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# Risks and mitigation strategies to prevent etoposide infusion-related reactions in children

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## Abstract

Etoposide is an antineoplastic agent widely used for treatment of many pediatric cancers. Etoposide has been associated with infusion-related reactions. In this brief report, we compare etoposide infusion-related reactions that occurred over a 10-year period at two freestanding pediatric hospitals. Infusion reactions occurred in 1% of patients at two hospitals across the study period. Rates of 4.8%, 3.4%, and 7.9% were observed at Children's Mercy Hospital during 2018, 2019, and 2020, respectively, after the implementation of in-line filters during etoposide infusions in late 2017. Of the 32 patients who experienced adverse reactions, 41% were rechallenged after the reaction and all were able to tolerate at least one future dose with either pre-treatment or extending infusion duration. This work highlights the importance of a multicenter approach to investigating adverse drug reactions (ADRs) as variation in practice can provide key information about ADRs and potential risk factors.

### Keywords

child; drug hypersensitivity; drug-related side effects and adverse reactions

## 1 | INTRODUCTION

Etoposide is an antineoplastic agent used in more than a dozen pediatric chemotherapeutic regimens including treatments for various leukemias, lymphomas, sarcomas, neuroblastomas, rhabdoid and germ cell tumors. Case reports have described

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CONFLICT OF INTERESTS

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infusion-related reactions with etoposide.[1–4] The package insert reports anaphylactic-like reactions including chills, fever, tachycardia, bronchospasm, dyspnea, and hypotension occurring in 0.7%–2% of patients receiving etoposide.[5] Primary literature estimates infusion reactions occur in 1.3%–27.1% of patients receiving etoposide.[6,7] We present a 10-year experience of etoposide use and describe infusion-related reactions at two freestanding pediatric hospitals.

## 2 | METHODS

After institutional review board approval, total doses of etoposide and etoposide phosphate were identified and infusion-related reactions were retrospectively evaluated from January 1, 2010 to July 31, 2020 at Children's Mercy Hospital (CMH), Kansas City, MO, and Riley Hospital for Children (RH), Indianapolis, IN. Both institutions used a standard etoposide concentration of 0.4 mg/ml. In-line filter (ICU Medical, 12" Ext Set w/ MicroClave®, 0.2 Micron Low Protein Binding Filter) use was standard protocol for etoposide administration at CMH starting in October 2017, due to potential for precipitation and recommendation in the package insert.[5] No filters were used at RH during the study period. Etoposide was infused over 1 h at CMH and 2 h at RH, but infusion rate could be modified by providers. Both institutions identified etoposide infusion reactions using multiple detection methods including adverse drug reactions (ADRs) entered into the electronic medical record (EMR); international classification of disease (ICD)-9 and ICD-10 codes for anaphylaxis, flushing, rash, or hypotension; orders for diphenhydramine, hydrocortisone, or epinephrine within 24 h of etoposide dose; and orders for etoposide phosphate as this formulation is used when patients have had an etoposide infusion reaction. These triggers prompted manual EMR review to collect data related to the infusion reaction. modified Hartwig's Severity Assessment Tool was used to classify ADR severity.[8] A mild reaction is when a drug was continued without any treatment, a moderate reaction is when the drug was stopped and/or required treatment, and a severe reaction caused hospital admission, permanent disability, delayed discharge, or was life threatening.[8,9] CMH has a prospective pharmacovigilance program; therefore, a clinical pharmacist was available to review EMR documentation and interview patients or clinicians to gather any additional data that was absent from the EMR. However, data collection at RH was completed retrospectively. Statistical significance between groups was evaluated using a chi-square analysis.

