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Study objectives: To determine the extended chemical and physical stability of cisplatin infusions in PVC containers at normal in-use concentrations in saline, with and without added electrolyte combinations relevant to clinical practice.
Methods: Cisplatin infusions 0.1–0.4 mg/mL were prepared in normal saline, with and without magnesium sulphate and potassium chloride supplements in 500 mL PVC bags, and stored at 25°C protected from light. Chemical stability was assessed by a stability-indicating LC method. Evidence for precipitation was detected by a light-blocking particle count method for sub-visible particles, supported by visual examination. pH and weight changes were also monitored for at least 28 days.
Results: Both 0.1 mg/mL and 0.4 mg/mL infusions, with or without the added electrolyte supplements, were chemically stable over 28 days at 25°C. The pH of infusions varied by no more than 0.2 units over this time, there was no visible precipitation, and no significant changes in sub-visual particulate levels or infusion weight. The study was restricted to 28 days because small, visual precipitation was evident in some infusions after 35 days.
Conclusion: Cisplatin infusions at concentrations ranging from 0.1–0.4 mg/mL, in 500 mL PVC bags containing either 0.9% sodium chloride or 0.9% sodium chloride + 20 mmoL KCl + 8 mmoL $MgSO_4$ were physically and chemically stable for up to 28 days at 25°C, when protected from light. Extending shelf lives beyond this period is unsafe due to the potential development of precipitates.

Keywords: Chemical and physical stability, cisplatin, saline infusions, shelf life

Introduction

Cisplatin is an oncology agent used in a number of indications, either alone or in combination chemotherapy. It is administered as an IV infusion after reconstitution and dilution in 0.9% sodium chloride. It is a poorly soluble compound, maximum solubility in aqueous solution being approximately 1 mg/mL [1]. Chemical stability is adversely affected by the diluent, pH and light. Cisplatin is unstable in aqueous solution unless chloride ions are present in sufficient concentration (not less than ca. 0.2% w/v [2]). The optimum pH for stability is within the range 3.5–5.5 [3]. Cisplatin is also relatively sensitive to light [4].

Cisplatin must be diluted in saline infusion. Because of the risk of precipitation, storage at ambient temperature, even for extended periods, is recommended. Most studies confirm that cisplatin is chemically stable when diluted in saline in PVC infusions containers stored around ambient temperature over the concentration range of 0.6–1 mg/mL for at least 14 days [5]. Since this evidence suggests that cisplatin may be chemically stable for longer periods than previously investigated, the present study was performed to investigate the stability of cisplatin for extended periods in PVC infusion containers, determining chemical degradation and precipitation over extended periods, in order to provide evidence to support longer shelf lives.

The purpose of this study was to determine the extended chemical and physical stability of cisplatin infusions in PVC containers at normal in-use concentrations in saline, with and without electrolyte additive combinations of relevance to standard clinical practice.

Material and methods

Materials

Cisplatin 1 mg/mL, 100 mL vials, B.No. 06C27QA, were provided by Teva Ltd (Leeds, UK). Sodium chloride 0.9% in 500 mL PVC bags, B.No. 07B12H, was obtained from MacoPharma Ltd (Twickenham, Middlesex, UK), magnesium sulphate 50% injection, B.No.701103, from Torbay Hospital (Torquay, Devon, UK) and potassium chloride 15% injection, B.No. 0700-460-0101210, from B Braun Ltd (Thorncliffe Park, Sheffield, UK).

Preparation of infusions: All cisplatin infusions were prepared under EU Class A conditions, in accordance with the principles of Good Pharmaceutical Manufacturing Practice. Doses of cisplatin range between 50–120 mg/m^2, and although manufacturers recommend dilution of this dose in 2 L 0.9% sodium chloride, in practice volumes of less than 2 L are normally used. In view of the hydration regimens used with cisplatin, electrolyte supplements of potassium chloride (up to 20 mmoL) and magnesium sulphate (up to 8 mmoL) may be added to infusions. Refrigeration of cisplatin infusions is not recommended. The study was therefore designed to be inclusive of the range of cisplatin concentrations likely to be required, with and without maximal amounts of electrolyte supplements, and was conducted at room temperature (25°C).

