Intravenous Cetirizine Premedication to Mitigate Infusion-Related Reactions

TIMOTHY TYLER,[1] PharmD, ERIK STOJANOFF,[2] PharmD, JOAN CANNON,[2] PharmD, MBA, JESSIE J. UM,[2] PharmD, BCPS, STACIA YOUNG,[2] PharmD, BCOP, MBA, JARROD P. HOLMES,[3] MD, FACP, LONNIE D. BRENT,[2] PharmD, and NANCY MARTIN,[2] MD, PharmD

From [1]Comprehensive Cancer Center at Desert Regional Medical Center, Palm Springs, California; [2]TerSera Therapeutics, Deerfield, Illinois; [3]Providence Medical Group, Santa Rosa, California

Authors' disclosures of conflicts of interest are found at the end of this article.

Correspondence to: Joan Cannon, PharmD, MBA, 520 Lake Cook Road, Suite 500, Deerfield, IL 60015
E-mail: jcannon@tersera.com

https://doi.org/10.6004/jadpro.2024.15.2.5

Abstract

Infusion-related reactions (IRRs) are a recognized concern for chemotherapy, biologic agents, and newer immunotherapies. Antihistamines are frequently recommended to prevent or manage these reactions. For over 60 years, diphenhydramine has been the only H_1 antihistamine for intravenous (IV) administration. It has been considered the standard of care as part of premedication regimens to prevent IRRs associated with these therapies despite the lack of a US Food and Drug Administration (FDA)-approved indication and no evidence of efficacy data. Intravenous cetirizine was approved in 2019 for acute urticaria treatment, making it the only second-generation H_1 antihistamine that can be administered intravenously. Compared with diphenhydramine, cetirizine has an improved safety profile with less sedation, fewer contraindications, lower incidence of anticholinergic side effects, and minimal risk of adverse events in elderly patients. A head-to-head study demonstrated that IV cetirizine is as effective as IV diphenhydramine in reducing IRRs and may decrease chair time, treatment center visits, and the need for rescue medication. Over the past 3 decades, the FDA has addressed the issue of IRRs by mandating language regarding the requirement or recommendation for premedication in the label of over 50 FDA-approved infusion products. As more therapeutics have premedication required or recommended, IV cetirizine should be considered an antihistamine for preventing and treating IRRs. In this article, we describe a patient whose IRR was successfully managed with IV cetirizine and discuss first- vs. second-generation H_1 antihistamines and their use in treating and preventing IRRs.

CASE STUDY

A 62-year-old woman with bilateral infiltrating ductal carcinoma (grade II estrogen receptor/progesterone receptor [ER/PR] positive, HER2/neu negative breast cancer) was administered intravenous (IV) diphenhydramine (DPH, Benadryl) 25 mg as a premedication for paclitaxel (Taxol) after undergoing four cycles of doxorubicin (Adriamycin) +

J Adv Pract Oncol 2024;15(2):125–135

cyclophosphamide (Cytoxan), or A/C chemotherapy. Soon after receiving IV DPH, she experienced a paradoxical reaction reported as significant discomfort and restlessness in her legs. Her premedication regimen initially included dexamethasone for the first dose of A/C. However, further steroid premedication therapy was withheld due to her preexisting diabetes and newly reported hyperglycemia after a cortisone injection to the right ankle. The paradoxical reaction to DPH worsened in severity with each subsequent paclitaxel cycle culminating in psychomotor agitation, leading the oncology nurse to request that DPH be withheld after the patient raised it as a complaint during her seventh paclitaxel dose. A decision was made to substitute IV DPH with IV cetirizine (Quzyttir) 10 mg before her next paclitaxel infusion. Psychomotor agitation ceased as the patient tolerated the IV cetirizine premedication with each of the remaining five paclitaxel infusions to complete the 12-course treatment without further incident and successfully underwent surgical treatment afterward.

Infusion-related reactions (IRRs) remain problematic and are often underreported with most systemic anticancer therapies (Roselló et al., 2017; Lenz, 2007). Taxane agents (e.g., paclitaxel [Abraxane], docetaxel [Taxotere]) and platinum drugs (e.g., cisplatin [Platinol], carboplatin [Paraplatin], oxaliplatin [Eloxatin]) are well-known instigators of IRRs despite remaining the backbones of solid tumor therapy (Boulanger et al., 2014; Hayes et al., 2021). Similarly, monoclonal antibodies (e.g., rituximab [Rituxan], obinutuzumab [Gazyva]) may result in high IRR rates (Rombouts et al., 2020). Although severe IRRs occur in less than 5% of cases, their occurrence can significantly impact patient outcomes (Clemmons et al., 2021). Clinicians must choose between discontinuing a vital and possibly life-saving therapy or continuing the treatment with the risk of inducing a severe IRR (Boulanger et al., 2014).

Management of IRRs can have significant economic consequences, including increased use of resources, such as bedside care to accommodate extended infusion times, reduced dosages, treatment delays, discontinuations, and prolonged hospital stays (Clemmons et al., 2021; Holmes et al., 2021b; Fortner & Viale, 2009). A 2006 time and motion study indicated that each IRR results in an average of 72 to 139 minutes of human resources for providing extra care and a $51 to $134 increase in cost per patient (Fortner & Viale, 2009; Houts et al., 2006). A recommended strategy to prevent or reduce both the health-related and financial consequences of IRRs is to administer premedication before infusion therapy (Clemmons et al., 2021). Routine use of premedication has generally been adopted in clinical practice, even though the US Food and Drug Administration (FDA)-approved US prescribing information (USPI) for the medications used as pretreatment do not necessarily specify the regimen (Clemmons et al., 2021; Holmes et al., 2021b).

