REVIEW ARTICLE

Premedication of Ranitidine and the Action of Hypersensitivity Reactions to Paclitaxel

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ABSTRACT

Paclitaxel is used asa chemotherapeutic agent for curing various types of cancer. To reduce the hypersensitivity of the chemotherapeutic effect, premedication of antihistaminic drugs like ranitidine, cetirizine, diphenhydramine, fexofenadine and desloratadine are prescribed. The antihistaminic drugs are given as premedication to prevent the formation of hives on the body. Ranitidine can be replaced by another antihistaminic drug which reduces the side effects and increases the efficacy of the drug. Studies were conducted comparing the antihistamine and non-antihistamine groups and tests like the chi-square test, and the Wilcoxon-Mann-Whitney test to determine the extent of hypersensitivity. There are immediate and non-immediate drug hypersensitivity reactions occurring in cells that initiate the allergic reaction. These allergic reactions like flushing, itching, dizziness, nausea, vomiting, swelling, etc lead to affect the respiratory, cardiovascular, gastrointestinal, and other body parts. In this article, the method used for the study of hypersensitivity reaction is specified with the test to determine the allergic reaction on the skin and desensitization of the rapid hypersensitivity of the drug.

Keywords: Antihistamine, Hypersensitivity Reaction, Chemotherapy agents, Study design, Allergy.

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INTRODUCTION

Among the most often prescribed anti-cancer medications in the world is paclitaxel. It is efficacious in treating a broad range of cancers, including head and neck, ovarian, breast, lung, and oesophageal cancer.[1] Originally extracted from the bark of the western yew, *Taxus brevifolia*. Early drug research was limited by poor solubility, so paclitaxel is formulated using a polyoxethylated castor oil carrier (cremophor EL).[2] Advanced ovarian cancer and melanoma have been demonstrated to be responsive to the antitumor drug taxol, which is currently undergoing clinical trials. One of the hazards associated with the administration of this medication has been hypersensitivity responses (HSRs). Many medications, including most of the anticancer treatments used in clinical practice, can cause hypersensitivity reactions (HSRs). These anticancer medication responses typically exhibit type I hypersensitive characteristics. However, a lot of them don't seem to be caused by immunoglobulin E. (IgE).[3] Ranitidine holds primary approval for managing ulcer disease and gastroduodenal reflux disease. In a departure from its conventional use, our approach extends its application. Integrating an H2 antagonist, such as ranitidine, into the standard premedication regimen for paclitaxel draws inspiration from established protocols designed to mitigate hypersensitivity reactions during the administration of urographic radiocontrast media, showcasing an innovative and cross-disciplinary therapeutic strategy.[1] Histamine H2-receptor antagonists, commonly deployed in treating peptic ulcers, acute stress ulcers, and acid hypersecretion conditions, play a pivotal role in managing gastroesophageal reflux. Their routine use before surgery serves as a proactive measure, effectively reducing the risk of pulmonary aspiration, acid reflux, and postoperative nausea and vomiting.[4] Paclitaxel's significant adverse effect, hypersensitivity reactions (HSR), potentially severe, is attributed to its solvent, cremophor EL. Premedication with ranitidine, dexamethasone, and a histamine-1 receptor antagonist markedly reduces this risk. The precise components of this three-drug regimen, encompassing H1 and H2 receptor antagonists along with dexamethasone, necessary for halting allergic reactions remain unclear. Although ranitidine alone may cause hypersensitivity responses in 0.7% of infusions, its theoretical justification is the weakest among the three drugs, lacking comprehensive clinical investigation into the additional benefits of an H2-receptor antagonist.[5]

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Chemotherapeutic Treatment for Cancer with Hypersensitivity Reactions

Distinguishing between the temporal manifestation of symptoms, drug hypersensitivity reactions (DHRs) are dichotomized into immediate (IDHRs) and nonimmediate (NIDHRs). While NIDHRs typically unfold days or weeks post-administration, IDHRs swiftly emerge within the initial 1 to 6 hours. The intricate tapestry of DHRs unravels through endotypes, representing the cellular and molecular underpinnings, while the observable clinical features constitute phenotypes. Immediate reactions to chemotherapeutic drugs and monoclonal antibodies encompass a spectrum, featuring type 1 reactions, cytokine release phenomena, mixed responses, and reactions with indistinct characteristics as mentioned in Figure 1.