The following infusions were prepared under EU Class A conditions, in accordance with the principles of Good Pharmaceutical Manufacturing Practice:

a. Cisplatin 0.1 mg/mL in 500 mL 0.9% sodium chloride, in 500 mL PVC bag
b. Cisplatin 0.4 mg/mL in 500 mL 0.9% sodium chloride, in 500 mL PVC bag
c. Cisplatin 0.1 mg/mL + 20 mmoL KCl + 8 mmoL $MgSO_4$ in 500 mL 0.9% sodium chloride, in 500 mL PVC bag
d. Cisplatin 0.4 mg/mL + 20 mmoL KCl + 8 mmoL $MgSO_4$ in 500 mL 0.9% sodium chloride, in 500 mL PVC bag

Duplicates of each of the above infusions were stored, well protected from light in double-layer blue polythene overwraps, at 25 + 1°C (room temperature).

LC analysis for cisplatin

Cisplatin content was determined at zero time and after 7, 14 and 28 days, using a fully validated stability-indicating LC assay. The modular HPLC system comprised PU-2089 Plus quaternary pump, AS-2057 autosampler, CO-2060 Plus column thermostat, MD-2010 Plus multiwavelength UV detector, LC-NetII/ADC interface linked to Dell PC running ChromPass version 1.7 software. All supplied by Jasco UK, Dunmow, UK. Waters Spherisorb® S5CN column, 5 µm particle size, 250 x 4.6 mm (HiChrom, Reading, UK) was used at ambient temperature, with a HiChrom guard column containing a CN 5 µm cartridge. Separation was achieved under isocratic conditions using a mobile phase of 0.005 M phosphate buffer, pH 6.5 at a flow-rate of 1 mL/min^{-1} with UV detection at 204 nm. Sample volume injected was 20 µL.

Method validation

Intra- and inter-day precision was determined for the analytical method (2-step dilutions to within the concentration range 5–100 ug/mL cisplatin) and analysis using LC for cisplatin by preparing five different dilutions of three different concentrations on either the same day (intra-day) or on consecutive days (inter-day). The intra-day RSD was between 1.35% (5 ug/mL) and 0.32% (35 ug/mL) and the inter-day RSD was 2.01% and 1.04% respectively. The accuracy of the assay was determined for cisplatin at cisplatin concentrations of 5, 15 and 35 ug/mL. Recovery ranged between 100.07% and 100.51%.

Linearity of analytical response

Calibration plots of peak area versus concentration were produced for cisplatin over the concentration range 0.5–100 µg/mL, n = 8. The plots were linear over the concentration range with least-squares regression analysis giving a slope of 3.42 and intercept of –2.53. The correlation coefficient indicated good linear dynamic range ($R^2 \geq 0.999$).

Limit of detection (LOD) and limit of quantification (LOQ)

LOD was defined as the analyte concentration giving a signal to noise ratio of 3:1. For cisplatin this was 0.62 µg/mL. The LOQ was defined as the analyte concentration giving a signal to noise ratio of 10:1. For cisplatin this concentration was 2.06 µg/mL. Clearly, the LOD and LOQ values are of little significance for infusion stability studies and routine QC assays, since relatively large drug concentrations are available. Dilution to within the concentration range identified in the calibration plot for each drug is required.

Forced degradation studies

The degradation of platinum II drugs is mainly effected by acid or base catalysed nucleophilic substitution or aquation reactions. These mechanisms were exploited in forced degradation studies to demonstrate the stability-indicating attributes of the LC assay.

Individual solutions (1 mL) of cisplatin (1 mg/mL) were subjected to stress treatment by incubating at 50°C with 1 mL of, a) water for four hours; b) 0.1 M hydrochloric acid for two hours; c) 0.1 M sodium hydroxide for two hours. Controls were prepared by incubating the individual drug solutions with water at 5°C. After incubation, the solutions were allowed to equilibrate to room temperature and were adjusted to volume with water. The solutions were then diluted to give a nominal drug concentration of 20 µg/mL and analysed in duplicate by the LC assay. Analyte peak areas from stressed samples were compared with controls, and analyte peak purity was assessed by the photodiode-array detector.

The amount of cisplatin remaining after forced degradation depended on the conditions. Heating alone had little effect on drug degradation, with less than 5% loss after four hours at 50°C, but heating in the presence of base resulted in greater than 90% degradation. Treatment of cisplatin with hydrochloric acid was not expected to exert an effect since this would provide an excess of chloride ions in solution which would stabilise cisplatin. In each case, the peak purity of the remaining analyte peak, determined by the photodiode-array detector, was > 95%, indicating that there was no interference of the analyte peak by degradation products. This was not surprising since the two main degradation products, mono- and di-aqua platinum species [6] are ionised and would be expected to elute at the solvent front.

Visual inspection: At all above sample times, against dark and white backgrounds.