Premedication protocols comprise various drugs, including antihistamines and corticosteroids (Fauziah et al., 2022; Roselló et al., 2017). Most patients with IRRs to paclitaxel and docetaxel may tolerate resumption of therapy after administration of an antihistamine and corticosteroid (Roselló et al., 2017). Despite not being explicitly FDA-approved for this indication, the first-generation H_1 antihistamine, diphenhydramine (DPH, Benadryl), has been the de facto gold standard commonly used to prevent IRRs, despite its well-known central nervous system (CNS) side effects (BD Rx Inc., 2013; Durham et al., 2019). Developed when drugs were not required to undergo stringent safety or efficacy testing before release, intravenous (IV) DPH received FDA approval in 1955 (Blaiss et al., 2022; FDA, 2006). Research findings on the effectiveness of DPH as premedication have mixed results (Fauziah et al., 2022). Nevertheless, since DPH was the only IV antihistamine available for over 6 decades, health-care practitioners frequently included it as part of the premedication protocols (Holmes et al., 2021b; Blaiss et al., 2022; Fauziah et al., 2022).

In 2019, IV cetirizine (Quzyttir) became the only second-generation H_1 antihistamine approved as an injection when it was FDA-approved to treat acute urticaria in adults and children aged 6 months or older (TerSera Therapeutics LLC,

2020; Blaiss et al., 2022). Recent research suggests that IV cetirizine can address several unmet needs regarding antihistamines used in premedication for anticancer treatment (Holmes et al., 2021b). Consequently, it may provide a favorable alternative to DPH in preventing IRRs (Durham et al., 2019).

GUIDANCE ON THE USE OF PREMEDICATION

The USPI for several FDA-approved infusion products includes antihistamine premedication requirements and recommendations (Table 1). The FDA recommends that premedication instructions be included in the Dosage and Administration, Warnings and Precautions, and in some cases, the Boxed Warning sections of the USPI label. According to the FDA Dosage and Administration guidelines, "If there is important information about administering other drugs before initiating the subject drug, this information should be included in the Dosage and Administration section [of the label]" (FDA, 2023). The guidelines additionally state that "If premedication is recommended to minimize potential hypersensitivity reactions, this section should describe the premedication regimen and include a cross-reference to the detailed discussion of hypersensitivity reactions elsewhere in labeling (e.g., Warnings and Precautions, Adverse Reactions)" (FDA, 2023).

Information in the Warnings and Precautions section may warrant the inclusion of a Boxed Warning, which highlights "...an adverse reaction so serious in proportion to the potential benefit of the drug" or "...a serious adverse event that can be prevented or reduced in frequency or severity by appropriate use...or addition of another drug" (FDA, 2011). For example, in the case of paclitaxel, the USPI features a Boxed Warning preceding all other sections, indicating that "anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2% to 4% of patients receiving paclitaxel in clinical trials...All patients should be pretreated with corticosteroids, DPH, and H_2 antagonists" (Bristol-Myers Squibb, 2011). The USPI for naxitamab-gqgk (Danyelza) starts with a Boxed Warning advising the use of a premedication regimen to mitigate or prevent the incidence of IRRs (Y-mAbs Therapeutics, Inc., 2020). With these FDA regulations, it is beneficial for health-care providers to have a selection of various premedication regimens, particularly those that have proven favorable patient outcomes. In the past 3 decades, the USPI of over 50 infusion products continue to repeatedly reflect language regarding premedication regimens that are either required or recommended to mitigate IRRs. Table 1 provides a summary of evidence-based decisions upon which product sponsors may rely upon as approved by the FDA. It is noted as the frequency of infusion products increases over the years, as shown in Figure 1, it becomes increasingly important to shift the paradigm to recognize that premedication with a more favorable IV antihistamine (e.g.,

Table 1. Guidance on FDA-Approved Medications That Require/Recommend Antihistamine Premedication

Medication class	DPH only	DPH (or equivalent)	DPH or other H_1 antihistamine	Cetirizine or DPH	General antihistamine	Non-sedating antihistamine	*N*
Monoclonal antibodies	12	5	1	1[a]	13	0	32
Platinum agents	0	0	0	0	2	0	2
Taxane agents	1	1	0	0	0	0	2
Other infusion agents	7	6	4	0	6	1[b]	24
Total							60

Note. DPH = diphenhydramine; FDA = US Food and Drug Administration; IV = intravenous.
[a]Ofatumumab injection, for intravenous use: Administration of oral/IV antihistamine (DPH 50 mg or oral/IV cetirizine 10 mg [or equivalent]) 30 minutes to 2 hours prior to each infusion.
[b]Vestronidase alfa-vjbk injection, for intravenous use: Administration of a non-sedating antihistamine with or without an antipyretic medication is recommended 30 to 60 minutes before the start of the infusion for patient comfort.