Type 1 reactions entail the direct stimulation of mast cells through C3a and C5 complement fractions, in addition to stimulation *via* the MRGPRX2 receptor. This activation extends to mast cells and basophils, triggering the release of mediators *via* pathways involving both IgE-mediated and non-IgE-mediated mechanisms.

The increase of cytokines such as tumor necrosis factor, alpha (TNF-α), interleukin (IL) 1 and IL-6 in the cytokine release endotype can come from a variety of types, including T cells, monocytes, and macrophages.[6,7]

Cytokine release reaction (CRR) and monoclonal antibodies (mAb) are both used. Mast cell activation symptoms and other phenotypic-specific symptoms are both part of phenotype 2. Both typical symptoms and CRR-specific symptoms make up the CRR phenotype. The indeterminate phenotype solely consists of common symptoms, while the mixed phenotype combines all the aforementioned.[7]

Method for the Study

There are various methods to conduct the study for premedication, but the study method mentioned below can give the desirable result for better results.

Study design

An investigation into premedication protocols, sans the inclusion of ranitidine, was conducted in comparison to the conventional regimen featuring ranitidine. The pre-intervention cohort received the standard combination of ranitidine, clemastine, and dexamethasone, while the post-intervention group underwent the experimental premedication without the H2 antagonist ranitidine. Monitoring persisted for a minimum of two to a maximum of six cycles of paclitaxel infusions in both groups and until the onset of the first hypersensitivity reaction (HSR) within the initial six cycles, whichever transpired earlier. Each paclitaxel infusion carried the inherent risk of triggering HSRs or an immune response to paclitaxel.[1]

Navigating patient identification and selection for targeted care

Identification of patients was accomplished through the hospital's medical information management system, CHARM (Citadel Health, 2020), designed for cancer therapy authorization, clinical validation, and administration. Eligible individuals needed enrolment in a chemotherapy program involving paclitaxel for breast, head and neck, or lung cancer, and should be naïve to paclitaxel treatment at the protocol's commencement. Notably, there was a complete absence of patient transfers between the two groups.[6]

Data collection

A comprehensive data collection approach employed three distinct clinical databases – CHARM, integrated electronic medical record (ieMR), and the incident reporting system RiskMan. Upon study enrolment initiation, patient demographic details encompassing cancer type, gender, and age were meticulously compiled. Additional recorded parameters included the chemotherapy cycle number, paclitaxel dose, administered premedication, the occurrence of hypersensitivity reactions (HSR) with severity ratings, and any implemented protocol modifications. The integrity of documented HSR data underwent rigorous validation through cross-referencing with the RiskMan database, ensuring robust and reliable information.[6]

Data analysis

To explore potential shifts post-recall, the comparative analysis delved into the frequency and magnitude of paclitaxel hypersensitivity reaction (HSR) events within the two groups. Employing a percentage test, it was scrutinized whether a statistically significant difference existed in HSR occurrence between the ranitidine and non-ranitidine cohorts. A logistic regression analysis, facilitated by the random effects logit dynamic panel command, probed into the predictive capacity of patient features and treatment characteristics for HSR events. Prior to constructing a comprehensive multivariate model encompassing five variables (Ranitidine or no ranitidine, gender, age at service entry, cancer type, and cycle number), individual variable prediction potential was evaluated through univariate models. The ensuing insights were then leveraged to discern the unique impact of each variable on HSR occurrences.[6]

