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Stability of carboplatin infusion solutions used in desensitization protocol

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Abstract

Carboplatin hypersensitivity reactions are one of the major clinical challenges in treating patients with relapse/recurrent ovarian malignancies. Desensitization protocols allow the continuation of treatment in patients who have presented hypersensitivity reactions by gradually re-introducing small amounts of the drug up to full therapeutic doses. Carboplatin desensitization protocol is based on three solutions that are usually prepared in the chemotherapy centralized units of hospital pharmacies. First and second solutions are diluted under the established concentration limit to guarantee the stability of the preparation. We developed a specific high-performance liquid chromatography assay to determine the stability of carboplatin infusion solutions that have been diluted to 0.2 mg/mL and 0.02 mg/mL in 250 mL of 5% dextrose in polypropylene infusion bags which were stored 24 h protected from light at room temperature. Samples were withdrawn at $t = 0$ h, 3 h, 6 h, and 24 h. The analytical column was a Zorbax eclipse XDB-C18 (150 mm × 4.6 mm; 5 μm particle size). The mobile phase had a flow rate of 1 mL/min under isocratic conditions of water–methanol (98:2, v/v). For 0.2 mg/mL solution, the high-performance liquid chromatography assay revealed no significant losses in carboplatin concentration. However, in 0.02 mg/mL solution remaining carboplatin was > 105% the initial dose after 3 h of storage at room temperature. The ultraviolet–visible spectra analysis showed that carboplatin remained intact during the study in 0.2 mg/mL solution, but some changes were detected in 0.02 mg/mL solution. Thus, 0.2 mg/mL carboplatin solution is stable for 24 h at room temperature in 5% dextrose polypropylene infusion bags but stability could not be proved for 0.02 mg/mL solution.

Keywords

Carboplatin, desensitization, hypersensitivity, stability

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Introduction

Carboplatin represents the main drug in the management of ovarian cancer, included in first-line chemotherapy protocols for advanced ovarian carcinoma and recurrent ovarian carcinomas in platinum sensitive relapses.[1,2]

The management of hypersensitivity reactions (HSRs) is one of the major clinical challenges when treating patients with relapse/recurrent ovarian malignancies. Patients receiving multiple doses of chemotherapy can become sensitized and the subsequent exposure can lead to HSRs. This phenomenon has been observed more frequently in patients with extended carboplatin exposure with peak incidence occurring in the seventh cycle.[3] Some of these HSRs could be serious and even life-threatening.[4] Symptoms and signs of HSRs vary widely and may include throat tightness, hypotension, and anaphylactic shock.[5] The incidence of HSRs to chemotherapy agents has increased because of the growing number of cancer survivors who are exposed to repeated courses of sensitizing agents and using an

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alternative chemotherapy regimen is often limited by tumor sensitivity.

Desensitization offers an effective way to keep the treatment in patients who have presented HSRs.[6] This methodology has emerged as a powerful tool for safely reintroducing medications that are beneficial for the management of patients with HSRs. Several desensitization protocols have been successfully implemented in order to re-administer the same platinum agent by gradual re-introduction of small amounts of drug up to get full therapeutic doses; patients receive their target dose of medication in divided incremental steps.[4–6] Despite desensitization, supposing there is a high risk by reintroducing a potentially lethal medication into an allergic patient, still the demand for such procedures has increased in order to continue treatment with the preferred therapeutic agent instead of using alternative drugs that might be poorly tolerated, more expensive, or less effective compared with the preferred one. Carboplatin desensitization protocols have proved to be safe and effective.[5,7]

Gradual administration of suboptimal doses of antigen requires continuous or fixed intervals.[8] Castell et al.[5] proposed a carboplatin desensitization protocol based on three solutions that are delivered in 12 consecutive steps with increasing infusion rates (Table 1). First solution is a 100-fold dilution of the final target concentration (steps 1–4), second solution is a 10-fold dilution of the final target concentration (steps 5–8), and the concentration of the last solution is calculated by subtracting the cumulative dose administered in steps 1–8 from the total target dose (steps 9–12). Total administration time lasts 6 h.

Table 1. Standard desensitization protocol using a total dose of 500 mg.