Infusion pH: At all above sample times, measured with glass electrode, calibrated with standard buffer solutions. The infusion pH was measured using a Hanna Instruments pH 302 pH meter and glass electrode, calibrated at pH 4.0 and 7.0.

Weight change: At all above sample times, recorded using 4-figure analytical balance.

Sub-visual particulates: Measured at sample times 0, and 28 days (25°C), using light-blocking counting system, in accordance with the method described in the *British Pharmacopoeia*, 2006, for particles ≥ 10 µm and ≥ 25 µm/mL.

Results

The physical and chemical stability of cisplatin is summarised in Table 1. Both 0.1 mg/mL and 0.4 mg/mL infusions, with or without the added electrolyte supplements, were chemically stable over 28 days at 25°C, with the cisplatin concentration remaining within acceptance limits of 95–105% of the initial concentration. The pH of infusions varied by no more than 0.2 units over this time, there was no visible precipitation, and no significant changes in sub-visual particulate levels or infusion weight. The study was restricted to 28 days because small, visual precipitation was evident in the infusions (b) and (c) after 35 days. Attempts to identify this precipitate using an array of sophisticated analytical methods were inconclusive.

Table 1: Physical and chemical stability data for cisplatin (Teva) infusions

Time (days)	pH[a]	Weight change %	Subvisual particles/mL[a]		Visual appearance	% Concentration cisplatin remaining[a]
			≥ 10 µM	≥ 25 µM		
0.1 mg/mL in 0.9% sodium chloride in 500 mL						
0	4.2	–	29.2	0.6	Pass	100% = 0.097 mg/mL
7	4.3	< 0.2	–	–	Pass	103.3
14	4.3	< 0.2	–	–	Pass	102.0
28	4.4	< 0.2	37.3	0.8	Pass	103.7
0.4 mg/mL in 0.9% sodium chloride in 500 mL						
0	3.8	–	37.4	0.5	Pass	100% = 0.398 mg/mL
7	3.8	< 0.2	–	–	Pass	104.9
14	3.7	< 0.2	–	–	Pass	103.4
28	3.8	< 0.2	43.3	0.6	Pass	100.4
0.1 mg/mL in 0.9% sodium chloride + 20 mmoL KCl + 8 mmoL MgSO4 in 500 mL						
0	4.4	–	28.1	0.3	Pass	100% = 0.098 mg/mL
7	4.3	< 0.2	–	–	Pass	102.4
14	4.4	< 0.2	–	–	Pass	102.4
28	4.5	< 0.2	37.5	0.9	Pass	103.9
0.4 mg/mL in 0.9% sodium chloride + 20 mmoL KCL + 8 mmoL MgSO4 in 500 mL						
0	3.9	–	38.3	0.2	Pass	100% = 0.385 mg/mL
7	3.8	< 0.2	–	–	Pass	101.1
14	3.8	< 0.2	–	–	Pass	103.6
28	3.9	< 0.2	36.3	0.9	Pass	103.6

[a] Mean of duplicate determination

Discussion

Theuer et al. [7] reported that cisplatin infusions at a concentration of 0.5 mg/mL were stable for 27 days at room temperature, and Rochard et al. [8] provided evidence of stability over a similar period in ambulatory pump reservoirs. The current investigation provides further evidence of the extended stability of cisplatin within the concentration range of 0.1–0.4 mg/mL, provided infusions are stored around 25°C. The addition of potassium and magnesium salts does not influence chemical or physical stability. This study also examined infusions for the appearance of precipitates. Results showed that this was manifested by the appearance by visual examination of small particles. In fact, continuation of the study beyond 28 days was precluded by the appearance of small particles, at least in some infusions. This observation would suggest that the maximum safe shelf life for cisplatin infusions is around 28 days, at least where the concentration does not exceed 0.4 mg/mL.

Conclusion

Cisplatin (Teva) infusions at concentrations ranging from 0.1–0.4 mg/mL, in 500 mL PVC bags containing either 0.9% sodium chloride or 0.9% sodium chloride + 20 mmoL KCl + 8 mmoL $MgSO_4$ were physically and chemically stable for up to 28 days at 25°C, when protected from light. Extending shelf lives beyond this period is unsafe due to the potential development of precipitates. As with all aseptically-prepared infusions, and particularly those with extended shelf lives stored at room temperature, aseptic units preparing these infusions must be fully validated to ensure the absence of microbiological contamination. It is also recommended that cisplatin infusions are carefully inspected to ensure the absence of visible particulates immediately before infusion.

Disclosure of financial interest

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