Prevention and handling of acute allergic and infusion reactions in oncology

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Drug hypersensitivity reactions (HSR) are adverse events resembling allergy which occur at therapeutic doses. Both anticancer chemotherapeutics and monoclonal antibodies have the potential for acute HSR. All infusion reactions involve the immune system; however, some (anaphylactic) are allergic in nature and usually are mediated by immunoglobulin E (IgE), whereas others (anaphylactoid) are not true allergic reactions and are not mediated by IgE. Although HSR can be allergic or nonallergic, the clinical manifestations are the same and require prompt, accurate assessment and management to avoid severe adverse events, including fatality. Monoclonal antibodies have a unique side-effect profile that includes the potential for nonallergic HSR caused by cytokine release. Chemotherapeutic agents with the highest potential for acute HSR include the platinum salts, taxanes, procarbazine, asparaginase and the epipodophyllotoxins. From all anticancer agents, rituximab causes the majority of HSR (27%), followed by paclitaxel (10%). The most frequent symptoms in patients experiencing acute HSR include chest pain, dyspnea, wheezing and exanthema for the taxanes, dyspnea and exanthema for platinum salts, chills and rigor for antibodies. Patients with mild-to-moderate acute HSR can be rechallenged following intensified prophylaxis, but rechallenge is usually not recommended following severe HSR.

Key words: antigen–antibody reaction, chemotherapy, drug hypersensitivity, immediate hypersensitivity infusion therapy

background

Drug hypersensitivity reactions (HSR) are adverse events resembling allergy which occur at therapeutic doses [1]. Only when immunologic mechanisms are demonstrated should these reactions be classified as drug allergy. Drug allergy and nonallergic HSR are difficult to differentiate, and referral to an allergist–immunologist should be considered in severe cases. The European Network for Drug Allergy, working under the aegis of the European Academy of Allergy and Clinical Immunology, has categorized HSR into two types, according to the onset of symptoms after drug exposure [2]: (i) immediate reaction after <1 h, with urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm or overt anaphylaxis; (ii) nonimmediate reaction after >1 h, with cutaneous symptoms such as late-occurring urticaria, maculopapular eruptions, fixed drug eruptions, vasculitis, toxic epidermal necrolysis, Stevens–Johnson syndrome or drug reaction with eosinophilia and systemic symptoms. Immediate reactions are mostly immunoglobulin E (IgE)-mediated, whereas nonimmediate reactions are T-cell-mediated. Immediate (acute) HSR are handled in this overview.

