

# Aerodigestive adverse effects during intravenous pentamidine infusion for *Pneumocystis jirovecii* pneumonia prophylaxis

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## Abstract

Aerodigestive adverse effects (AD-AE) during intravenous pentamidine (IV-P) infusion for *Pneumocystis jirovecii* pneumonia prophylaxis are uncommon in retrospective chart review studies. We conducted a survey in patients on IV-P, which included 31 specific questions. Twenty-five patients were included in the analysis; AD-AE were observed in 22 (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.

## KEYWORDS

adverse reactions, aero-digestive, children, intravenous, pentamidine

## 1 | INTRODUCTION

Intravenous pentamidine (IV-P) is used for *Pneumocystis jirovecii* pneumonia (also known as *Pneumocystis carinii* pneumonia [PCP]) prophylaxis in immunocompromised children successfully who could not tolerate standard trimethoprim/sulfamethoxazole therapy.<sup>1</sup> 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 is nausea at 11.9%; paresthesia of the perioral area is reported in less than 5%.<sup>2,3</sup> 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 prophylaxis had appeared higher; therefore, we investigated the incidence and characteristics of AD-AE during IV-P infusion.

## 2 | MATERIALS AND METHODS

This study 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 6 months were 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 31 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) is prepared in 50 mL of 5% dextrose as suggested in the package insert

**Abbreviations:** AD-AE, aerodigestive adverse effects; HSCT, hematopoietic stem cell transplantation; IV-P, intravenous pentamidine; PCP, *Pneumocystis jirovecii* pneumonia

(the dose to be diluted in 50-250 mL of 5% dextrose). The solution is infused in the outpatient clinic at 4 mg/kg dose with a maximum dose of 300 mg over 1 h in the range recommended in the package insert (60-120 min). 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 were entered in table format and the numbers of interested frequencies were manually calculated, since the number of participants was small.

### 3 | RESULTS

In this study, 29 patients completed the survey and four declined to participate. Four patients less than 4 years of age were excluded due to concerns about the accuracy of certain subjective symptom reporting; 25 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 seven were HSCT recipients. None of the patients developed PCP during the follow up (Table 1).

Reactions were observed in 22 (88%) patients and 20 reported onset of symptoms within the first 30 min of infusion. Patients with AD-AE received a median of 17 IV-P doses (3-38) until the survey. Symptoms did not subside upon infusion completion in 20 patients and recurrence of symptoms with subsequent treatment were seen in 21 patients with reactions. The five leading symptoms were nasal congestion (48%), lip tingling (32%), nausea despite ondansetron premedication (28%), tongue tingling (24%), 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 five overrepeated IV-P infusions (Table 1). No patients discontinued IV-P due to side effects. Two patients were given diphenhydramine without resolution of the symptoms.

### 4 | 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 106 patients, adverse reaction incidence was 17.8% as monthly doses at 4 mg/kg infused over 4 h. Nausea was seen in 11.9%; tachycardia, dyspnea, skin itching each in 2.5%; and hypotension, fever, paresthesia each in 1.7%. The drug was discontinued in 1.7% of the patients.<sup>2</sup> In 111 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

**TABLE 1** 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 by patients	
8	1
7	2
5	3
3	3
2	6
1	7
Symptom recurrence	21

IV-P discontinued.<sup>3</sup> In another retrospective study, 6% discontinued due to adverse reactions, including tachycardia in 2.1% and shortness of breath in 1.2% of the 333 HSCT cases reviewed.<sup>4</sup>

The results of this study are quite different than the published literature; AD-AE incidence was much higher at 88%. There are several

potential factors in play for the observed differences. The most important one is the method used; the results in this study are based 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 survey were helpful in identifying the IV-P infusion-associated symptoms. An interesting 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 administered; however, wonder if increasing the dilution and/or infusion time could help with AD-AE development. Since two cases in our series did 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 the high 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, including discontinuation 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 had paused infusions in many cases, while some experienced returning symptoms at a much lower intensity upon resumption of infusion in this cohort. Overall, all cases but one with reactions 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 nonallergic 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.<sup>5</sup> Grade 3 or grade 4 reactions were seen in 13.5% and 41.2% in two different studies using pegaspargase and L-asparaginase, respectively.<sup>5</sup> The observed AD-AE in this study population could be due to an allergic reaction. However, the high incidence raises the possibility of a nonimmunological operational mechanism. Drug-induced nonallergic reactions have different mechanisms and mediators as exemplified in drug-induced angioedema and cyclophosphamide-induced facial discomfort, which are reminiscent of nonallergic rhinitis.<sup>6-8</sup> 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-mentioned conditions, such as oropharyngeal tingling and nasal congestion, are shared by several affected patients 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. Although 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 an immunological mechanism.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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