## 3 | RESULTS

We identified 32 patients experiencing etoposide infusion-related reactions (Table 1). Overall, 17,134 doses of etoposide were administered to 3445 unique patients and 32 patients (1%) experienced etoposide infusion-related reactions (Figure 1). At RH, 7489 doses of etoposide were administered to 652 unique patients and three patients (0.5%) experienced etoposide infusion-related reactions. At CMH, 9645 doses of etoposide were administered to 2793 unique patients and 29 patients (1%) experienced infusion-related reactions over the 10-year period. Twenty-eight of these etoposide infusion-related reactions occurred at CMH between 2018 and 2020 with ADR rates of 4.8%, 3.4%, and 7.9% during 2018, 2019, and 2020, respectively (Figure 2). Incidence of etoposide infusion-related reaction with respect to filter was compared using a chi-square analysis. At CMH, only

one reaction occurred in 2198 patients prior to filter use and 28 reactions occurred in 566 patients after filter ($p < 0.01$). Overall, at CMH and RH, four reactions occurred in 2847 patients when no filter was used and 28 reactions occurred in 566 patients when a filter was used ($p < 0.01$).

The age of patients experiencing etoposide infusion-related reactions was 8.5 ± 5.8 years (mean ± standard deviation (SD)), with 17 male and 15 female patients, 26 (81%) patients were white/non-Hispanic, 3 Hispanic (9%), 1 black (3%), 1 multiracial (3%), and 1 race marked as other. Sixteen patients (50%) had a history of a previous food or drug allergy, and six patients (19%) had a documented past medical history of an allergic (seasonal allergies, 1 patient) or inflammatory condition (asthma, 3 patients; eczema, 2 patients).

Infusion reactions occurred with the first dose in 17 (53%) patients. These etoposide infusion-related reactions were not associated with a single manufacturer or lot number, as a variety of manufacturers and lots were administered over this time period. Seven (22%) of the etoposide infusion-related reactions were characterized as severe and 25 (78%) were characterized as moderate. No patients required admission to the intensive care unit and all fully recovered.

Twenty-eight patients (88%) experienced multiple symptoms during the etoposide infusion, with an average of 2.8 ± 1.1 symptoms per patient. The most common symptoms were flushing and difficulty breathing (including chest or throat tightness) which occurred in 23 patients (71%), coughing in 16 patients (50%), facial or lip swelling in 14 (44%), redness or rash in 11 (34%), and nausea and vomiting in 11 patients (33%).

Multiple treatments were administered to 19 patients (59%) with an average of 2.2 ± 1.5 treatments per patient. The most common treatment was diphenhydramine which was given to 30 patients (94%), hydrocortisone in 8 patients (25%), histamine H2-receptor antagonist in 6 patients (19%), and intravenous fluids in 5 patients (16%). The infusion time was extended in 9 patients (28%).

Thirteen patients (41%) were rechallenged with etoposide after the reaction, and all were initially able to tolerate at least one future dose with either pre-treatment and/or extending infusion duration. Twelve patients were pre-treated with a histamine-1 antagonist (diphenhydramine or cetirizine), two patients were pre-treated with a histamine-2 antagonist (famotidine), and 10 had the infusion time extended. However, despite pre-treatment, 3 of the 13 patients rechallenged did subsequently experience a second reaction with etoposide resulting in a change to etoposide phosphate formulation. Nineteen patients (59%) were never rechallenged with the standard etoposide formulation, and treatment was changed to etoposide phosphate. Overall, 22 patients (69%) ultimately received etoposide phosphate and no infusion reactions were reported with this formulation.

## 4 | DISCUSSION

We report a series of etoposide infusion-related reactions occurring at two free standing pediatric institutions. Specifically, our results highlight three key findings: (1) etoposide infusion-related reactions appear to be associated with high rates when in-line filters are

used during infusion, (2) most patients who have experienced etoposide infusion-related reactions will tolerate subsequent administrations by premedicating with antihistamine drugs and slowing of the infusion rate, and (3) flushing and difficulty breathing were the most commonly encountered symptoms and should be monitored for closely during an etoposide infusion.

