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A sequential temperature cycling study for the investigation of carboplatin infusion stability to facilitate dose-banding

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A sequential temperature cycling study for the investigation of carboplatin infusion stability to facilitate 'dose-banding'

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Study objective. To determine the physical and chemical stability of carboplatin infusion for dose-banding, with cycling between refrigerated storage and room temperature in-use conditions.

Design. A sequential study design was selected to closely simulate the temperatures and conditions experienced by drug infusions in pharmaceutical storage and in clinical use. Carboplatin infusions, 0.70 and 2.15 mg/mL, were stored refrigerated for up to 84 days, followed by incubation at 25°C for 24 h. The infusions were also returned to refrigerated storage for 3 and 7 days, to replicate a situation in which returned, unused infusions are kept for re-issuing. On pre-determined time-points, infusion chemical and physical stability were determined by HLPC, sub-visual particulate counts, pH-measurement, and weighing of infusions.

Results. Light protected carboplatin infusions at both study concentrations were chemically and physically stable following refrigerated storage for 84 days, followed by a further 24 h under 'in-use' conditions at 25°C. Additionally, the infusions were stable following return to refrigerated storage again for at least 7 days.

Conclusion. This study has demonstrated extended stability of carboplatin infusions which enables batch-scale preparation of standard infusions for dose-banding schemes. ***J Oncol Pharm Practice (2007) 13: 119–126.***

Key words: carboplatin; dose-banding; sequential temperature; stability

INTRODUCTION AND AIM

The antineoplastic agent carboplatin, *cis*-Diammine(cyclobutane-1,1-dicarboxylato)platinum, is a second-generation platinum II compound and a structural analogue of cisplatin.[1,2] Carboplatin is indicated in the treatment of ovarian carcinoma of epithelial origin and small cell lung carcinoma, and has been used as an alternative to cisplatin in other solid tumours.[2,3] Carboplatin may be used both as a single agent and in combination with other chemotherapy drugs, for example paclitaxel or gemcitabine.[4–7] The main difference between cisplatin and carboplatin is the lower toxicity profile of carboplatin, which has reduced levels of non-hematological toxicities, such as nephrotoxicity, ototoxicity, peripheral neurotoxocity, and emesis.[2] The dose-limiting toxicity of carboplatin is myelosuppression, with thrombocytopenia being more pronounced than leukopenia.[8–12]

Carboplatin is administered intravenously over 15 min to 1 h, in the UK with a recommended dose of 400 mg/m^2 for previously untreated adults with normal renal function.[2] Dose reductions of 20–25% are recommended for patients who have previously been treated with myelosuppressive therapy or who have a poor performance status, while dose reductions in renal impairment may be based on the patient's creatinine clearance.[2,3] Alternatively,

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carboplatin dosage may be determined with the Calvert formula, using the glomerular filtration rate (GFR) and area under the plasma concentration - time curve (AUC):

$$\text{Dose(mg)} = \text{target AUC (mg/mL} \times \text{min)} \times [\text{GFR(mL/min)} + 25].^{10}$$

The recommended target AUCs in the Calvert formula are 5 mg/mL/min in previously treated patients and 7 mg/mL/min in those who have not previously received chemotherapy.[2,10] Subsequent doses are adjusted according to white cell and platelet count nadirs.[2] Dosing in accordance with the Calvert formula is generally preferred over body-surface area-based dose calculations.

Carboplatin is presented as a 10 mg/mL solution in water for injection, which is diluted in 5% glucose (500 mL) immediately before administration.[3,10,13] The drug may also be diluted in 0.9% sodium chloride,[3] however, nucleophilic attack by chloride ions can convert part of the carboplatin to chloride-substituted derivatives, including cisplatin.[14] The mono- and di-chloride platinum species can then react with water to produce active (and toxic) aquated platinum adducts.[14-16]

To avoid disadvantages associated with patient specific chemotherapy doses, including drug wastage and long treatment delays for out-patients while chemotherapy is prepared, the batch-preparation of pre-made syringes or infusions using a system called 'dose-banding' has been proposed.[17] In dose-banding, individually calculated doses of intravenous cytotoxic drugs are placed within defined ranges (bands). A pre-determined standard dose for each band (usually the mid-point of the band) is administered using one or a combination of pre-filled syringes or infusions. For each drug, the dose-banding charts are constructed so that the maximum variation of the adjustment between the standard dose and the dose actually prescribed is 5% or less. Some of the advantages with dose-banding are reduced chemotherapy preparation costs, reduced delays in treating patients, and the possibility of end-product quality control testing for drug-assay and sterility.[17,18] In the UK, several drugs with doses based on body surface area are commonly provided in dose-banding schemes for outpatient chemotherapy treatment, including cyclophosphamide, methotrexate, doxorubicin, epirubicin, vincristine, 5-fluorouracil, and folinic acid.[17,19-21] However, a fundamental requirement for any drug to be dose-banded is long-term stability in infusion bags or syringes.[17] In the case of carboplatin, published stability studies limit the shelf-lives of carboplatin infusions to 21 days under refrigerated conditions.[22]

