocystis jirovecii*Pneumonia Prophylaxis

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Intravenous Pentamidine	IV-P
Pneumocystis jiroveci pneumonia	PCP
Hematopoietic stem cell transplantation	HSCT
Aerodigestive adverse effects	AD-AE
Hematopoietic stem cell transplantation	HSCT

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Abstract

Aerodigestive adverse effects (AD-AE) during intravenous pentamidine (IV-P) infusion for *Pneumocystis jirovecii*pneumonia prophylaxis are uncommonin retrospectivechart review studies. We conducted a survey in patients on IV-P, which included thirty-one specific questions. Twenty-five patients were included in the analysis; AD-AE were observed in twenty -two (88%) with recurrence of symptoms in 88% participants with subsequent infusions. Five leading symptoms were congestion (48%), lip tingling (32%), nausea (28%), tongue tingling (24%), vomiting, and throat swelling (17%); multiple symptoms were reported in 72% of the patients. In conclusion, AD-AE of IV-P infusion are common, self-limited and tend to be recurrent.

Introduction

Intravenous pentamidine (IV-P) isused for *Pneumocystis jirovecii*pneumonia (aka *Pneumocystis carnii* pneumonia;PCP) prophylaxis in immunocompromised children successfully who could not tolerate standard trimethoprim/sulfamethoxazole therapy.[1]Overall well-tolerated,IV-P has been associated with some adverse reactions observed during infusion, reported often by reviewing charts in the published literature. The most common side effect in children include nausea at 11.9%;paresthesiaof the perioral areain less than 5%.[2,3]According to the package insert, aerodigestive symptoms were seen in less than 1% of patients. In preliminary observations, the incidence of aerodigestive adverse effects (AD-AE) associated with IV-P infusion for PCP prophylaxishad appeared higher; therefore, we investigated the incidence and characteristics of AD-AE during IV-P infusion.

Material and Methods

Thisstudy was approved by the Institutional Review Board at Wayne State University. A survey platform was utilized with the expectation that recall bias is minimized; the survey was taken on the day patients were receiving IV-P infusion in all, but one patient. Patients undergoing chemotherapy or following hematopoietic stem cell transplantation (HSCT) receiving IV-P or those who had

received treatment within the last six monthswere included in the study as IV-P is the preferred choice for PCP prophylaxis in our practice for patients who do not tolerate trimethoprim/sulfamethoxazole. Survey was given after signed consents were obtained from either patients (18 and older) or their guardians (younger than 18) along with signed assent forms when necessary.During the study period, participants were asked to complete a one-time survey that included thirty-one questions on their experience with repeated administrations. Both participating patients and their parents contributed to the completion of the survey.

Pentamidine (Pentam 300; APP Pharmaceuticals; Schaumburg, IL, USA) is prepared in 50mL of 5% dextrose as suggested in the package insert (the dose to be diluted in 50–250mL of 5% dextrose).The solution is infused in the outpatient clinicat4mg/kg dose with amaximum dose of 300mg over one hourin the range recommended in the package insert (60–120 minutes). All patients receiving IV-P were given ondansetron prior to initiating the infusion.

The survey asked participants for the presence of the following symptoms: tingling, itching, swelling or pain in the lips/tongue/throat, nausea, vomiting, congestion, runny nose, itchy nose, cough, wheezing, chest tightness, chest pain, skin rash and other symptoms or signs. The data was entered in table format and the numbers of interested frequencies were manually calculated, since the number of participants was small.

Results

In this study, twenty-nine patients completed the survey and four declined to participate. Four patients less than four years of age were excluded due to concerns about the accuracy of certain subjective symptom reporting; twenty-five patients were included in the final analysis.Twenty four patients were on active chemotherapy or post–HSCT and one had completed treatment at the time of survey. Median age was eight (4–21), all but two were children;twenty were males and five females.The most common diagnosis was leukemia. Eighteen patients were treated on

chemotherapy and sevenwere HSCT recipients. None of the patients developed PCP during the follow up (Table1).

Reactions were observed in twenty-two (88%) patients and twenty (80%) reported onset of symptoms within the first thirty minutes of infusion. Patients with AD-AE received a median of 17IV-P doses (3-38) until the survey. Symptoms did not subside upon infusion completion in twenty (80%) patients and recurrence of symptoms with subsequenttreatmentwere seen in twenty-two (88%). The five leading symptoms were nasal congestion (48%), lip tingling (32%), nausea despite ondansetron premedication (28%), tongue tingling (24%), and vomiting, and throat swelling (16%). A single symptom was reported in seven (28%) patients. One participant experienced a combination of eight symptoms, two had seven, and three reported fiveoverrepeated IV-P infusions (Table1). No patients discontinued IV-P due to side effects. Two patients were given diphenhydramine without resolution of the symptoms.