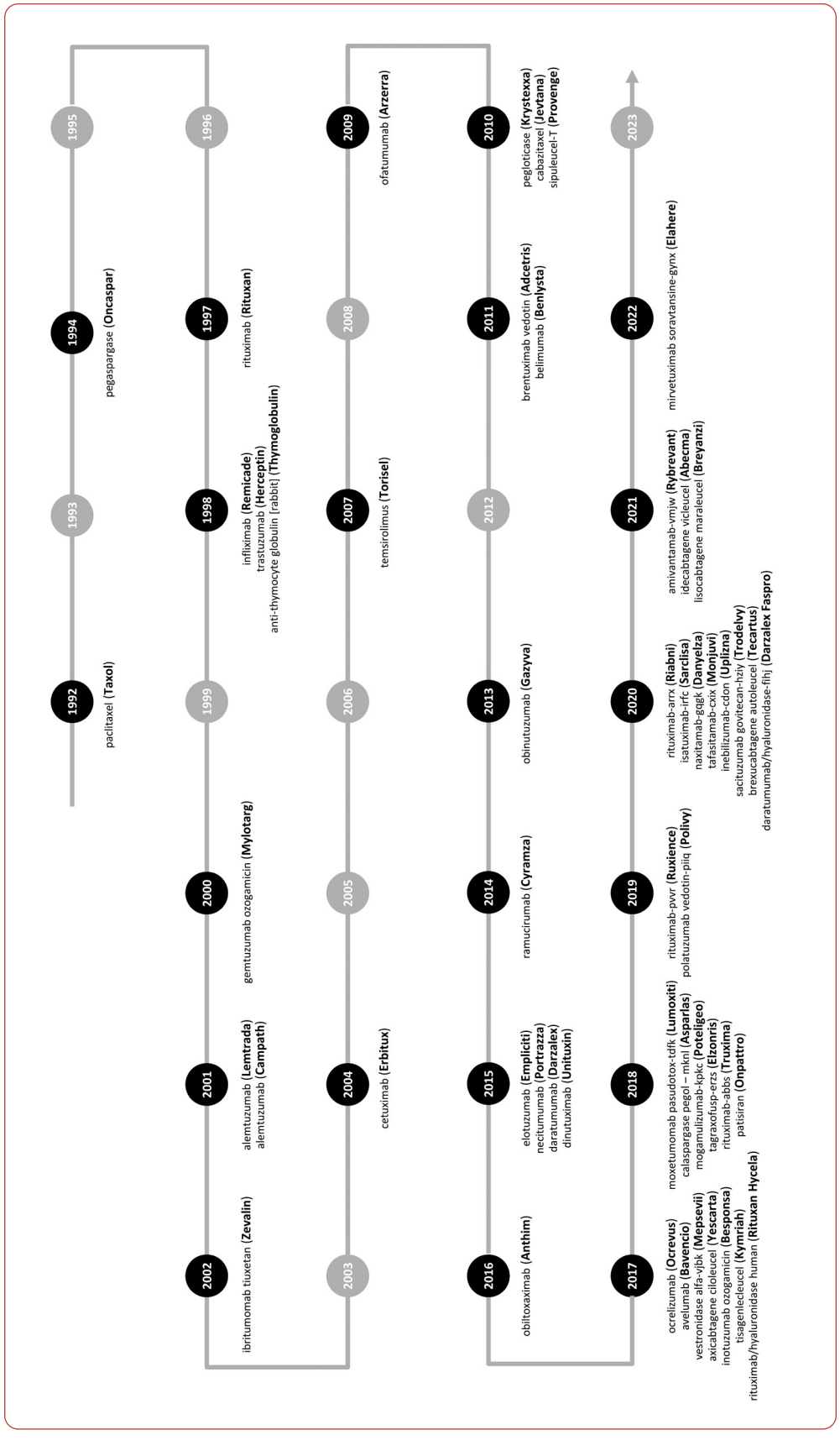

Figure 1. Infusion products approved in the past 30 years.

IV cetirizine) can improve outcomes, particularly in infusion care settings.

CONSIDERATIONS FOR IV DPH OR IV CETIRIZINE

Diphenhydramine remains the only FDA-approved first-generation IV H_1 antihistamine available (Blaiss et al., 2022). It is indicated for various conditions, including allergic reactions to blood or plasma transfusions, as adjunctive therapy during anaphylaxis after acute symptoms have been controlled, and for other uncomplicated allergic conditions when oral therapy is not appropriate (BD Rx Inc., 2013; Blaiss et al., 2022). Two retrospective studies, a recent prospective study, and a decades-old review article, have shown the merit of DPH as a premedication to prevent and manage IRRs related to cetuximab, rituximab, oxaliplatin, and paclitaxel therapy (Zanotti & Markman, 2001; Kidera et al., 2011; Durham et al., 2019; Barroso-Sousa et al., 2021). Until the IV cetirizine phase II study in pretreatment, no randomized controlled trials (RCTs) have examined the impact of IV DPH on IRR associated with anticancer agents (Blaiss et al., 2022).

Compared with second-generation H_1 antihistamines, DPH, as a first-generation H_1 antagonist, has a significant side effect profile since it penetrates the blood-brain barrier more easily, resulting in increased sedation, drowsiness, and cognitive function impairment (Durham et al., 2019; Blaiss et al., 2022). The 2023 NCCN Clinical Practice Guidelines (NCCN Guidelines®) for Older Adult Oncology state that first-generation H_1 antihistamines, like DPH, should only be used in select circumstances. For most instances, they recommend using alternatives like second-generation H_1 antihistamines, such as cetirizine, desloratadine, fexofenadine, and levocetirizine (NCCN Clinical Practice Guidelines in Oncology [NCCN 106 Guidelines®] Older Adult Oncology, 2023). Per the 2023 Beers Criteria for potentially inappropriate medication use in older adults, individuals 65 years or older are strongly advised to avoid using DPH whenever possible (American Geriatrics Society Beers Criteria Update Expert Panel, 2023). Its use in hospitalized elderly patients has been linked to a higher risk of delirium, cognitive decline, behavioral disturbance, urinary retention resulting in catheterization, and longer median length of stay (Agostini et al., 2001; Wolfson et al., 2022). In adults aged 65 or older, prolonged use of DPH is associated with a higher likelihood of developing dementia and Alzheimer's disease (Wolfson et al., 2022).

Falls in vulnerable populations and more severe reactions such as agitation, behavioral changes, dystonia, dyskinesia, hallucinations, and psychosis have also been reported with DPH use (McKeirnan et al., 2020; Simons & Simons, 2011; Letourneau et al., 2022). It is worth noting that the simultaneous use of alcohol or other CNS depressants like hypnotics, sedatives, benzodiazepines, opioids, or tranquilizers can worsen the CNS effects. Patients taking DPH should be advised to exercise caution while engaging in activities that demand mental alertness, such as driving and operating appliances or machinery (BD Rx Inc., 2013). In a randomized, double-blind study, administration of oral DPH 50 mg for hypersensitivity reactions was shown to impair driving comparable to alcohol intoxication with a blood alcohol level of 0.1% (Weiler et al., 2000). Sen and colleagues (2007) reported that out of the 5,383 aviation accidents between 1990 and 2005, 338 postmortem samples from pilot fatalities were found to contain first-generation H_1 antihistamines, such as DPH. Levels of antihistamines in the blood were in the subtherapeutic to toxic range (Sen et al., 2007).