Acute HSR may be caused by platinum salts, taxanes, procarbazine, asparaginase or the epipodophyllotoxins (teniposide, etoposide) [3, 4]. Doxorubicin (Adriamycin, Pfizer, New York) and 6-mercaptopurine are infrequently causing acute HSR, and agents such as 5-fluorouracil, cyclophosphamide (Endoxane, Baxter, USA) and cytarabine are rarely causing HSR [4, 5]. Acute HSR cause substantial stress among patients, their families, nurses, other patients and physicians [6]. Forty-two percent of nurses feel that physicians do not adequately inform patients about the risk of HSR [7]. According to an overview in 30,850 infusions and 4000 patients [8], the incidence of HSR was 0.7% (222 cases). Platinum salts were most likely to cause acute HSR with extensive exposure. In 12 cases (5%), HSR occurred while the drug was given for a second treatment cycle. As an individual drug, rituximab caused the majority of HSR (27%), followed by paclitaxel (Taxol, Bristol-Myers Squibb, 10%). Immunotherapeutics accounted for half of all HSR, with rituximab accounting for 54% of HSR from immunotherapeutics. Patients with acute HSR experienced the following symptoms in >50% of cases: chest pain, dyspnea, wheezing and exanthema for the taxanes, dyspnea and exanthema for platinum salts, chills and rigor for antibodies (Table 1). Severe acute HSR are reported in ≤5% of all chemotherapy infusions (mainly taxanes and platinum salts) [3]. Patients with mild-to-moderate acute HSR can be rechallenged following intensified prophylaxis. Rechallenge is contraindicated...
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<tr>
<td>Alemtuzumab</td>
<td>CD52</td>
<td>Humanized</td>
<td>n.a.</td>
<td>Hypotension, RIG, fever, DYSP, ARDS, rash and pruritus</td>
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<td>ErbB1 (EGFR)</td>
<td>Chimeric</td>
<td>3</td>
<td>F, hypotension, and A</td>
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<td>Discontinuation after severe reactions; rechallenge at 50%&lt;sup&gt;b&lt;/sup&gt; after mild to moderate reactions</td>
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<tr>
<td>Panitumumab</td>
<td>ErbB1 (EGFR)</td>
<td>Humanized</td>
<td>0.1</td>
<td>DYSP, F, hypotension, and A</td>
<td>–</td>
<td>Discontinuation after severe reactions; rechallenge at 50%&lt;sup&gt;b&lt;/sup&gt; after mild to moderate reactions</td>
<td></td>
</tr>
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<td>Trastuzumab</td>
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<td>Humanized</td>
<td>&lt;1</td>
<td>URT, DYSP, AE and hypotension</td>
<td>–&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Discontinuation should be considered after A; rechallenge with premedication after mild to moderate reactions</td>
<td></td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>ErbB2 (HER2)</td>
<td>Humanized</td>
<td>2</td>
<td>DYSP, ARDS, rash and pruritus</td>
<td>–</td>
<td>–</td>
<td>n.a.</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>CTLA-4</td>
<td>Humanized</td>
<td>&lt;1</td>
<td>Pruritus, rash, flushing and DYSP</td>
<td>Paracetamol</td>
<td>Discontinuation after severe reactions; rechallenge at 50%&lt;sup&gt;b&lt;/sup&gt; after mild-to-moderate reactions</td>
<td></td>
</tr>
<tr>
<td>Denosumab</td>
<td>RANK ligand</td>
<td>Humanized</td>
<td>n.a.</td>
<td>Rash</td>
<td>–</td>
<td>–</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

HSR, hypersensitivity reactions; AB, antibodies; n.a., not available; ARDS, acute respiratory distress syndrome; URT, urticaria; F, fever; AE, angioedema; DYSP, dyspnea; RIG, rigor; A, anaphylaxis.

<sup>a</sup>In all cases of acute HSR, infusion is interrupted, close monitoring is initiated and supportive measures such as oxygen, i.v. fluids and bronchodilators are given

<sup>b</sup>Rechallenge with a reduced infusion rate of 50%.

<sup>c</sup>Because rituximab is given before ibritumomab tiutexan, premedication corresponds to paracetamol and diphenhydramine given before rituximab.

<sup>d</sup>During dose escalation and thereafter if indicated.

<sup>e</sup>Leucocyte count should be reduced to 30'000 G/L before the administration of gemtuzumab ozogamicin to reduce the risk of acute HSR.

<sup>f</sup>Paracetamol may be given for the first infusions.
following severe HSR. This report summarizes acute HSR to anticancer drugs; iron and blood products are not covered.

**the immune system**

The administration of any xenobiotic is likely to elicit some immune response, mostly minor, subclinical and transient. Severe symptoms arise with sudden and severe immune overreactions. The immune response can be innate, adaptive or a combination thereof. An innate response is a nonspecific, rapid response that is present before drug exposure. In contrast, the adaptive response is an acquired, specific immune response, and each successive xenobiotic exposure increases the immune response. Adaptive immune responses are directed by lymphocytes and are either humoral or cell-mediated. Infusion reactions are either IgE-mediated, allergic reactions to foreign proteins or non-IgE-mediated (anaphylactoid) reactions. Nonallergic HSR are complex and primarily result from cytokine release. Most HSR to chemotherapeutic agents are IgE-mediated type 1 reactions [3]. Allergic reactions are immediate, usually occurring within minutes of exposure, although delayed reactions (10–12 h after exposure) may occur. The shorter the interval between exposure and symptoms, the more severe the HSR. During initial exposure, IgE antibodies are produced and bind to receptors on mast cells and basophils. With subsequent exposure, the target-fixed antibodies react with the antigen and trigger the release of mediators such as histamines, leukotrienes and prostaglandins, resulting in characteristic symptoms (fever, chills, bronchospasm, tachycardia, urticaria and nausea). Very rarely, death occurs from hypoxemia or shock.