Discussion

Several studies used chart review as their method to determine IV-P treatment-related adverse effects in the published literature. In a retrospective study of one hundred six patients, adverse reaction incidence was 17.8%as monthly doses at 4mg/kg infused over fourhours. Nausea was seen in 11.9%, tachycardia, dyspnea, skin itching each in 2.5%, hypotension, fever, paresthesia each in 1.7%. The drug was discontinued in 1.7% of the patients.[2]In one hundred eleven HSCT recipients treated with IV-P twice monthly, hypotension was reported in 3.6%, pancreatic dysfunction in 3.6%, perioral numbness/tingling in 2.7%, skin rash/pruritus in 2.7%, dyspnea/tachycardia in 1.8%, nausea/vomiting in 1.8% and abdominal pain in 0.9% in this chart review; 12.6% of the patients had IV-P discontinued.[3] In another retrospective study, 6% discontinued due to adverse reactions, including tachycardia in 2.1% and shortness of breath in 1.2% of the three hundred thirty-threeHSCT cases reviewed.[4]

The results of this study are quite different thanthe published literature;AD-AEincidence wasmuch higher at 88%. There are several potential factors in play for the observed differences. The most important one is themethod used; the results in this study arebased on active reporting by the patients and/or their caregivers, rather than retrospectively reviewing the medical records. Furthermore, directed and detailed questions included in the surveywere helpful in identifying the IV-P infusion-associated symptoms. Aninteresting finding of this study is the mild and transient nature of the aerodigestive symptoms, which could be difficult to capture in a retrospective chart review due to potential lack of proper documentation. We do not think that higher frequency is primarily due to the way drug was administrated; however, wonder if increasing the dilution and/or infusion time could help with AD-AEdevelopment. Since two cases in our seriesdid not benefit from diphenhydramine treatment when they had symptoms, we did not use it in the treatment or included as a premedication. However, it might be reasonable to try adding diphenhydramine to premeds to test its efficacy in prevention of AD-AE.

It is important to realize thehigh incidence of AD-AE, since these may be easily mistaken as early signs of a developing serious allergic reaction and may lead to unnecessary interventions, includingdiscontinuation of IV-P. We evaluated all the patients experiencing AD-AE very closely and were ready to escalate the interventions, if symptoms worsened. In fact, we hadpaused infusions in many cases;whilesome experienced returning symptomsata much lower intensity upon resumption of infusionin this cohort. Overall, 88% of the patients experienced recurrence of symptoms with subsequent IV-P treatments;however, they were mild and did not require additional interventions.

Drug hypersensitivity can be allergic or non-allergic in nature. Allergic reactions are either IgE-, IgG- or cell-mediated. Pegaspargase-associated allergic reactions are mainly mediated by anti-PEG, but not anti-L-asparaginase antibodies.[5]Grade 3 or grade 4 reactions were seen in 13.5% and 41.2% in two different studies using pegaspargase and L-Asparaginase, respectively.[5]Theobserved AD-AEin this study population could be due to aallergic reaction.However, the high incidence raises the

possibility of a non-immunological operational mechanism. Drug-induced non-allergic reactions have different mechanisms and mediators as exemplified in drug-induced angioedema and cyclophosphamide-induced facial discomfort, which are reminiscent of non-allergic rhinitis.[6-8] Symptoms result from secretion of different mediators including bradykinin as a direct effect of the drugs on certain tissues or autonomic nervous system stimulation.Some of the symptoms documented in above-mentionedconditions, such as oropharyngeal tingling and nasal congestion,are shared by severalaffectedpatients in our series raising the possibility of a common underlying pathophysiology.On the other hand it is possible that some individuals may have allergic reactions to IV-P and require appropriate interventions.

Our results indicate that AD-AE of IV-P are common, typically start early during infusion, are generally mild,well-tolerated, self-limited in nature,and tend to be recurrent. Though, this study has the advantage of dependence on the patients'/caregivers' reporting in the form of responses to specific questions compared to retrospective chart review approach, studies with larger numbers would give more accurate frequencies. It is possible that observed AD-AE are not mediated through animmunological mechanism.

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Table1. Characteristics of patients and adverse effects observed in the study.

Study participants	**25**
Average age	8 (4 – 21)
Gender	
Male	20 (80%)
Female	5 (20%)
Pneumocystis carinii prophylaxis indication	
Chemotherapy	18 (72%)
Hematopoietic stem cell transplant recipient	7 (28%)
Pentamidine therapy status	
Active	24 (96%)
Completed	1
Patients with adverse effects	22 (88%)
Number of Pentamidine doses received until survey in patients with reactions	
Median	17 (3 – 38)
Adverse events	
Nasal congestion	12 (48%)
Lip tingling	8 (32%)
Nausea	7 (28%)
Tongue tingling	6 (24%)
Vomiting	4 (16%)
Throat swelling	4 (16%)
Throat tingling	3 (12%)
Throat itching	3 (12%)
Runny nose	3 (12%)
Nose itching	3 (12%)
Cough	3 (12%)
Tongue swelling	2 (8%)
Chest tightness	2 (8%)
Lip swelling, lip itching, lip pain, wheezing, chest pain, skin rash	1 each
Combination of different symptoms experienced throughout	
8	1
7	2
5	3
3	3
2	6
1	7
Symptom recurrence	22 (88%)