First-generation H_1 antihistamines have poor selectivity for the H_1 receptor, as they bind indiscriminately with other receptors, such as muscarinic, serotonin, and alpha-adrenergic receptors, possibly resulting in multisystem side effects like dizziness, dry mouth, mydriasis, constipation, urinary hesitancy, urinary retention, increased appetite, weight gain, and orthostatic hypotension. Standard doses and overdose have been associated with cardiac effects, such as sinus tachycardia, prolongation of the QTc interval, abnormal ventricular repolarization, and ventricular arrhythmia (Simons & Simons, 2011; Shah et al., 2015). Diphenhydramine use in children younger than 5 is not recommended, as an overdose can lead to paradoxical stimulation causing signs of agitation and confusion, followed by extreme sedation and coma (Wolfson et al., 2022). Concurrent use of monoamine oxidase (MAO) inhibitors can prolong and amplify the anticholinergic effects. Due

to its atropine-like effects, DPH should be used cautiously in patients with a history of bronchial asthma, hypertension, hyperthyroidism, cardiovascular illness, or elevated intraocular pressure (BD Rx Inc., 2013). The potential of anticholinergic toxicity coupled with the sedative effects of DPH may have a detrimental impact on a patient's hospital stay, their ability to cooperate with medical staff, and their capacity to return home safely (Beaucage-Charron et al., 2022).

Diphenhydramine can elevate dopamine levels in reward-associated neural pathways and produce sensations of euphoria and enhanced mood when used recreationally (Letourneau et al., 2022). It is among the most frequently abused medications in the US. According to a 2018 report by the National Center for Health Statistics, DPH overdoses accounted for 3.2% of all drug overdose deaths in the US in 2016 (Hedegaard et al., 2018). The report also revealed that DPH was among the top 15 drugs associated with drug overdose deaths in the country (Hedegaard et al., 2018). The rates of misuse among older adults are consistent with national epidemiologic trends in poisonings and drug overdoses (Nemanich et al., 2021).

Both oral and IV administration of DPH pose opportunities for misuse. Parenteral administration of DPH presents a unique challenge for individuals undergoing home infusion. This method permits rapid drug absorption and is frequently the most potent means to induce euphoria for many medications (Letourneau et al., 2022). Unintentional misuse can occur with oral therapy, as many adults in the US rely on over-the-counter (OTC) medications containing DPH to manage their sleep difficulties or pain and may be unaware of the safety risks (Abraham et al., 2017). Also, combination product labeling often prioritizes indications over drug content, so patients may be unaware that their OTC medication contains DPH (McKeirnan et al., 2020). Individuals who consume doses greater than 300 mg, but less than 1 g, may experience cognitive changes such as agitation, confusion, and hallucinations. Conversely, amounts exceeding 1 g are typically associated with self-harm attempts and can result in psychosis, coma, and seizures (McKeirnan et al., 2020).

Intravenous cetirizine is the sole second-generation H_1 antihistamine formulated for injection with high selectivity for peripheral H_1 receptors due to its limited ability to cross the blood-brain barrier (TerSera Therapeutics LLC, 2020; Beaucage-Charron et al., 2022; Blaiss et al., 2022). As a result, it is less sedating and generally produces minimal CNS adverse effects and less cognitive impairment (Banerji et al., 2007; Simons & Simons, 2011; Fein et al., 2019). Across three head-to-head comparison studies, the mean sedation ratings at 1 hour, 2 hours, and time to discharge were lower with IV cetirizine than with IV DPH (Abella et al., 2020; Holmes et al., 2021a; Holmes et al., 2021b). A phase III RCT comparing IV DPH and IV cetirizine for acute urticaria treatment revealed that the rate of treatment-related adverse events in patients who received IV cetirizine was 3.9%, compared with 13.3% in those who received IV DPH; one patient in the IV cetirizine group reported experiencing dysgeusia, paresthesia, and a sensation of warmth, while multiple patients in the IV DPH group reported dizziness and nausea (Abella et al., 2020).

Cetirizine is more pharmacodynamically potent than DPH based on affinity for the H_1 receptors (K_i value: 6 nM vs. 9.6–16 nM, respectively; Portnoy & Dinakar, 2004; Ghoneim et al., 2006; Krystal et al., 2013). Despite both IV formulations having a comparable onset time, cetirizine has an 8-hour half-life with a duration of action of ≥ 24 hours with minimal adverse effects. In contrast, DPH has a half-life ranging from 3.4 to 9.2 hours, with increased risk of falls from dizziness, sedation, and hypotension among elderly patients as DPH remains in the body well after patients leave the outpatient setting (Sicari and Zabbo, 2022). Intravenous cetirizine is associated with reduced rescue drug usage, lower symptom recurrence, and lower requirement for additional medication (Abella et al., 2020).

In contrast to IV DPH, IV cetirizine is associated with a shorter time in the treatment center and a lower revisit rate to the treatment center at 24 and 48 hours. A randomized, double-blind phase II trial was conducted with 33 adults who required H_1 antihistamines due to acute urticaria (with or without angioedema). Participants were given either IV cetirizine 10 mg or IV DPH 50 mg. Patients treated with cetirizine had a shorter stay at the treatment center (1.7 hours) compared with those receiving DPH (2.3 hours), and

fewer patients who received cetirizine returned to the treatment center within 24 hours (Blaiss et al., 2022).

Paradoxical excitation has been reported among patients receiving DPH who are ultrarapid metabolizers of the cytochrome P450 2D6 (CYP2D6) enzyme (de Leon & Nikoloff, 2008). This affects 1.5% to 4.8% of the US population, in whom DPH acts as a CYP2D6 substrate and competitively inhibits other drugs that bind the same metabolic enzyme (de Leon & Nikoloff, 2008). Cetirizine is not affected by CYP2D6 and undergoes limited metabolism by oxidative O-dealkylation (TerSera Therapeutics LLC, 2020). Since a proportion of ultrarapid metabolizers of CYP2D6 are known to exhibit paradoxical reactions with DPH, it is a plausible explanation for why the paradoxical reaction was observed in our case with IV DPH but not IV cetirizine. Due to constraints in the clinical setting, our patient was not explicitly genotyped for CYP2D6.