Step	Solutiona	Rate (mL/h)	Time (min)	Administered dose (mg)	Cumulative dose infused (mg)
1	A	2	15	0.010	0.010
2	A	5	15	0.025	0.035
3	A	10	15	0.050	0.085
4	A	20	15	0.100	0.185
5	B	5	15	0.250	0.435
6	B	10	15	0.500	0.935
7	B	20	15	1.000	1.935
8	B	40	15	2.000	3.935
9	C	10	15	5.000	8.935
10	C	20	15	10.000	18.935
11	C	40	15	20.000	38.935
12	C	75	184.4	461.065	500
			Total time 5.82h		Total dose infused = 500mg

[a]Solution A: 5 mg/250 mL (0.02 mg/mL). Solution B: 50 mg/250 mL (0.2 mg/mL). Solution C: 500 mg/250 mL (2 mg/mL)

These solutions are prepared in the chemotherapy centralized units of hospital pharmacies, so it is critical for hospital pharmacists to have data about their stability. There is controversy about the optimal conditions of carboplatin infusion solutions used in desensitization because there is a lack of data about the solutions stability when the drug concentration is reduced below 0.5 mg/mL.[9] First and second solutions are diluted below the minimum established concentration. The physico-chemical stability of carboplatin has been thoroughly studied and it is confirmed that stability is inversely related to concentration.[10] The lack of available stability data and the fact that the carboplatin administration in a patient with hypersensitivity can be severe and potentially life-threatening, contribute to distrust of the carboplatin desensitization protocols.

The aim of this study is to determine the stability of carboplatin solutions diluted to 0.2 mg/mL and 0.02 mg/mL (100-fold and 10-fold dilutions of the final target concentration and calculated for a total target dose of 500 mg of carboplatin) in 250 mL of 5% dextrose in polypropylene (PP) infusion bags stored 24 h at room temperature.

Materials and methods

We developed a specific high-performance liquid chromatography (HPLC) method in order to determine detected and quantify the presence of carboplatin in the different samples solutions studied.

The HPLC method of Carballar et al.[11] for carboplatin was adapted to our conditions. The HPLC system consisted of an Agilent 1200 system comprising a quaternary pump, an autosampler, a column compartment, and a diode array ultraviolet-visible (UV–vis) detector. The analytical column was a Zorbax eclipse XDB-C18 (150 mm×4.6 mm; 5 µm particle size). The mobile phase had a flow rate of 1 mL/min under isocratic conditions of water–methanol (98:2, v/v) and the injection volume was 50 µL. The UV detector was set at 230 nm. Under these conditions, the retention time for carboplatin was 5.2 min.

The method was validated following the ICH Q2 (R1) guidelines for stability studies.[12] Linearity, accuracy, and repeatability were evaluated. Suitability of the HPLC method was proven by analyzing forced degraded samples (HCl, NaOH, H_2O_2, and heat). Limit of detection (LOD) and limit of quantification (LOQ) were calculated.

Carboplatin infusion solutions of 0.02 and 0.2 mg/mL were prepared in biological safety cabinet class II-type B,

by injecting 0.5 mL and 5 mL respectively, from the carboplatin glass vial (Carboplatin 10 mg/mL 450 mg vial; Teva; lot 17H15KC; expiry date: 08/2019), into 250 mL of 5% dextrose PP prefilled infusion bags (5% dextrose solution 250 mL FreeFlex; Fresenius Kabi; lot. 14KI7311; expiry date: 08/2018). They were stored protected from light in UV light protection bags (Ultramedic; MIRAMED; Lot: 15085; expiry date: 02/2020) at room temperature over a period of 24 h. A solution of 0.5 mg/mL of carboplatin was used as standard reference, and it was prepared by injecting 12.5 mL from carboplatin glass vial into 250 mL of 5% dextrose PP prefilled infusion bags. For each concentration (0.02, 0.2, and 0.5 mg/mL) the infusion solutions were prepared in triplicate and a sample aliquot of 2 mL was taken immediately before each time point at $t = 0$ h, 3 h, 6 h, and 24 h analyzed by stability-indicating HPLC. Duplicate HPLC determinations were performed for all samples, resulting in a total of 18 assays at each time point (six sample aliquot per concentration). The sample aliquots were discarded after analysis in appropriate waste container.

Chemical stability was defined as retention of at least 95% of the initial concentration.

Test solutions without changes or precipitates were defined as physically stable. They were visually checked before quantitative analysis.

Qualitative analysis was performed using the diode array detector; the UV–vis absorption spectrum enables the identification of cytotoxic agents thanks to their characteristic UV spectra. The presence of carboplatin into the infusion solutions was evaluated by comparing the absorption spectrum obtained with the reference spectra at $t = 0$ h.