The rate of etoposide infusion-related reactions at CMH was more than twice that at RH, but more interestingly across both institutions, two etoposide infusion-related reactions occurred in 2012, one at each institution, and the remaining 30 ADRs all occurred during the 4-year period between 2017 and 2020, with no etoposide infusion-related reactions reported in 2010, 2011, 2013–2016. The increased number of etoposide infusion-related reactions at CMH was not associated with an increased number of patients receiving etoposide as the rates of ADRs per unique patients were 4.8%, 3.4%, and 7.9% in 2018, 2019, and 2020, respectively. This increased rate of etoposide infusion-related reactions and clustering over this time period at CMH prompted both centers to evaluate potential differences in practice between our respective institutions and during the different time periods. Two distinct differences between institutional standard practices are infusion time and use of an in-line filter. At RH the standard infusion time for etoposide is 2 h and the standard infusion time at CMH is 1 h. After extending the infusion time, 28% of CMH patients were able to tolerate future doses of etoposide. Rate of infusion has previously been associated with etoposide infusion-related reactions, as faster rates result in more reactions.[7] The standard infusion times at each institution did not change during this study period, but the ability of clinicians to modify infusion times on a patient-by-patient basis is a potential limitation to our report. single-center study evaluating etoposide infusion-related reactions, a higher rate of infusion reactions occurred during the period when filters were used.[11] Although not conclusive, the clustering of etoposide infusion-related reaction between 2017 and 2020 at CMH occurred during the time when a filter was being used in clinical practice. The association with filters and anaphylaxis is not unique to etoposide. Four patients with thalassemia were reported to experience a type I allergic hypersensitivity reaction following transfusion that was linked to the ethylene oxide that was used to sterilize the heat sensitive leucocyte filter.[12] Although the filter used at CMH

The use of an in-line filter at CMH was standard of care to prevent precipitation as recommended by the package insert starting in late 2017.[5] Filters were not used at RH during this study period. The use of a filter has been discussed as a possible factor for anaphylactic infusion reactions with etoposide in previous reports.[10,11] Ina was not sterilized with ethylene oxide, it is uncertain if another component of this filter could be associated with these infusion-related reaction. Although filters may not be the first thing one would associate with an ADR, it is important to evaluate all components of the filter and properties of the drug being filtered.[13] At this point, our findings are observational and further evaluation is needed to understand the mechanism associated with the use of a filter in relation to etoposide infusion-related reactions. In-line filters and faster infusion ates are potential risk factors for etoposide infusion-related reactions and evaluation of practice across institutions could be informative o determine strategies to minimize ADR risk.

Often times when a patient experiences an ADR, the patient is not rechallenged and a therapeutic alternative is prescribed.[14] In cancer treatment, alternative therapeutic agents are often not an option. In our 10-year cohort, all 32 patients who experienced etoposide infusion-related reactions were successfully rechallenged with either etoposide or etoposide phosphate in order to complete their prescribed regimen. Sixty percent of patients were empirically changed to the etoposide phosphate formulation, which has comparable efficacy and has been shown to be associated with fewer infusion-related reactions compared to standard etoposide formulations, but due to the higher price, it is not typically used as first-line therapy.[7,15] The hospital cost of a 100-mg dose of the standard etoposide formulation would be approximately $5 compared to approximately $112 for a 100-mg dose of etoposide phosphate. The remaining 40% of patients who experienced etoposide reactions received premedication and/or modifications of infusion rates and tolerated subsequent infusions. Interestingly, no infusion-related reactions were associated with etoposide phosphate which although less likely than the standard etoposide formulation, it has been previously reported to occur.[7]

Etoposide infusion-related reactions are reported in both the package insert and previously published literature with a wide variety of symptomology.[1–5,7] Although in our cohort we present many possible symptoms, 71% of patients experienced flushing and respiratory distress. This is important, as monitoring for these symptoms should occur during etoposide infusions.

Due to the retrospective nature of this study, it is possible that some etoposide infusion-related reactions could have been missed, however, multiple approaches were used to identify reactions. There is the potential that a mild or early reaction could have been quickly aborted by an attentive clinician who adjusted the rate, thus avoiding a severe reaction which would have then warranted treatment. Our work highlights the importance of looking across sites at ADRs as variation in practice can provide key information about ADR and potential risk factors emphasizing the critical need for a systematic approach to identifying ADR trends across institutions. Future etoposide infusion-related reactions may be prevented or quickly identified by implementing slower infusion times, eliminating in-line filter use, administering standard premedication, and closely monitoring patients during infusions.

