Relationship between free platinum/cisplatin in antineoplastic: influence on type I hypersensitivity reactions.

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Abstract
Use of cisplatin can induce type I hypersensitivity reactions that may also be linked to the quality of the drug utilized. We observed cases of hypersensitivity that appeared to be associated with the brand of cisplatin used. The aim of this study was to compare two different brands of cisplatin in relation to type I hypersensitivity reactions.

Key words: adverse drug event, hypersensitivity reactions, quality control.

Introduction
Although hypersensitivity reactions to cisplatin are well known, cases in our service drew attention because they occurred over a short period and after the introduction of a new brand of the medicine. Until the end of 2012, the brand of cisplatin used in our hospital (brand A) was not associated with any case of hypersensitivity reaction. Following the introduction of brand B in January 2013, cases of hypersensitivity started to appear. Thus, we hypothesized that type I hypersensitivity reactions to cisplatin may be related to the quality of brand B, and our objective was to investigate the comparative chemical composition of the two products.

Results and Discussion
From January to August 2013 (8 months), 127 outpatients had used brand B cisplatin (571 administrations, mean of 4.52 administrations/patient), and four patients developed type I hypersensitivity after drug administration (frequency of 3.15%). Cisplatin of both brands was analysed by high-performance liquid chromatography (HPLC)\(^1\) and high-resolution electrospray ionization mass spectrometry (ESI-(+)MS) and characterized according to US Pharmacopeia\(^2\). The two brands were in accordance with the US Pharmacopeia parameters, and there was no significant difference in the total platinum levels between the two brands when analysed by HPLC. However, high resolution ESI-(+)MS analyses show that brand B contains approximately 2.7 times more hydrolysed cisplatin than brand A (Image 1).

Image 1. Mass spectrometry characterization of brands A (a) and B (b), respectively.

Conclusions
We hypothesized that cisplatin can be more allergenic in its hydrolysed form with more free platinum. High-resolution ESI-(+)-MS allows the extent of hydrolysis to be estimated. Drug regulatory agencies and manufacturers should consider including measurement of hydrolysed cisplatin as a quality criterion for cisplatin formulations.

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