Original Article

Assessment of Antihistamines and Corticosteroids as Premedication in Rapid Drug Desensitization to Paclitaxel: Outcomes in 155 Procedures

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What is already known about this topic? Rapid drug desensitization is a helpful therapeutic tool that enables paclitaxel to be safely administered to paclitaxel-hypersensitive patients.

What does this article add to our knowledge? It is unclear whether systematic premedication with antihistamines and corticosteroids makes rapid drug desensitization to paclitaxel safer.

How does this study impact current management guidelines? Premedication regimens for rapid drug desensitization may be increasingly tailored to prevent adverse effects from unnecessary systematic administration of drugs.

BACKGROUND: In early clinical trials, infusion reactions during the administration of taxanes were managed using systematic premedication with antihistamines and corticosteroids before standard infusions. Consequently, these premedications are also administered before rapid drug desensitization (RDD) with taxanes. However, their role in RDD has not been studied.

OBJECTIVE: To assess the need for premedication with antihistamines and corticosteroids to prevent hypersensitivity reactions in RDD to paclitaxel.

METHODS: Over a 4-year period, we selected patients with confirmed hypersensitivity to paclitaxel (positive skin testing and/or drug provocation testing results) who had received paclitaxel through RDD. These patients were assigned to 2 prospective noninception cohorts: one cohort premedicated with antihistamine and corticosteroids and another cohort that was not.

RESULTS: We assessed 66 paclitaxel-reactive patients, of whom 22 met the inclusion criteria. A total of 155 RDDs to paclitaxel were performed. There were no significant differences in tolerance to RDD between the cohorts.

CONCLUSIONS: Administering systematic premedication with corticosteroids and antihistamines had no significant effect on the effectiveness or safety of RDD in patients with confirmed hypersensitivity to paclitaxel in the study population. Moreover, these premedications can mask early signs of hypersensitivity and delay treatment. We believe that systematic premedication with these drugs for patients undergoing RDD should be carefully and individually assessed if their only purpose is to prevent breakthrough reactions during RDD. **(J Allergy Clin Immunol Pract 2017;■:■-■)**

Key words: *Drug allergy; Paclitaxel; Hypersensitivity; Desensitization; Chemotherapy; Premedication*

Taxanes are antineoplastic drugs that are widely used to treat solid tumors.[1-3] However, their administration is often associated with unwanted infusion reactions, which sometimes require withdrawal of taxane therapy and substitution with alternative treatments.[1,3]

A high incidence of immediate infusion reactions was recorded in early clinical trials with the taxane known as Taxol (paclitaxel).[4-6] The frequency of these infusion reactions was reduced by premedication with antihistamines and corticosteroids. Therefore, the summary of product characteristics prepared for Taxol recommended premedication with 20 mg dexamethasone, 50 mg ranitidine, and 5 mg diphenhydramine.[3]

Even with premedication, up to 10% of patients experience an infusion reaction to taxanes.[7,8] Consequently, rapid drug desensitization (RDD) may be necessary to ensure safe delivery of first-choice therapy. RDD is a therapeutic technique that induces a temporary state of tolerance to the drug responsible for a proven drug hypersensitivity reaction (DHR).[9,10] Paclitaxel RDD protocols use the same premedication (including corticosteroids and antihistamines) as used in standard regimens.[1,8-11] However, previous studies[11-14] report good results with RDD protocols that do not involve premedications for the prevention of DHRs to drugs other than taxanes.

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Abbreviations used
DHR- Drug hypersensitivity reaction
DPT- Drug provocation testing
IDT- Intradermal test
RCUH- Ramon y Cajal University Hospital
RDD- Rapid drug desensitization
SPT- Skin prick test
ST- Skin testing

Drug interactions and adverse effects have been observed with the administration of corticosteroids (eg, hyperglycemia and immunosuppression) and antihistamines (eg, drowsiness and electrocardiogram alterations).[15-18] Therefore, the unnecessary use of these medications should be avoided whenever possible. In fact, some groups have studied whether premedication with corticosteroids before standard sessions of paclitaxel may be withdrawn in nonreactive patients after several uneventful regular infusions, with promising results.[2] In addition, *in vitro* studies suggest that dexamethasone can interfere with the cytotoxic action of paclitaxel and its effect on cell apoptosis.[19,20]

To our knowledge, it remains unclear whether paclitaxel-reactive patients who undergo paclitaxel RDD—designed to induce tolerance to drugs causing DHRs—really need additional premedication with the corticosteroids and antihistamines administered in standard regimens.

The primary outcome of this study was to assess the need for premedication with antihistamines and corticosteroids used as premedication to prevent DHRs in RDD to paclitaxel.