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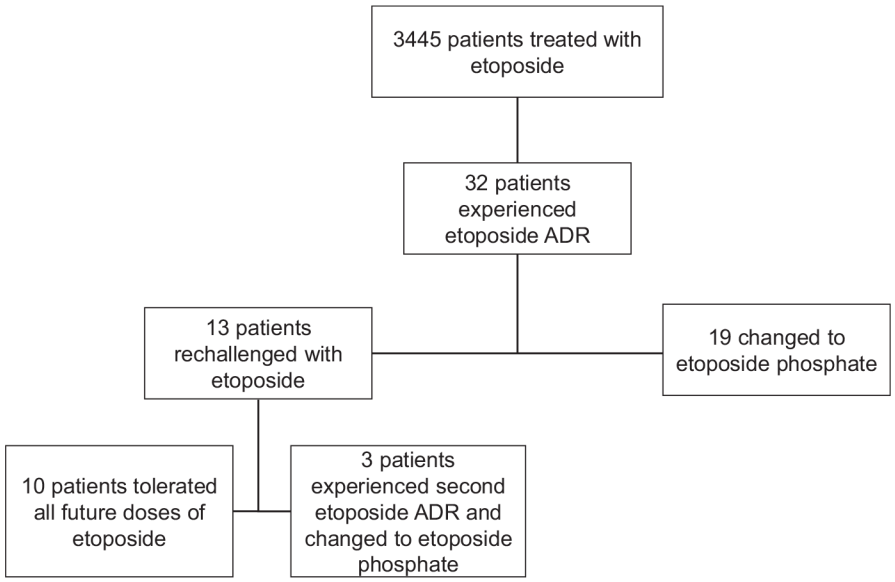


**FIGURE 1.**

Etoposide patients. This figure shows the breakdown of how many patients initially received etoposide, patients who tolerated future doses, and patients who were changed to etoposide phosphate. ADR, adverse drug reaction