PREVENTING INFUSION-RELATED REACTIONS

While IV cetirizine has shown efficacy in preventing chemotherapeutic agent–induced IRRs, at the present time, IV cetirizine is only indicated for acute urticaria. Durham and colleagues (2019) conducted a retrospective analysis to compare the effectiveness of oral cetirizine (83 patients) and IV or oral DPH (124 patients) in preventing hypersensitivity reactions to paclitaxel, rituximab, or cetuximab. The results showed that the incidence of IRRs was similar between the two groups (19.3% for cetirizine vs. 24.2% for DPH; $p = .40$), supporting the use of cetirizine as an alternative to DPH in this context (Durham et al., 2019). However, employing oral antihistamines as a premedication for IRRs presents multiple concerns. Adherence is an issue, as it is difficult to ascertain whether patients have taken the oral medication within the necessary timeframe to make it effective as premedication. Oral medication takes longer to reach maximum concentration (T_{max}) than IV medication and can be delayed with meals (TerSera Therapeutics LLC, 2020). Oral cetirizine 10 mg has a T_{max} of about 1 hour on an empty stomach and 2.7 hours with food, whereas the T_{max} of IV cetirizine 10 mg is 1.8 minutes (TerSera Therapeutics LLC, 2020). Administration timing and achieving rapid peak drug concentrations are essential in the premedication setting (Holmes et al., 2021b).

Intravenous cetirizine was utilized by Holmes and colleagues (2021b) in the phase II RCT comparing the second-generation H_1 antihistamine to IV DPH as premedication for IRRs associated with anti-CD20 treatments (such as rituximab, its biosimilar, or obinutuzumab) or paclitaxel. Results showed that 11.8% of patients receiving IV cetirizine and 17.6% receiving IV DPH experienced an IRR. Patients given IV cetirizine spent an average of 24 minutes less at the treatment center than those given IV DPH (4.3 hours vs. 4.7 hours, respectively; Holmes et al., 2021b). Patients on IV cetirizine had a lower level of sedation at all measurement points than those on IV DPH, even upon discharge (0.1 vs. 0.4). The incidence of treatment-related adverse events was 11.8% in the IV cetirizine group compared with 23.5% in the IV DPH group (Holmes et al., 2021b).

Intravenous cetirizine has shown effectiveness in older adults, who are often more susceptible to the anticholinergic effects of first-generation H_1 antihistamines such as DPH (Durham et al., 2019). Of the 34 patients who participated in the study conducted by Holmes and colleagues (2021b), 21 were 65 years or older. Among this subgroup, the incidence of IRRs was 11.1% with IV cetirizine and 16.7% with IV DPH. The median time for patients to be ready for discharge was 30 minutes shorter with IV cetirizine compared with IV DPH. Consistent with the results of the entire study population, this subset of older adults had a lower level of sedation at all measurement points, even upon discharge (0.1 vs. 0.4). In terms of safety, treatment-related adverse events were observed in 11.1% of patients in the IV cetirizine group, as opposed to 33.3% in the IV DPH group (Holmes et al., 2021b). In the phase III RCT comparing IV cetirizine and IV DPH for acute urticaria, post-hoc subanalysis indicated that IV cetirizine was equally effective in achieving the primary efficacy outcome for patients aged 65 years and older compared with those younger than 65 years. Overall safety between these two groups of patients was similar (Abella et al., 2020).

There are different types of IRRs to taxanes, with the majority being immediate reactions that

develop within minutes of starting the first or second infusion (Picard and Castells, 2014). Given that the risk of IRRs is generally not cumulative or progressively worse with later cycles of therapy, clinicians may consider utilizing IV cetirizine upfront during the early cycles of taxane therapy that pose the highest risk of IRRs.

THE FUTURE OF PREMEDICATION WITH ANTIHISTAMINES

The expansion of immunotherapy has provided clinicians with various cancer-fighting drugs, including monoclonal antibodies, immune checkpoint inhibitors, and adoptive cell therapies like chimeric antigen receptor T-cell therapy. Infusion-related reactions to immunotherapy, while uncommon, may result in prolonged infusion times, additional medical interventions, hospitalizations, treatment cessation, and in severe cases, death (Peterson, 2022). As cancer treatment advances and new therapies are developed, staying informed about the potential risks of IRRs and the safest and most effective approaches to managing them will be essential.

Several immunotherapies, such as monoclonal antibodies (e.g., programmed cell death protein 1 [PD-1]–blocking antibodies and programmed cell death ligand 1 [PD-L1] blocking antibodies) and other drug classes (e.g., platinum agents, taxanes) include premedication recommendations for IRRs in their USPI (Table 1). Intravenous cetirizine may be a viable option for patients on PD-1/PD-L1-blocking antibodies, as avoidance of steroid premedication has been suggested since it may counteract the therapeutic PD-1/PD-L1 effects (Adorisio et al., 2021).

Approximately 35% of these immunotherapy USPIs recommend using an antihistamine as premedication but do not mention a specific product. Some USPIs offer precise instructions for administering DPH, while others only state it without specifying the dosage (Table 1). The USPI for ofatumumab (Arzerra) is the only one that specifies the use of IV/oral DPH or cetirizine as premedication (Novartis, 2009), while the USPI for vestronidase alfa-vjbk (Mepsevii) recommends administering a non-sedating antihistamine, with or without an antipyretic medication, 30 to 60 minutes before the infusion to enhance patient comfort (Ultragenyx Pharmaceutical Inc., 2017). Notably, of all the USPIs listed in Table 1, the term "non-sedating" is only mentioned in the USPI for vestronidase alfa-vjbk.