METHODS

Patient population and study design

We assessed all paclitaxel-reactive patients referred to the Ramon y Cajal University Hospital (RCUH) Desensitization Program between January 2011 and January 2015. Patients underwent the same diagnostic protocol to confirm or exclude hypersensitivity to paclitaxel.

To ensure the highest quality of the data obtained, only those patients who received paclitaxel by means of RDD after a confirmed diagnosis of hypersensitivity to paclitaxel (positive skin test results and/or positive drug provocation test results) were selected. These selected patients were assigned to 2 prospective noninception cohorts.

Cohort A included all patients selected from January 2011 to December 2012. The patients had received premedication with corticosteroids (dexamethasone 20 mg) and antihistamines (dexchlorpheniramine 5 mg) before the administration of paclitaxel through RDD.

Cohort B included all patients selected from January 2013 to December 2014. None of these patients had received premedication with corticosteroids or antihistamines before the administration of paclitaxel by means of RDD.

Informed consent statement

The RCUH Ethics Committee approved the study protocol and validated the informed consent documents, which were signed by the patient, allergist, and referring physician.

Diagnostic protocol: Clinical history/initial reaction

Signs and symptoms from initial reactions and characteristics of patients were collected as in previous studies by our group.[11-14,21-23]

The severity of the initial reaction was classified into 3 groups according to Brown[24]: Grade 1 or mild reactions (skin and subcutaneous tissue only), defined as generalized erythema, urticaria, periorbital edema, or angioedema; grade 2 or moderate reactions (features suggesting respiratory, cardiovascular, or gastrointestinal involvement), defined as dyspnea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest/throat tightness, or abdominal pain; grade 3 or severe reactions (hypoxia, hypotension, or neurologic compromise), defined as cyanosis or peripheral oxygen saturation of 92% or less at any stage, hypotension (systolic blood pressure <90 mm Hg in adults), confusion, collapse, loss of consciousness, or incontinence.

Diagnostic protocol: Risk assessment

As in previous studies by our group,[11-14,21-23] patients were classified as high-risk or medium/low-risk.

We considered high-risk patients to be those who met any of the following criteria: previous life-threatening reaction (such as a history of intubation and cardiovascular collapse), comorbidities where exposure might provoke situations beyond medical control (such as unavoidable use of beta-blockers, mastocytosis, uncontrolled asthma or lung disease with EFV_1 <1 L), and pregnancy.

Diagnostic protocol: Skin testing

Trained personnel in adequate settings performed skin testing (ST) and assessed the results in all referred patients according to previous articles.[11-14,21-23] Skin prick test (SPT) concentrations for paclitaxel were 1 and 6 mg/mL, and the intradermal test (IDT) concentration was 1 mg/mL.[11-14,21-23] Positive results with IDT concentrations of 6 mg/mL were not considered as positives because recent findings suggest that this concentration may be irritant.[22]

For SPT, a drop of the drug at the maximal concentration was applied to the volar surface of the forearm using an SPT lancet. If the result was negative, IDT was performed (0.03 mL of the drug was injected intradermally into the volar surface of the forearm). A positive reaction was defined as a wheal with a diameter at least 3 mm larger than that produced by a negative control (saline solution). Histamine (10 mg/mL for SPT and 0.01 mg/mL for IDT) was used as a positive control.

Diagnostic protocol: Drug provocation test

Patients were assessed for drug provocation testing (DPT), which involves the controlled administration of a drug to study DHRs and is considered to be the criterion standard for establishing or excluding a diagnosis of hypersensitivity.[22-23,25] The final multidisciplinary decision on DPT was based on a safety-first policy and on a thorough assessment of the benefits for the patient. The patient was empowered to make the final decision by considering 2 fundamental cornerstones: (1) data on the indication and need for treatment of the referring oncologist, and (2) data on the risk assessment of the allergist. As in previous articles by our group,[11-14,21-23] high-risk patients were encouraged to avoid DPT. A recent study found that positive ST with nonirritant concentrations is a good predictor of a diagnosis of hypersensitivity to paclitaxel[22]; therefore, patients with such profile were discouraged to undergo DPT. However, we have found negative DPT results in paclitaxel-reactive patients with positive IDT result with the irritant 6 mg/mL concentrations[22]; thus, patients with this profile were not necessarily discouraged to undergo DPT provided their risk assessment was favorable.

DPT was performed during the next scheduled treatment and following the same detailed recommendations described in recent articles by our group.[11-14,21-23] For DPT, we carefully administered the desired dose of the culprit drug according to the manufacturer's