Results

The HPLC developed method was found to be suitable for the stability study of carboplatin. The method was robust. Forced degradation assays revealed peaks corresponding to the intact carboplatin and additional peaks of unknown degradation products (Figure 1), which were clearly resolved from the carboplatin peak. The correlation coefficient of the calibration curve was 0.9997 proving linearity. LOD was 0.0007 mg/mL and LOQ was 0.002 mg/mL.

For each solution the concentration at $t = 0$ h was considered 100% of initial carboplatin concentration.

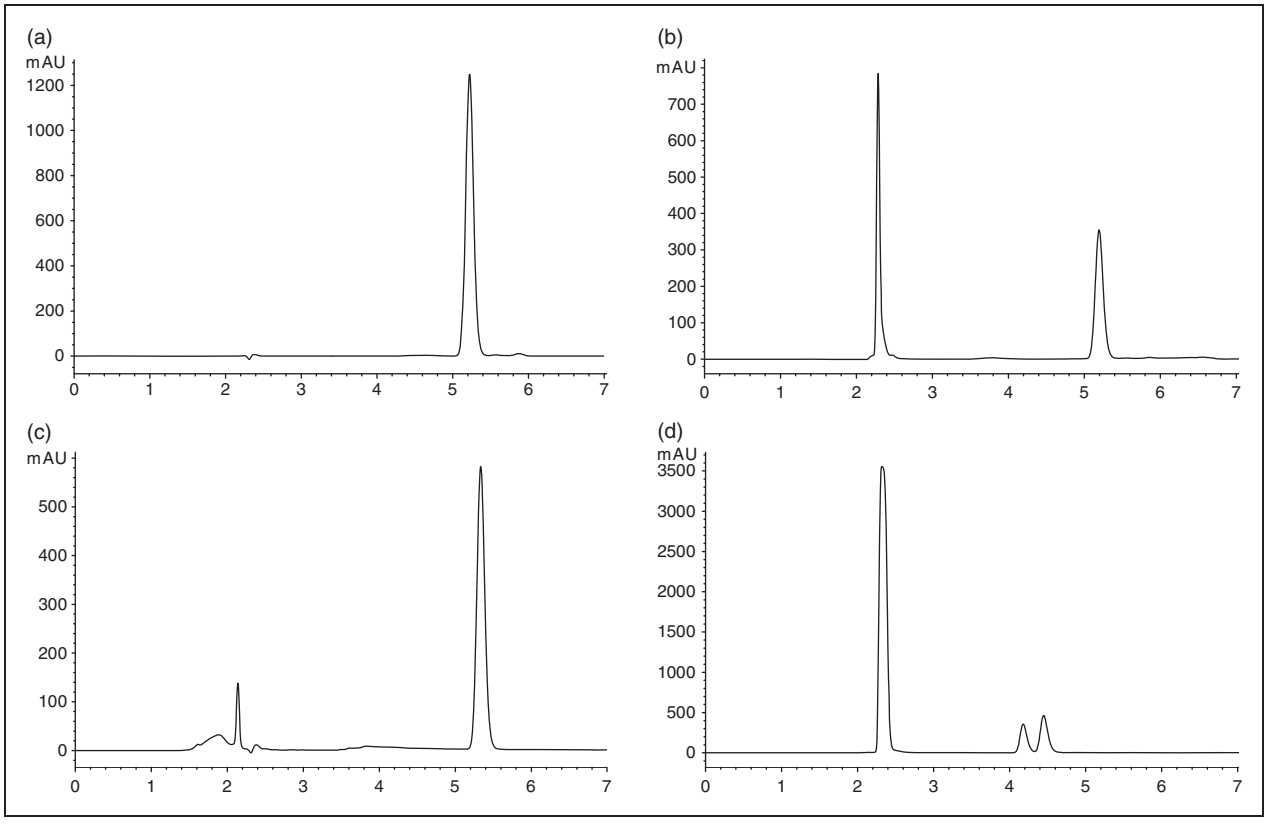

Figure 1. Forced degradation chromatograms of carboplatin for temperature (60 °C) (a), acid (HCl 0.1N) (b), basic (NaOH 0.1N) (c) and oxidative (H_2O_2 3%) (d) conditions.

Table 2. Stability of carboplatin desensitization solutions.

Samples	Time of storage	Remaining concentration (mean±SD %)
0.2 mg/mL	$T = 0$ h	100 ± 1.6
	$T = 3$ h	98.27 ± 0.2
	$T = 6$ h	97.3 ± 2.5
	$T = 24$ h	101.5 ± 0.9
0.02 mg/mL	$T = 0$ h	100 ± 11.5
	$T = 3$ h	106.7 ± 14.2
	$T = 6$ h	108.9 ± 21.8
	$T = 24$ h	154.9 ± 13.1

The percentages of the initial carboplatin concentration remained for each solution during the study are presented in Table 2.