**chemotherapy**

Acute HSR to chemotherapeutics are infrequent and usually mild. Still, acute HSR are a significant problem with platinum compounds, taxanes, i-asparaginase, epipodophyllotoxins and procarbazine. Chemotherapeutics are categorized into three groups with high, intermediate or low potential to cause HSR. The clinical manifestations are variable and unpredictable. Severe reactions always develop during drug infusion, whereas mild-to-moderate reactions may occur up to 3 days after chemotherapy [9]. The more severe acute HSR involve drug-specific IgE, while mild reactions are usually caused by other mechanisms, such as direct mast cell or basophil degranulation or activation of the complement cascade.

**drugs with high potential for HSR**

**platinum salts**

‘Oxaliplatin’ causes acute HSR in 0.5%–25% of cases [10]. The HSR is usually mild to moderate in nature, with <1% of reactions being life-threatening [11]. Oxaliplatin-associated HSR often cause itching and erythema, especially on palms and soles. More severe reactions are characterized by urticaria, facial swelling, diffuse erythrodermia and bronchospasm, and may evolve into anaphylaxis in about 1% of cases. On average, oxaliplatin-associated HSR occur at the seventh to eighth administration, 5–10 min after the start of infusion, and have to be treated with intravenous antihistamines and steroids, and rarely require epinephrine [10]. Usually, the first HSR to oxaliplatin is mild, but it may become more severe at rechallenge. The role of platinum-specific IgE antibodies in the development of HSR to oxaliplatin is well documented [12]. The risk of oxaliplatin-associated acute HSR increases with cumulative dose, suggesting that sensitization to the drug is needed. Intradermal skin tests are sensitive for the diagnosis of oxaliplatin-associated HSR, with a sensitivity of 75% and 100% [13]. Premedication schedules to prevent oxaliplatin-associated HSR have not been reliable [14]. If oxaliplatin is considered fundamental for a patient after experiencing a severe HSR, desensitization should be tried (Table 2).

For ‘carboplatin’ (Paraplatin, Bristol-Myers Squibb, NY, USA), the incidence of HSR is <1%, 6.5%, 7% and 19.5% for patients who have undergone <5, 6, 7 and 8 cycles of carboplatin, respectively [15]. A retreatment interval >2 years predicts the development of HSR [16]. Most carboplatin-associated acute HSR are mild and include itching, localized erythema, facial flushing, and respond to oral antihistamines. More severe reactions occur in 30%–40% of cases, develop about 30 min after the start of infusion, and include facial swelling, diffuse erythrodermia, abdominal cramps, diarrhoea, dyspnea, chest pain, angina pectoris, tachycardia, hypo- or hypertension [17]. In patients with a previous HSR to carboplatin and a positive skin test, desensitization is necessary [18]. As with other IgE-mediated severe HSR, premedication with antihistamines and steroids is insufficient to suppress HSR [19]. Substitution of carboplatin with, e.g. cisplatin may be of limited value due to cross-reacting IgEs [19]. However, if skin testing is negative for another platinum compound, the alternative drug may be applied.

‘Cisplatin’ causes HSR in 1%–5% of cases [20], with most reactions being mild. Most reactions occur a few minutes after the start of chemotherapy, and usually develop after ≥6 treatment cycles. Therefore, specific IgEs probably play an important role in the pathogenesis of cisplatin-associated HSR. Experiences with skin tests are limited. A pretreatment with antihistamines and steroids is insufficient to suppress HSR [20]. If oxaliplatin is considered fundamental for a patient after experiencing a severe HSR, desensitization should be tried (Table 2).