As more infusion therapies requiring premedication become available, finding alternative IV antihistamine options remains crucial. Despite the potential for unpleasant anticholinergic side effects, increased risk of motor impairment and falls in the elderly, and recommendations against its use in older patients, approximately 19.5 million doses of IV DPH are administered annually (Abraham et al., 2017; Symphony Health, 2022). Over 3.3 million IV DPH doses per year are administered for premedication purposes (IQVIA, 2020). This high utilization of IV DPH may be a reflection of its relatively low cost as a readily available generic product. Perseverance is needed to navigate prior authorization for IV cetirizine as a branded, viable, and effective alternative to DPH if it is not already on the institutional formulary. In three separate trials, IV cetirizine consistently exhibited favorable outcomes compared with IV DPH, such as reduced sedation, less time spent in the treatment facility, a lower incidence of revisits (the need for a second visit after discharge) to the treatment center, and fewer treatment-associated adverse events (Abella et al., 2020; Holmes et al., 2021a; Holmes et al., 2021b). Cetirizine has a longer duration of action, fewer contraindications, and less anticholinergic side effects than DPH (Blaiss et al., 2022). Medical contraindications to IV DPH include but are not limited to breastfeeding, concurrent use of other hypnotics (e.g., benzodiazepines commonly used in cancer patients), arrhythmias, and concurrent use of MAO inhibitors; these are not concerns with IV cetirizine (BD RX Inc, 2013; TerSera Therapeutics LLC, 2020). The use of IV cetirizine has also resulted in fewer adverse effects on the vulnerable elderly population (Durham et al., 2019).

Prior to the availability of IV cetirizine, no head-to-head RCT had been conducted for antihistamine use in premedication for IRRs (Holmes et al., 2021b). Carrying out such a trial would be infeasible and unethical since it would require withholding treatment crucial for ensuring patient safety and would go against the widely accepted FDA-approved labeling for over 50 infusion products.

From the phase III acute urticaria study showing shorter time spent in the treatment center, lower rates of revisits to the treatment center, and less need for rescue medications, coupled with the phase II IRR study showing less sedation and decreased chair time, IV cetirizine can enhance patient satisfaction and improve health-care costs (Holmes et al., 2021b; Blaiss et al., 2022; Abella et al., 2020). These advantages of IV cetirizine far outweigh the risks of problematic adverse events associated with IV DPH (Durham et al., 2019; Blaiss et al., 2022). Despite the long-standing use of IV DPH as premedication for anticancer IRRs, it is apparent that IV cetirizine offers a clinically appropriate alternative. Clinicians should consider their current DPH prescribing habits and thoroughly evaluate the selection of available products, especially given the accessibility of alternative choices. They should be encouraged to form their own opinions on this topic, using clinical judgment and available resources to make well-informed decisions about patient care.

Acknowledgment

Medical writing support was provided by Vamsi Ahobila, MD, and LoAn K. Ho, PharmD, of Forward WE Go, a division of Wesley Enterprise, Inc, and was funded by TerSera Therapeutics.

Disclosure

Dr. Tyler is a consultant to TerSera Therapeutics, AstraZeneca, Sandoz, and Urogen, and on the speakers bureaus for Bristol-Myers Squibb, Amgen, Pfizer, Sanofi, Incyte, G1 Therapeutics, and Pharmacosmos. Drs. Stojanoff, Cannon, Um, Young, Brent, and Martin are employed by TerSera Therapeutics. Dr. Holmes was a principal investigator for the phase II study of IV cetirizine for the prevention of hypersensitivity IRRs, and has been a paid consultant for TerSera Therapeutics.

References

Abella, B. S., Berger, W. E., Blaiss, M. S., Stiell, I. G., Herres, J. P., Moellman, J. J.,...Du, J. (2020). Intravenous cetirizine versus intravenous diphenhydramine for the treatment of acute urticaria: A phase III randomized controlled noninferiority trial. *Annals of Emergency Medicine*, 76(4), 489–500. https://doi.org/10.1016/j.annemergmed.2020.05.025

Abraham, O., Schleiden, L., & Albert, S. M. (2017). Over-the-counter medications containing diphenhydramine and doxylamine used by older adults to improve sleep. *International Journal of Clinical Pharmacy, 39*(4), 808–817. https://doi.org/10.1007/s11096-017-0467-x

Adorisio, S., Cannarile, L., Delfino, D.V., & Ayroldi E. (2021). Glucocorticoid and PD-1 cross-talk: Does the immune system become confused? *Cells, 10*(9), 2333. https://doi.org/10.3390/cells10092333

Agostini, J. V., Leo-Summers, L. S., & Inouye, S. K. (2001). Cognitive and other adverse effects of diphenhydramine use in hospitalized older patients. *Archives of Internal Medicine, 161*(17), 2091–2097. https://doi.org/10.1001/archinte.161.17.2091

American Geriatrics Society Beers Criteria Update Expert Panel. (2023). American Geriatrics Society 2023 updated AGS Beers Criteria for potentially inappropriate medication use in older adults. *Journal of the American Geriatrics Society*, *71*(7), 2033–2357. https://doi.org/10.1111/jgs.18372

Banerji, A., Long, A. A., & Camargo, C. A., Jr. (2007). Diphenhydramine versus nonsedating antihistamines for acute allergic reactions: A literature review. *Allergy and Asthma Proceedings*, *28*(4), 418–426. https://doi.org/10.2500/aap.2007.28.3015

Barroso-Sousa, R., Vaz-Luis, I., Di Meglio, A., Hu, J., Li, T., Rees, R.,...Lin, N. U. (2021). Prospective study testing a simplified paclitaxel premedication regimen in patients with early breast cancer. *The Oncologist*, *26*(11), 927–933. https://doi.org/10.1002/onco.13960

BD Rx Inc. (2013). Diphenhydramine hydrochloride injection, USP. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/091526lbl.pdf

Beaucage-Charron, J., Gaudet, L., Lamothe, S., Pelletier, C., Pépin, A. S., Roy, V.,...Picard, M. (2022). A randomized, double-blind feasibility study comparing cetirizine and diphenhydramine in the prevention of paclitaxel-associated infusion-related reactions: The PREMED-F1 Study. *Supportive Care in Cancer,* 30(4), 3389–3399. https://doi.org/10.1007/s00520-021-06734-4