Stability of carboplatin 0.2 mg/mL solution

The mean percentage of the initial concentration remaining was between 95% and 105% for all samples during the study time. No degradation product was detected (Figure 2). No macroscopic alterations were observed.

Stability of 0.02 mg/mL carboplatin solution

The mean percentage of the initial concentration remaining was > 105% after 3 h of storage at room temperature. During the storage time, the peak areas increased but no degradation products were detected (Figure 2). No macroscopic alteration was observed.

We detected changes in the retention time during the stability study for both concentrations studied, but this was not observed during the validation of the method.

UV–vis absorption studies

The absorption spectra of 0.02 mg/mL and 0.2 mg/mL solutions at $t = 0$ h was compared with the spectrum of 0.5 mg/mL carboplatin standard solution. The maximum absorption in the UV range is at 210 nm; carboplatin exhibits a strong band at 210 nm and a shoulder at 230 nm. The absorption spectra of 0.02 mg/mL and 0.2 mg/mL carboplatin solution for each time ($t = 3$ h, $t = 6$ h, and $t = 24$ h) were compared with the reference spectra at $t = 0$ h (Figure 2). The spectra analysis showed that carboplatin remained intact during the study in 0.2 mg/mL solution (Figure 3(a)); however it could not be guaranteed in 0.02 mg/mL solution (Figure 3(b)).

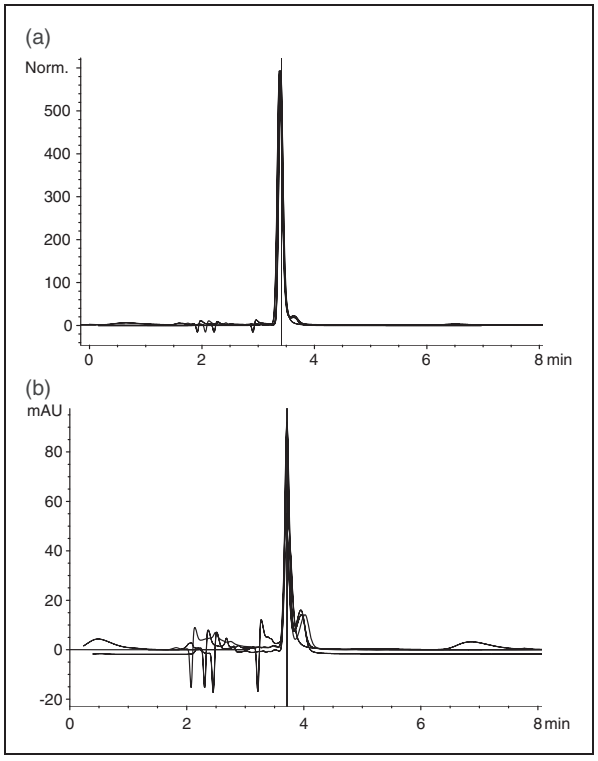

Figure 2. Overlaid chromatograms of 0.2 mg/mL (a) and 0.02 mg/mL (b) carboplatin solutions in 5% dextrose stored at room temperature at $t = 0$ h, $t = 3$ h, $t = 6$ h, and $t = 24$ h.

Discussion

Usually anticancer drugs are prepared in the centralized units in hospital pharmacies under strict aseptic techniques. The physico-chemical stability of the final product will depend on drug concentration, vehicles, and containers used in clinical situations.[13]

The stability of carboplatin has been extensively studied and 0.5 mg/mL carboplatin solution in 5% dextrose PP bags has proved to be stable for 21 days.[14] However, solution concentrations used in carboplatin desensitization protocols are below this stability limit. In this context, we have demonstrated that 0.2 mg/mL carboplatin solution in 5% dextrose PP bags is stable for at least 24 h at room temperature, filling an unmet need in real clinical situations and confirming that this solution is optimum for the desensitization protocol administration in patients. 24 h stability is usually enough in daily practice to allow the centralized units to optimize their workload. This stability recommendation assumes that aseptic techniques are fully validated and respected in practice. The use of this stability data can have a great impact on patient (reducing waiting time), pharmaceutical (workload facilitated), nursing staff (better availability of infusions), and also on the economic aspects.[13]