Statistical analysis

The distinctive traits of the sample data are delineated through descriptive statistics, elucidating medians, and ranges for continuous variables, while categorical variables are expressed in percentages alongside confidence intervals. Exploring the potential association between categorical variables and premedication groups involves the utilization of the chi-square test, with Fisher's exact test deployed for scenarios with low cell counts. In the realm of premedication comparisons, the Wilcoxon-Mann-Whitney test takes center stage, specifically tailored for non-symmetrically distributed continuous variables, adding precision to the analytical framework.[7,8]

Other anti-histaminic drugs as pre-medication for paclitaxel treatment

In the context of breast cancer patients, pre-emptive antihistamine administration is recommended to mitigate

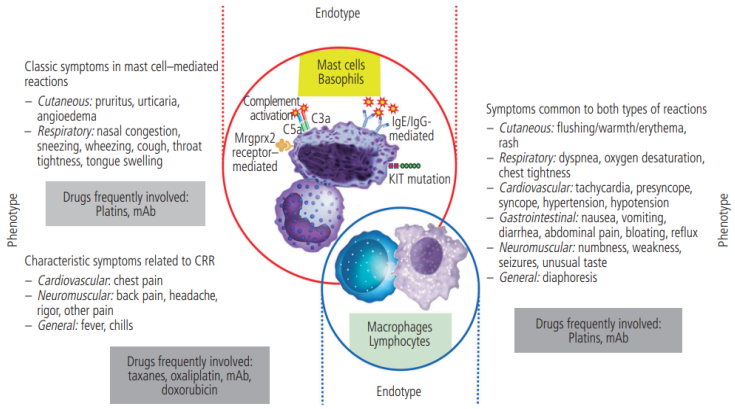

Figure 1: Diverse phenotypic and endotypic responses characterize reactions to chemotherapeutic drugs and monoclonal antibodies.[13]

drug-induced hypersensitivity during the use of various chemotherapies, including paclitaxel. The exploration of IV cetirizine, a second-generation intravenous antihistamine, has showcased its efficacy in treating acute urticaria with a reduced incidence of side effects compared to IV diphenhydramine. The study's authors postulated that extending the effectiveness of IV cetirizine beyond acute treatment could position it as a viable preventative measure for infusion responses, forming a novel avenue for improving patient care.[7]

Previously, diphenhydramine served as a pre-emptive measure before cetuximab, rituximab, and paclitaxel administration due to the potential risk of life-threatening infusion reactions. Research has underscored that premedication incorporating an H1-antagonist and corticosteroids effectively diminishes the incidence of such reactions. While diphenhydramine has traditionally been the preferred H1-antagonist, second-generation antihistamines have emerged as promising alternatives. Distinctively, diphenhydramine, as a first-generation antihistamine, is characterized by more noticeable side effects and a greater likelihood of penetrating the central nervous system (CNS) compared to its second-generation counterparts, introducing considerations for optimizing premedication strategies.[8] In a randomized double-blind study, it was discovered that the administration of diphenhydramine at 50 mg orally for hypersensitivity reactions leads to impairment in driving abilities, akin to the impact of a 0.1% blood alcohol content. This revelation highlights the noteworthy influence of diphenhydramine on psychomotor function, underscoring the importance of considering potential cognitive effects when utilizing this medication for hypersensitivity reactions.[8-12]

Cetirizine and its second-generation H1 antihistamine counterparts minimize side effects by precisely targeting H1 receptors and exhibiting limited blood-brain barrier penetration. Renowned for their excellent safety and efficacy, these modern H1 antihistamines have ascended to the forefront, establishing themselves as the preferred first-line treatment for allergic rhinitis and urticaria.[10] With its reduced impact on the central nervous system and comparable efficacy to diphenhydramine, cetirizine emerges as a prime recommendation in cases of hypersensitive reactions, standing out as the optimal alternative for enhanced patient safety and effectiveness.[8]