**taxanes**

HSR to paclitaxel or docetaxel are primarily due to type I reactions to cremophor (polysorbate 80), the pharmaceutical vehicle for paclitaxel and docetaxel, respectively. Taxane-related HSR occur in up to 30% of patients without premedication, decreasing to ≤4% with premedication using antihistamines and steroids [21]. Taxane-associated HSR are dose- and rate-dependent, occur within the first minutes of infusion, most frequently occur at first or second exposure (95% of all HSR), may be severe during the first treatment cycles, but usually disappear on rechallenge and adequate premedication [4]. Reactions are probably not IgE-mediated, as they may occur at first administration. Taxane-associated HSR occur more frequently in patients with a history of atopy [4]. Symptoms include dyspnea, hypotension, bronchospasm, urticaria and erythematous rashes [22]. Because paclitaxel is often infused in combination with carboplatin, the distinction...
Table 2. Incidence, prevention and management of hypersensitivity reactions with frequently used chemotherapeutics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Drug class</th>
<th>Schedule</th>
<th>Incidence of severe HSR (%)</th>
<th>Specific symptoms</th>
<th>Recommended premedication</th>
<th>Rechallenge after HSR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxaliplatin</td>
<td>Platinum</td>
<td>2 week (85–100 mg/m²)</td>
<td>&lt;1</td>
<td>Pruritus, rash, URT, DYSP and A</td>
<td>Steroid and 5HT3-antagonist</td>
<td></td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Platinum</td>
<td>3 week (AUC 5–6)</td>
<td>5–8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Rash, pruritus, AE, URT, DYSP, AP, and tachycardia</td>
<td>Steroid and 5HT3-antagonist</td>
<td>Consider desensitization or replacement by another platinum compound</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Platinum</td>
<td>3 week (75–100 mg/m²)</td>
<td>&lt;1</td>
<td>Rash, pruritus, and URT</td>
<td>Steroid, 5HT3-antagonist, and aprepitant</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Taxane</td>
<td>3 week (175–225 mg/m³)</td>
<td>&lt;4</td>
<td>DYSP, hypotension, URT, and AE</td>
<td>Steroid, diphenhydramine, ranitidin and 5HT3-antagonist</td>
<td>After 2 subsequent HSR: Replacement by the other taxane, intensified premedication and slower infusion rate</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Taxane</td>
<td>3 week (75 mg/m²)</td>
<td>&lt;2</td>
<td>DYSP, hypotension, URT, and AE</td>
<td>Steroid, diphenhydramine, ranitidin, 5HT3-antagonist</td>
<td></td>
</tr>
<tr>
<td>L-Asparaginase</td>
<td>Enzyme</td>
<td>6000 units/m²/day</td>
<td>&lt;10</td>
<td>Pruritus, DYSP, URT, and hypotension</td>
<td>Steroid, antihistamines</td>
<td>Replace with the less immunogenic PEG-asparaginase, intensified premedication (steroids, antihistamines)</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>Alkylator</td>
<td>100–150 mg/m²/day</td>
<td>2</td>
<td>Rash, URT, toxic necrolysis, and F</td>
<td>Steroid and diphenhydramine</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Etoposide</td>
<td>TOPO2 inhibitor</td>
<td>100 mg/m² days 1–3</td>
<td>&lt;1</td>
<td>URT, pruritus and A</td>
<td>Steroid and 5HT3-antagonist</td>
<td>Intensified premedication (steroids), slower infusion rate</td>
</tr>
<tr>
<td>Doxorubicin and Epirubicin</td>
<td>Anthracyclines</td>
<td>60/m²; 50 mg/m²</td>
<td>&lt;1</td>
<td>URT, pruritus, rash and A</td>
<td>Steroid and 5HT3-antagonist</td>
<td>Slower infusion rate, desensitization</td>
</tr>
<tr>
<td>Methotrexate (MTX)</td>
<td>Antifolate</td>
<td>3500 mg/m² (high dose)</td>
<td>&lt;1</td>
<td>F, hypotension, URT, AE and tachycardia</td>
<td>Metoclopramide</td>
<td>Premedication (steroids, antihistamines), desensitization</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Nucleoside</td>
<td>100–200 mg/m²/day/7 days</td>
<td>&lt;1</td>
<td>URT, hypotension and DYSP</td>
<td>Metoclopramide</td>
<td>Premedication (steroids, antihistamines), desensitization</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>Alkylator</td>
<td>1.2–2.4 g/m²/day/5 days</td>
<td>&lt;1</td>
<td>URT, rash, and AE</td>
<td>Steroid and 5HT3-antagonist</td>
<td>Premedication (steroids, antihistamines), desensitization</td>
</tr>
</tbody>
</table>

HSR, hypersensitivity reactions; w, weekly; AUC, area-under-the-plasma-concentration-time-curve; n.a., not available; URT, urticaria; F, fever; AE, angioedema; DYSP, dyspnea; RIG, rigor; A, anaphylaxis; AP, angina pectoris; TOPO2, topoisomerase 2.