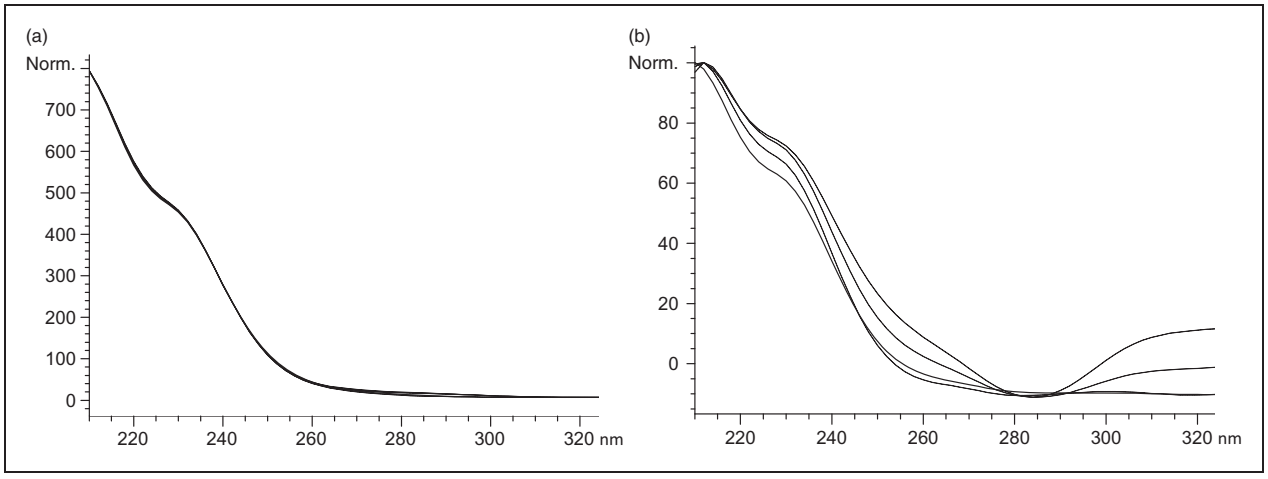

Figure 3. Overlaid normalized absorption spectra of 0.2 mg/mL (a) and 0.02 mg/mL (b) carboplatin solutions in 5% dextrose stored at room temperature at $t = 0$ h, $t = 3$ h, $t = 6$ h, and $t = 24$ h.

Stability could not be proved for 0.02 mg/mL carboplatin solution stored for more than 3 h at room temperature in 5% dextrose PP infusion bags. We observed an increase in the peak areas. Although the studied concentrations was above LOQ and the resolution of the peaks was satisfactory at the beginning of the study, changes in the retention time may lead to interferences between carboplatin peaks and the UV absorption of other peaks, which were also detected when we injected a sample of 5% dextrose alone. The impact of these interferences could be higher in the case of lowest carboplatin concentrations acting as a confusion factor. However, 0.02 mg/mL carboplatin solution exposes spectral changes indicating probable reactions of the drug. Therefore, the minimum concentration of carboplatin solution, which could guarantee stability, still must be elucidated.

Other approaches suggest to use protocols based on a multistep infusion of a single solution with a concentration of 1 mg/mL, ensuring stability. Although this protocol seems to be effective and safe, it has only been reported in very few patients and requires standardization.[15,16]

Stability problems related with carboplatin concentration

In aqueous solution, the decomposition of carboplatin is solely determined by its hydrolysis. Hydrolysis rate constant for carboplatin is highly dependent on the starting concentration of the drug in solution and it has been found that high concentrations in water prevent hydrolysis. Carboplatin exists in a monomer–dimer equilibrium; since self-association processes are inherently concentration dependent, carboplatin mainly exist as association complexes in concentrated aqueous solution, but, when the drug concentration is low the balance shifts in favor of the monomeric forms of these drugs.[17]

Changes in the retention time

The difficulty in reproducibility of retention times has been previously described by Schnurr et al.[18] and Cheung et al.[19] using different analytical methods. It seems to be related to changes in the alignment of the bonded-phase chains leading to interactions with carboplatin.[18] This phenomenon was observed also in the standard solution of 0.5 mg/mL, consequently it does not seem to be related to any stability problems.

Conclusions

Carboplatin solution of 0.2 mg/mL can be considered stable for 24 h at room temperature in 5% dextrose PP infusion bags. These results allow carboplatin desensitization solutions with concentrations above 0.2 mg/mL to be prepared in advance for better organization in the cytotoxic centralized units.

On the other hand, it cannot be proven that 0.02 mg/mL of carboplatin solution is stable for at least 3 h in the same conditions. Consequently, according to our study, 0.02 mg/mL carboplatin solutions should be extemporaneously diluted.

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Declaration of conflicting interests

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