Third-generation antihistamines, exemplified by fexofenadine and desloratidine, distinguish themselves as metabolites or enantiomers of existing medications, potentially ushering in heightened efficacy and safety enhancements. This unique classification positions them as promising advancements, anticipating benefits beyond their predecessors in the realm of antihistamine therapy.[4] Recent advancements in antihistamines (AHs) showcase superior safety, accelerated onset of action, and heightened efficacy, along with prolonged duration and increased potency, as evidenced by rigorous high-quality research, signaling a substantial leap forward compared to their earlier 1st generation counterparts.[8-13]

Skin test

Just a small subset of chemotherapeutic medicines, primarily platinum compounds and maybe taxanes, respond well to SPT and intradermal tests used to identify drug-specific IgE in reactions thought to be immune-mediated. Premedicated medications like steroids or serotonin 5HT3 receptor antagonists can also trigger responses. When it comes to taxanes, some publications have observed positive STs in patients who have been suspected of having HSRs to paclitaxel and docetaxel. These findings showed that IgE-mediated HSRs to taxanes are present, at least in some circumstances. We further stress the absence of any ST-related events involving the use of medication formulations that contain emulsifying agents. In Table 1 all the chemotherapeutic drug reactions are specified which affect the skin, head, neck, lungs, and other organs after the premedication.

ST is used to diagnose platinum compounds for the following reasons:

- Diagnostic precision
- Proactive intervention strategies
- Stratifying risks effectively
- Assessing cross-reactivity profiles[14]

Desensitization

Although they have been around for more than 50 years, antibiotic desensitization gradually exposes patients

Table 1: Signs of a rapid chemotherapeutic drug reaction[14]

Skin and mucosa	*A cascade of warmth, flushing hues, the itch of anticipation, paired with urticaria's canvas and the sculpted presence of angioedema – capture the essence of diverse hypersensitivity reactions succinctly.*
Head and Neck	Pruritus in the eyes, hyperemia, teardrops like nature's cascade, orbital puffiness, nasal pruritus, a symphony of rhinorrhea, nasal congestion, and the dance of sneezes. Lips and oral terrain tingling, a metallic taste sensation, and the grandeur of angioedema's embrace. A perceptible swelling sense in the throat, a shift in vocal melody, the timbre of hoarseness, and the challenge of swallowing, accompanied by the ominous strido r– an intricate portrayal of a myriad of sensory responses.
Respiratory	A breath's struggle, a chest's embrace, a cough's echo, the whisper of wheezing, and the subtle touch of cyanosis – an intricate snapshot of respiratory nuances.
Cardio vascular	Whispers of faintness, palpitations' rhythmic beats, syncope's fleeting dance, tunnel vision's narrowing gaze, the subtle descent into hypotension, and the ominous stillness of cardiac arrest – a concise glimpse into the spectrum of cardiovascular responses.

to inadequate amounts of drug antigens, making them momentarily resistant to full therapeutic doses.

The crux of the tolerization protocol lies in elevating the dosage to the therapeutic threshold with minimal adverse impact. The delicate orchestration of intervals between doses, the nuanced adjustments, and the pivotal starting point significantly shape its efficacy. Administration unfolds within a timeframe of 10 to 30 minutes, where the initial dose, often a fraction of the target dosage, sets the tone. Leveraging the strategy of doubling or tripling the prior dose at intervals, rather than conventional 10-fold increments, emerges as a more effective paradigm for mitigating adverse effects.

Unlocking the intricacies of successful *in-vivo* desensitization, in vitro desensitization of mast cells and basophils offers foundational insights. However, the current clinical approaches, despite their empirical nature and reliance on trial-and-error experiences, draw upon this knowledge, navigating the delicate balance between theoretical understanding and practical application.[15]

CONCLUSION

Consistency prevailed among patients, whether administered ranitidine as premedication or not, with no discernible difference in anaphylactic reaction frequencies during paclitaxel administration. Our data challenge the notion that ranitidine plays a decisive role in paclitaxel-induced hypersensitivity reactions (HSRs), highlighting the contentious nature of the neurobiological mechanism. Despite mirrored findings across diverse groups, the customary use of ranitidine for allergy prevention warrants meticulous scrutiny and a comprehensive reassessment in the realm of clinical research.

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