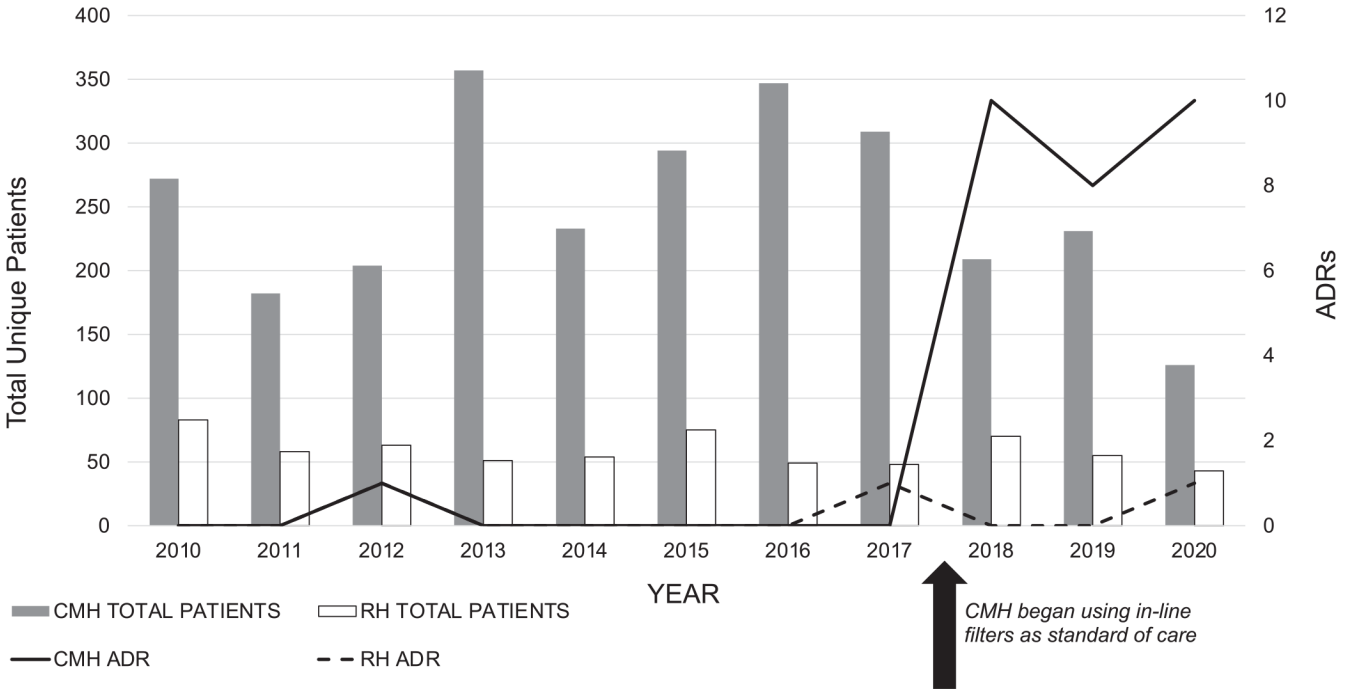


**FIGURE 2.**

Total etoposide patients and ADRs. Years are shown on the x-axis, total unique patients that received etoposide are shown in histogram plotted on the primary y-axis with CMH shown in dark bars and RH in the outlined bars. The overlaid lines are showing the ADRs that occurred at each institution per year plotted on the secondary y-axis, with the solid line for CMH and the broken line for RH. The arrow marks the beginning of standard of care in-line filter use at CMH in October 2017. ADR, adverse drug reaction; CMH, Children's Mercy Hospital; RH, Riley Hospital for Children

**TABLE 1**

Etoposide infusion reaction patient data

| Institution/ patient | Year of ADR | Age (months) | BSA ($m^2$) | Sex | Ethnicity | Etoposide dose number at time of reaction | Infusion time (min) | Etoposide rate (mg/$m^2$/h) | Symptoms | Severity | Treatment | Rechallenged | Able to tolerate future doses | Intervention for future doses |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| RH1 | 2012 | 78 | 1.1 | Female | Black | 1 | 60 | 180 | Anaphylaxis, shortness of breath, flushing, throat tightness | Severe | Diphenhydramine | No | – | Etoposide Phosphate |
| RH2 | 2017 | 147 | 1.25 | Male | White/ Non-Hispanic | 1 | 120 | 78 | Chest tightness | Moderate | Diphenhydramine | Yes | Yes | Pretreat with APAP and diphenhydramine |
| RH3 | 2020 | 178 | 1.51 | Female | White/ Non-Hispanic | 1 | 120 | 60 | Flushing, nausea, lip swelling | Severe | Diphenhydramine, lorazepam, ondansetron | Yes | Yes | Pretreat with APAP and diphenhydramine |
| CMH1 | 2012 | 142 | 1.4 | Female | White/ Non-Hispanic | 22 | 180 | 33 | Flushing, redness | Moderate | Diphenhydramine | Yes | Yes | Diphenhydramine |
| CMH2 | 2018 | 12.7 | 0.42 | Male | White/ Non-Hispanic | 1 | 60 | 140 | Facial swelling, flushing, redness, cough | Moderate | Hydrocortisone, diphenhydramine, IV fluids | No | – | Etoposide phosphate |
| CMH3 | 2018 | 232.2 | 2.2 | Male | White/ Non-Hispanic | 1 | 60 | 100 | Cough, numbness of face, redness, shortness of breath | Moderate | Hydrocortisone, diphenhydramine, oxygen | No | - | Etoposide phosphate |
| CMH4 | 2018 | 190.6 | 1.6 | Male | White/ Non-Hispanic | 6 | 60 | 100 | Throat tightness, shortness of breath | Moderate | Diphenhydramine | Yes | Yes, but second reaction | Pretreat with diphenhyd ramine, 2 h infusion. Second reaction and changed to etoposide phosphate |
| CMH5 | 2018 | 140.4 | 1.53 | Male | White/ Non-Hispanic | 13 | 60 | 150 | Headache, nausea, coughing, shortness of breath, flushing | Moderate | Diphenhydramine | Yes | Yes | Pretreat with diphenhydramine and 2 h infusion. |