*In all cases of acute HSR, infusion is interrupted, close monitoring is initiated and supportive measures such as oxygen, i.v. fluids and bronchodilators are given.

<sup>b</sup>In patients receiving up to eight cycles of carboplatin.
between the two potentially causative drugs should be considered: (i) carboplatin provokes HSR after several doses, paclitaxel at first or second exposure. (ii) Carboplatin-related HSR greatly vary in the timing of appearance and in severity, while paclitaxel-related HSR are more uniform. (iii) Paclitaxel-related HSR quickly resolve after discontinuation of the drug, whereas carboplatin-associated HSR often require hours to resolve. (iv) Premedication is effective with paclitaxel, but not with carboplatin. Premedication for paclitaxel usually includes oral administration of dexamethasone (8 mg) 12 and 6 h before infusion, diphenhydramine (2 mg) and ranitidine (50 mg) intravenously 30 min before infusion [23]. In patients with acute HSR to paclitaxel at rechallenge, a standardized 12-step desensitization protocol may be applied [18]. Cremophor-free formulations of albumin-bound paclitaxel do not cause HSR, and no premedication is usually required with this formulation. Premedication for docetaxel is different from paclitaxel and includes oral administration of dexamethasone for 3 days, starting 1 day before chemotherapy [22]. Sharing the same therapeutic indications, docetaxel could potentially substitute paclitaxel in cases of severe HSR, but Dizon et al. reported a cross-reactivity rate of 90% between the two drugs, suggesting that the taxane moiety may be responsible for cross-reactivity [24]. Therefore, substitution of one taxane with the other is not recommended.

L-asparaginase
The enzyme L-asparaginase originates from Escherichia coli or Erwinia chrysanthemi, and is also available as a polyethylene glycol (PEG-asparaginase). The administration of L-asparaginase carries a substantial risk of type I HSR of 40%, with severe HSR occurring in <10% of patients [25]. HSR are more frequent and severe with intravenous compared with intramuscular application, a time interval ≥1 week between applications compared with daily administration [4] and previous exposure to L-asparaginase. Retreatment with L-asparaginase after several months is associated with acute HSR in 24% of cases [26]. Additional risk factors include doses >6000 IU/m²/day and single-agent administration [25]. L-asparaginase-associated HSR occur within an hour of drug administration, with symptoms such as pruritus, dyspnea, urticaria and hypotension. There is a substantial risk for HSR to be severe. In cases of HSR towards E. coli and Erwinia-derived L-asparaginase, the less immunogenic PEG-asparaginase should be used, with success rates of 70% [27]. Alternatively, premedication with steroids and antihistamines or desensitization protocols may be used.

procarbazine
Procarbazine-associated HSR include type I, III and IV reactions, with an incidence of 6% to 18%, and symptoms including fever, maculopapular rash, urticaria and toxic epidermal necrolysis [28]. Once HSR to procarbazine occurs, rechallenge is usually not successful, despite steroid prophylaxis, and procarbazine usually has to be discontinued [28].

epipodophyllotoxins
The overall incidence of HSR to ‘teniposide’ varies from 6.5% in brain cancer patients to 41% in children with leukemia [22], and part of the reaction is probably due to the solvent cremophor EL. Most HSR are mild, but severe anaphylaxis may occur. HSR may occur after the first dose, but usually occur after repeated administration [28]. HSR to etoposide is less frequent than with teniposide, only occurs with the i.v. formulation of etoposide (polysorbate80 solvent), and may be prevented with adequate premedication and slow infusion rate. Replacement of etoposide by teniposide is not recommended [29].