Blaiss, M. S., Bernstein, J. A., Kessler, A., Pines, J. M., Camargo, C. A., Jr., Fulgham, P.,...Moellman, J. (2022). The role of cetirizine in the changing landscape of IV antihistamines: A narrative review. *Advances in Therapy*, *39*(1), 178–192. https://doi.org/10.1007/s12325-021-01999-x

Boulanger, J., Boursiquot, J. N., Cournoyer, G., Lemieux, J., Masse, M. S., Almanric, K.,...Comité de l'évolution des pratiques en oncologie. (2014). Management of hypersensitivity to platinum- and taxane-based chemotherapy: CEPO review and clinical recommendations. *Current Oncology (Toronto, Ont.), 21*(4), e630–e641. https://doi.org/10.3747/co.21.1966

Bristol-Myers Squibb. (2011). Taxol (paclitaxel) injection package insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020262s049lbl.pdf

Clemmons, A., Gandhi, A., Clarke, A., Jimenez, S., Le, T., & Ajebo, G. (2021). Premedications for cancer therapies: A primer for the hematology/oncology provider. *Journal of the Advanced Practitioner in Oncology*, *12*(8), 810–832. https://doi.org/10.6004/jadpro.2021.12.8.4

de Leon, J., & Nikoloff, D. M. (2008). Paradoxical excitation on diphenhydramine may be associated with being a CYP2D6 ultrarapid metabolizer: Three case reports. *CNS Spectrums, 13*(2), 133–135. https://doi.org/10.1017/s109285290001628x

Durham, C. G., Thotakura, D., Sager, L., Foster, J., & Herrington, J. D. (2019). Cetirizine versus diphenhydramine in the prevention of chemotherapy-related hypersensitivity reactions. *Journal of Oncology Pharmacy Practice, 25*(6), 1396–1401. https://doi.org/10.1177/1078155218811505

Fauziah H., Dinda M., & Bambang S. (2022). Review article: Mechanisms and efficacy of using diphenhydramine as a chemotherapy premedication. *Journal of Pharmaceutical Negative Results, 13*(6), 2268–2276. https://doi.org/10.47750/pnr.2022.13.S06.295

Fein, M. N., Fischer, D. A., O'Keefe, A. W., & Sussman, G. L. (2019). CSACI Position Statement: Newer generation H_1-antihistamines are safer than first-generation H_1-antihistamines and should be the first-line antihistamines for the treatment of allergic rhinitis and urticaria. *Allergy, Asthma, and Clinical Immunology, 15*, 61. https://doi.org/10.1186/s13223-019-0375-9

Fortner, B., & Viale, P. H. (2009). Health economic analysis of the burden of infusion reactions on patients, caregivers, and providers. *Oncology*, *23*(2 Suppl 1), 31–36. https://pubmed.ncbi.nlm.nih.gov/19385165/

Ghoneim, O. M., Legere, J. A., Golbraikh, A., Tropsha, A., & Booth, R. G. (2006). Novel ligands for the human histamine H_1 receptor: Synthesis, pharmacology, and comparative molecular field analysis studies of 2-dimethylamino-5-(6)-phenyl-1,2,3,4-tetrahydronaphthalenes. *Bioorganic & Medicinal Chemistry*, *14*(19), 6640–6658. https://doi.org/10.1016/j.bmc.2006.05.077

Hayes, H. M., Whalen, J., Schutz, N., & Levine, J. (2021). Evaluation of infusion-related and hypersensitivity reactions to chemotherapy over a decade at a community cancer center. *Journal of Hematology Oncology Pharmacy*, *11*(1), 30–36. https://jhoponline.com/issue-archive/2021-issues/february-2021-vol-11-no-1/18839-evaluation-of-infusion-related-and-hypersensitivity-reactions-to-chemotherapy-over-a-decade-at-a-community-cancer-center

Hedegaard, H., Bastian, B. A., Trinidad, J. P., Spencer, M., & Warner, M. (2018). Drugs most frequently involved in drug overdose deaths: United States, 2011-2016. *National Vital Statistics Reports: From the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System*, *67*(9), 1–14.

Holmes, J. P., Dasanu, C. A., Peguero, J., Ayad, A., Garland, R. C., O'Shea, A.,...Joseph-Ridge, N. (2021a). A phase 2 exploratory study of intravenous cetirizine versus intravenous diphenhydramine in the prevention of hypersensitivity infusion reactions in patients with breast cancer and other malignancies [Abstract 56]. *38th Annual Miami Breast Cancer Conference - Abstracts, 35*(1), 25–26.

Holmes, J. P., Peguero, J. A., Garland, R. C., North, J., Young, S., Brent, L. D., & Joseph-Ridge, N. (2021b). Intravenous cetirizine vs intravenous diphenhydramine for the prevention of hypersensitivity infusion reactions: Results of an exploratory phase 2 study. *Journal of Infusion Nursing, 44*(6), 315–322. https://doi.org/10.1097/NAN.0000000000000444

Houts, A.C., Fortner, B.V., Moore, K., Zhu, L., & Schwartzberg, A. (2006). Human resource (HR) costs of chemotherapy infusion reactions (IR) in community oncology (Abstract 14-084). *Supportive Care in Cancer, 14*, 626.

IQVIA. (2020). Health Plan Claims (December 2020) [Data set]. https://www.iqvia.com

Kidera, Y., Satoh, T., Ueda, S., Okamoto, W., Okamoto, I., Fumita, S.,...Nakagawa, K. (2011). High-dose dexamethasone plus antihistamine prevents colorectal cancer patients treated with modified FOLFOX6 from hypersensitivity reactions induced by oxaliplatin. *International Journal of Clinical Oncology, 16*(3), 244–249. https://doi.org/10.1007/s10147-010-0170-6

Krystal, A. D., Richelson, E., & Roth, T. (2013). Review of the histamine system and the clinical effects of H_1 antagonists: Basis for a new model for understanding the effects of insomnia medications. *Sleep Medicine Reviews*, *17*(4), 263–272. https://doi.org/10.1016/j.smrv.2012.08.001

Lenz, H. J. (2007). Management and preparedness for infusion and hypersensitivity reactions. *The Oncologist*, *12*(5), 601–609. https://doi.org/10.1634/theoncologist.12-5-601

Letourneau, M. B., Sievert, E., & MacInnis, A. (2022). A 10-year retrospective pilot study of parenteral diphenhydramine use in home infusion patients. *Infusion Journal*, *1*(1), 11–18.