*Pharmacotherapy*. Author manuscript; available in PMC 2021 November 26.

| Institution/ patient | Year of ADR | Age (months) | BSA ($m^2$) | Sex | Ethnicity | Etoposide dose number at time of reaction | Infusion time (min) | Etoposide rate ($mg/m^2/h$) | Symptoms | Severity | Treatment | Rechallenged | Able to tolerate future doses | Intervention for future doses |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CMH6 | 2018 | 186.9 | 1.9 | Male | White/ Non-Hispanic | 7 | 60 | 125 | Flushing, nausea, pressure | Moderate | Extended infusion time to 3 h, cetirizine, prednisone, diphenhydramine | Yes | Yes | 3-h infusion, cetirizine, prednisone |
| CMH7 | 2018 | 65.2 | 0.77 | Male | White/ Non-Hispanic | 1 | 60 | 100 | Abdominal pain, flushing | Moderate | Hydrocortisone, famotidine | No | – | Etoposide Phosphate |
| CMH8 | 2018 | 110 | 1.33 | Female | White/ Non-Hispanic | 1 | 60 | 101 | Throat irritation, difficulty breathing | Moderate | Diphenhydramine, ranitidine | Yes | Yes | 2-h infusion, diphenhydramine |
| CMH9 | 2018 | 32.9 | 0.61 | Male | White/ Non-Hispanic | 1 | 60 | 120 | Difficulty breathing, cyanosis, nausea, cough, lip swelling | Severe | Albuterol, diphenhydramine, epinephrine, hydrocortisone, IV fluids | No | – | Etoposide Phosphate |
| CMH10 | 2018 | 22.6 | 0.51 | Male | White/ Non-Hispanic | 4 | 60 | 53 | Rash, flushing, gagging | Moderate | Diphenhydramine | Yes | Yes, but second reaction | 2 h infusion, diphenhydramine, famotidine; Second reaction, changed to etoposide phosphate |
| CMH11 | 2018 | 90.4 | 0.92 | Male | White/ Non-Hispanic | 6 | 60 | 100 | Flushing, facial paresthesia, labored breathing | Moderate | Diphenhydramine, famotidine | Yes | Yes, but second reaction | 2 h infusion, diphenhydramine, famotidine; Second reaction, changed to etoposide phosphate |
| CMH12 | 2018 | 61 | 0.69 | Male | White/ Non-Hispanic | 1 | 60 | 100 | Anaphylaxis, coughing, hypotension, chest pain, periorbital swelling, flushing | Severe | Diphenhydramine, famotidine, epinephrine, hydrocortisone, IV fluids | No | – | Etoposide phosphate |
| CMH13 | 2019 | 76.5 | 0.74 | Female | Other | 4 | 60 | 88 | Flushing, facial swelling, throat irritation, cough | Moderate | Infusion stopped | No | – | Etoposide phosphate |

*Pharmacotherapy*. Author manuscript; available in PMC 2021 November 26.