drugs with intermediate potential for HSR
HSR to anthracyclines usually involve the skin, but may also include more severe symptoms [28]. No good data are available for the prevention of anthracycline-associated HSR, but slower infusion rate may be effective, whereas premedication is of no value. Successful desensitization to liposomal doxorubicin has been described [18]. HSR to ‘methotrexate (MTX)’ are infrequent, but may be severe [30]. Desensitization and/or premedication may be effective in patients experiencing MTX-associated HSR. Steroids are usually effective in treating subacute pneumonitis, but pulmonary toxicity may be fatal in rare cases. Potentially T-cell-mediated skin toxicity, including severe Stevens–Johnson syndrome, has been described [31].

drugs with low potential for HSR
Uncommon type I HSR to ‘cytarabine’ include dyspnea, chest pain, urticaria, hypotension. Other cytarabine-associated symptoms include subacute, non-immunogenic conjunctivitis and palmar-plantar erythema. Type I HSR to ‘cyclophosphamide and ifosfamide’ occur in <1% of patients [32], with urticaria usually appearing in the first minutes of infusion. There is the potential for ifosfamide and cyclophosphamide-associated HSR being mainly caused by the concurrent use of mesna [33].

antibodies
Chimeric antibodies are >50% human, humanized antibodies >90%, and fully humanized antibodies 100% human. However, anti-mouse antibodies may still occur with fully humanized antibodies and result in HSR. Monoclonal antibodies may lead to rare nonallergic, cytokine-mediated HSR within the first hours after infusion [34]. Unlike type I reactions, symptoms appear to subside with each subsequent dose. Reactions of cytokine release may be managed by short-term cessation of drug infusion, administration of H1/H2 inhibitors and restarting the infusion at a slower rate [35]. Most monoclonal antibodies have the potential to cause cytokine release, but rituximab and trastuzumab carry a higher risk (77% and 40% HSR for the first application, respectively) [36]. According to six clinical studies in patients with indolent non-Hodgkin’s lymphoma, rituximab-associated HSR occur in 77% of patients
during the first infusion (7% grades 3–4), 30% during the fourth infusion (2% grades 3–4) and still 14% during the eighth infusion (no grade 3–4 events) [37]. Still, rituximab-related HSR rarely necessitates discontinuation of treatment. Panitumumab and bevacizumab have a lower incidence of acute HSR (4% and <3%, respectively). Premedication using, e.g., paracetamol plus an antihistamine is recommended for most antibodies with the exception of bevacizumab and panitumumab. The anti-CD52 antibody alemtuzumab is given in a fractionated way to avoid cytokine release. Most antibody-associated HSR are mild. The National Cancer Institute has classified antibody-associated, acute HSR into four standardized severity grades [38]. In case of mild-to-moderate HSR, rechallenge is usually successful with a lower rate of infusion [34] (see also Table 1).

management of acute HSR

Prevention of acute HSR is preferable. Taking into account a thorough history of previous HSR is imperative. In patients with impaired compliance to oral premedication, i.v. premedication is chosen. When symptoms of potential HSR occur, the infusion is stopped and vascular access maintained with normal saline. Breathing and circulation are assessed immediately, and emergent equipment and medication are prepared, including epinephrine. Oxygen is essential in patients with prolonged HSR or pre-existing respiratory or cardiac disease [39]. Vital signs are assessed every 2–5 min until the patient is stable. Many HSR will resolve once the offending agent has been discontinued and supportive care is given. Once symptoms have completely resolved, the infusion may be restarted at 50% of the infusion rate and titrated to tolerance [35]. In the case of anaphylactic HSR, epinephrine 0.2–0.5 mg (1 mg in 1 ml) is necessary. Dopamine may be given for refractory hypotension after referral to the intensive care unit. Histamine antagonists (H1 and H2) are given for pruritus, angioedema and urticaria [39], but they are inferior to epinephrine in case of true anaphylaxis [39]. Due to their delayed onset of action, corticosteroids are not first choice for anaphylaxis, but they may decrease the duration of any acute HSR or prevent a biphasic reaction.

disclosure

The author has declared no conflicts of interest.

references