McKeirnan, K. C., Frazier, K. R., & Yabusaki, A. A. (2020). Patient fall risk caused by unintended diphenhydramine use. *The Senior Care Pharmacist*, *35*(3), 113–119. https://doi.org/10.4140/TCP.n.2020.113

Nemanich, A., Liebelt, E., & Sabbatini, A. K. (2021). Increased rates of diphenhydramine overdose, abuse, and misuse in the United States, 2005-2016. *Clinical Toxicology, 59*(11), 1002–1008. https://doi.org/10.1080/15563650.2021.1892716

Novartis. (2009). Arzerra (ofatumumab) injection, for intravenous use package insert. https://www.novartis.com/us-en/sites/novartis_us/files/arzerra.pdf

Peterson, C. (2022). An AP perspective on infusion reactions in the era of immunotherapy. *Journal of the Advanced Practitioner in Oncology*, *13*(3), 247–252. https://doi.org/10.6004/jadpro.2022.13.3.13

Picard, M., & Castells, M.C. (2014). Revisiting hypersensitivity reactions to taxanes: A comprehensive review. *Clinical Reviews in Allergy & Immunology*, *49*(2), 177–191. https://doi.org/10.1007/s12016-014-8416-0

Portnoy, J. M., & Dinakar, C. (2004). Review of cetirizine hydrochloride for the treatment of allergic disorders. *Expert Opinion on Pharmacotherapy*, *5*(1), 125–135. https://doi.org/10.1517/14656566.5.1.125

Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Older Adult Oncology V.1.2023. © National Comprehensive Cancer Network, Inc 2023. All rights reserved. Accessed April 26, 2023. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

Rombouts, M. D., Swart, E. L., Van Den Eertwegh, A. J. M., & Crul, M. (2020). Systematic review on infusion reactions to and infusion rate of monoclonal antibodies used in cancer treatment. *Anticancer Research*, *40*(3), 1201–1218. https://doi.org/10.21873/anticanres.14062

Roselló, S., Blasco, I., García Fabregat, L., Cervantes, A., Jordan, K., & ESMO Guidelines Committee (2017). Management of infusion reactions to systemic anticancer therapy: ESMO Clinical Practice Guidelines. *Annals of Oncology, 28*(suppl 4), IV100–IV118. https://doi.

org/10.1093/annonc/mdy158
Sen, A., Akin, A., Craft, K. J., Canfield, D. V., & Chaturvedi, A. K. (2007). First-generation H_1 antihistamines found in pilot fatalities of civil aviation accidents, 1990-2005. *Aviation, Space, and Environmental Medicine, 78*(5), 514–522.
Shah, A., Yousuf, T., Ziffra, J., Zaidi, A., & Raghuvir, R. (2015). Diphenhydramine and QT prolongation - A rare cardiac side effect of a drug used in common practice. *Journal of Cardiology Cases, 12*(4), 126–129. https://doi.org/10.1016/j.jccase.2015.06.002
Sicari, V., & Zabbo, C. P. (2022). Diphenhydramine. In StatPearles [Internet]. Treasure Island, FL: StatPearls Publishing; 2023 Jan. https://www.ncbi.nlm.nih.gov/books/NBK526010
Simons, F. E., & Simons, K. J. (2011). Histamine and H_1-antihistamines: Celebrating a century of progress. *The Journal of Allergy and Clinical Immunology*, *128*(6), 1139–1150.e4. https://doi.org/10.1016/j.jaci.2011.09.005
Symphony Health. (2022). *PHAST Source of Business* (September 2022) [Data set]. Symphony Health Solutions. https://symphonyhealth.com
TerSera Therapeutics LLC. (2020). Quzyttir (cetirizine hydrochloride injection) for intravenous use package insert. https://documents.tersera.com/quzyttir/Quzyttir-PrescribingInformation.pdf
Ultragenyx Pharmaceutical Inc. (2017). Mepsevii (vestronidase alfa-vjbk) injection, for intravenous use package insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761047s000lbl.pdf
US Food and Drug Administration. (2006). A history of the FDA and drug regulation in the United States. https://www.fda.gov/files/drugs/published/A-History-of-the-FDA-and-Drug-Regulation-in-the-United-States.pdf
US Food and Drug Administration. (2011). Guidance for industry: Warnings and precautions, contraindications, and boxed warning sections of labeling for human prescription drug and biological products – Content and format. https://www.fda.gov/media/71866/download
US Food and Drug Administration. (2023). Dosage and administration section of labeling for human prescription drug and biological products — Content and format: Guidance for industry. https://www.fda.gov/media/72142/download
Weiler, J. M., Bloomfield, J. R., Woodworth, G. G., Grant, A. R., Layton, T. A., Brown, T. L.,...Watson, G. S. (2000). Effects of fexofenadine, diphenhydramine, and alcohol on driving performance. A randomized, placebo-controlled trial in the Iowa Driving Simulator. *Annals of Internal Medicine*, *132*(5), 354–363. https://doi.org/10.7326/0003-4819-132-5-200003070-00004
Wolfson, A. R., Wong, D., Abrams, E. M., Waserman, S., & Sussman, G. L. (2022). Diphenhydramine: Time to move on? *The Journal of Allergy and Clinical Immunology: In Practice, 10*(12), 3124–3130. https://doi.org/10.1016/j.jaip.2022.07.018
Y-mAbs Therapeutics, Inc. (2020). Danyelza (naxitamab-gqgk) injection, for intravenous use package insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761171lbl.pdf
Zanotti, K. M., & Markman, M. (2001). Prevention and management of antineoplastic-induced hypersensitivity reactions. *Drug Safety*, *24*(10), 767–779. https://doi.org/10.2165/00002018-200124100-00005