| Institution/ patient | Year of ADR | Age (months) | BSA ($m^2$) | Sex | Ethnicity | Etoposide dose number at time of reaction | Infusion time (min) | Etoposide rate ($mg/m^2/h$) | Symptoms | Severity | Treatment | Rechallenged | Able to tolerate future doses | Intervention for future doses |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CMH14 | 2019 | 14.8 | 0.44 | Male | White/ Non-Hispanic | 1 | 60 | 52 | Wheezing, redness, swelling | Severe | Diphenhydramine, epinephrine, hydrocortisone, IV fluids, racemic epinephrine | No | – | Etoposide phosphate |
| CMH15 | 2019 | 104.5 | 1.23 | Female | Multiracial | 12 | 60 | 90 | Coughing, nausea, flushing | Moderate | Diphenhydramine | No | – | Etoposide phosphate |
| CMH16 | 2019 | 13.9 | 0.43 | Female | Hispanic | 1 | 60 | 51 | Coughing, flushing, emesis | Moderate | Diphenhydramine | Yes | Yes | 2 h infusion, diphenhydramine |
| CMH17 | 2019 | 76.2 | 0.88 | Female | White/ Non-Hispanic | 1 | 60 | 100 | Coughing, difficulty breathing | Moderate | Diphenhydramine | No | – | Etoposide phosphate |
| CMH18 | 2019 | 40.6 | 0.58 | Female | Hispanic | 6 | 60 | 97 | Coughing, itching, flushing, lip swelling | Moderate | Diphenhydramine | No | – | Etoposide phosphate |
| CMH19 | 2019 | 156.5 | 1.4 | Male | White/ Non-Hispanic | 1 | 60 | 100 | Shortness of breath, cyanosis, respiratory depression | Severe | Diphenhydramine, oxygen | No | – | Etoposide phosphate |
| CMH20 | 2020 | 185.1 | 1.25 | Female | White/ Non-Hispanic | 1 | 60 | 125 | Abdominal pain, throat discomfort | Moderate | Diphenhydramine | No | – | Etoposide phosphate |
| CMH21 | 2020 | 73.9 | 0.78 | Female | White/ Non-Hispanic | 4 | 60 | 100 | Urticaria | Moderate | Diphenhydramine | No | – | Etoposide phosphate |
| CMH22 | 2020 | 201.4 | 1.74 | Female | White/ Non-Hispanic | 1 | 60 | 125 | Difficulty breathing, nausea, flushing | Severe | Diphenhydramine, oxygen | No | – | Etoposide phosphate |
| CMH23 | 2020 | 197.4 | 1.73 | Female | White/ Non-Hispanic | 14 | 120 | 50 | Flushing, dyspnea, tachycardia | Moderate | Diphenhydramine | Yes | Yes | 3 h infusion |
| CMH24 | 2020 | 40.7 | 0.58 | Male | White/ Non-Hispanic | 1 | 60 | 57 | Itching, edema, cough, rash | Moderate | Diphenhydramine | No | – | Etoposide phosphate |
| CMH25 | 2020 | 25.8 | 0.56 | Female | White/ Non-Hispanic | 11 | 60 | 107 | Nausea, cough, flushing | Moderate | Diphenhydramine, famotidine, hydrocortisone | Yes | Yes | 2 h infusion, diphenhydramine |

*Pharmacotherapy*. Author manuscript; available in PMC 2021 November 26.

| Institution/ patient | Year of ADR | Age (months) | BSA ($m^2$) | Sex | Ethnicity | Etoposide dose number at time of reaction | Infusion time (min) | Etoposide rate (mg/$m^2$/h) | Symptoms | Severity | Treatment | Rechallenged | Able to tolerate future doses | Intervention for future doses |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CMH26 | 2020 | 19.1 | 0.46 | Female | White/ Non-Hispanic | 1 | 60 | 70 | Cyanosis, coughing, agitation | Moderate | Diphenhydramine | No | – | Etoposide phosphate |
| CMH27 | 2020 | 214.6 | 2.2 | Male | White/ Non-Hispanic | 5 | 60 | 125 | Anaphylaxis, facial swelling, chest tightness, shortness of breath | Severe | Diphenhydramine, hydrocortisone, epinephrine, albuterol, famotidine, IV fluids | No | – | Etoposide phosphate |
| CMH28 | 2020 | 25.1 | 0.57 | Male | White/ Non-Hispanic | 5 | 60 | 116 | Flushing, hypotension | Moderate | Diphenhydramine | No | – | Etoposide phosphate |
| CMH29 | 2020 | 128.4 | 1.37 | Male | Hispanic | 8 | 60 | 100 | Flushing, rash | Moderate | Diphenhydramine | Yes | Yes | 2 h infusion, diphenhydramine |

Abbreviations: ADR, adverse drug reaction; APAP, acetaminophen; BSA, body surface area; CMH, Children's Mercy Hospital; RH, Riley Hospital for Children.

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