The objective of this study was to determine the stability of carboplatin intravenous infusion, using a sequential temperature protocol to reflect clinical usage conditions for dose-banding. Most stability studies on aseptically prepared infusions are based on a parallel temperature design where stability is independently assessed at refrigerated (2-8°C) and room (20-25°C) temperatures. In this case, a sequential study design was selected to closely simulate the temperatures and conditions experienced by drug infusions in pharmaceutical storage and in clinical use. This type of study design has been previously advocated for cytotoxic infusions to examine the effect of temperature cycling, because it avoids the theoretical predictions of cumulative changes in chemical and physical drug stability which would be necessary with a traditional parallel temperature study design.[23]

A dose-banding scheme for carboplatin with a limited range of standard infusions has previously been proposed.[24] Preparation of higher and lower standard doses of this scheme in 500 and 50 mL infusion bags, respectively, would give concentrations of 2.15 mg/mL for the highest dose (1075 mg) and 0.70 mg/mL for the lowest dose (35 mg). These concentrations were therefore selected for the purpose of this study. Both concentrations were prepared as 100 mL 5% glucose polyolefin bags, although a separate set of 500 mL 5% glucose PVC bags were also prepared at the higher concentration to assess whether volume or container material influenced stability. Carboplatin infusions were stored refrigerated for up to 84 days. At pre-determined time-points, infusion bags were removed for sampling and analysis, prior to further incubation at 25°C for 24 h. On two occasions, the infusions were also analyzed following 3 and 7 days refrigerated storage after incubation at 25°C. This cycle replicated the release of infusions to the ward or clinic and, after a maximum of 24 h at room temperature, being returned to pharmacy for a further 7 days refrigerated storage before re-issue to the ward or clinic.

Chemical stability was determined by high performance liquid chromatography (HPLC), using a fully validated stability-indicating method.[25] Physical stability was assessed using visual examination for precipitate and color change, sub-visual particulate counting, and pH measurement. Weight changes

were monitored to establish if any moisture transfer occurred through the walls of infusion bags.

MATERIALS AND METHODS

Drugs, infusions, and chemicals

Carboplatin 10 mg/mL concentrate for infusion, batch 04L30LA, expiry 12/2006, was obtained from Teva Hospitals, Leeds, UK. The pharmaceutical diluent was glucose 5% w/v in Freeflex 100 mL polyolefin bags, Fresenius Kabi, UK, and Macoflex 500 mL PVC bags, Maco Pharma, UK. All other chemicals and solvents were of HPLC grade, including potassium dihydrogen phosphate and di-sodium hydrogen phosphate (Fisher Scientific, UK). HPLC grade water was prepared from Water for Irrigation (distilled and deionized), Baxter Healthcare, UK, which was filtered though a 0.2 μm cellulose acetate filter (Sartorius, UK) prior to use.

A reference standard of carboplatin British pharmacopoeal chemical reference substance (BPCRS), batch 2332 with declared purity of 99.7%, was obtained from the British Pharmacopoeia Laboratory, Stanmore, UK.

Stability studies

The infusions, 0.70 and 2.15 mg/mL, were prepared as pooled solutions which were carefully mixed prior to redistribution into 100 mL bags, while the 500 mL infusions (2.15 mg/mL) were prepared individually. All infusions were prepared, sampled, and diluted in a Biomat AC Class II safety cabinet (MAT, UK) in accordance with the principle of good pharmaceutical manufacturing practice.[26] Following preparation and initial ($t = 0$) sampling, 18 infusion bags (100 mL) at each concentration and 3 additional 500 mL infusion bags were transferred to a temperature monitored laboratory refrigerator (LEC, UK) operated at 4 ± 1°C.

At intervals of x days (see below) three infusions at each concentration were removed for sampling and analysis prior to incubation in a temperature monitored incubator with fan (Gallenkamp, UK), as shown in the following scheme:

Storage 4°C	→	Incubation 25°C	→	Storage 4°C
x days		$a = 24$ h		$b = 3$ and $c = 7$ days
↓		↓		↓
Analysis		Analysis		Analysis

For 100 mL infusions: $\boldsymbol{x} = 0, 3, 7, 14, 28, 56,$ or 84 days, followed by $\boldsymbol{a}$ on days $x = 3, 7, 14, 28, 56,$ or 84 days and followed by $\boldsymbol{a}$, $\boldsymbol{b}$, and $\boldsymbol{c}$ on days $x = 28$ and 84.

For 500 mL infusions: $\boldsymbol{x} = 0$, 56, or 84 days, followed by $\boldsymbol{a}$, $\boldsymbol{b}$, and $\boldsymbol{c}$ on day $x = 84$.

ANALYSIS

Infusion pH was measured using a Hanna Instruments pH 302 pH-meter and glass electrode, calibrated at pH 4.0 and 7.0. Weight changes from $t = 0$ to $t = x$, and accumulative weight changes from $t = 0$ to $t = a$, $t = b$ and $t = c$ were determined for all infusion bags using a Sartorius BL 1500 balance (Sartorius, UK) and a GF-300 precision balance (Precision Weighing Balances, UK) connected with an RS 244-632 printer (RS, UK).

Infusion bags were visually examined for any change in infusion color and/or particulate contamination against both white and dark backgrounds under normal laboratory lighting. Samples for subvisual particle counts were withdrawn using 10 mL syringes (Beckton-Dickinson, UK) and transferred into 15 mL polypropylene tubes (Fisher Scientific, UK), which were left undisturbed for 2 h prior to analysis. Syringes and tubes were flushed three times with water for irrigation before use. Particle counts (10×1 mL for each infusion) were performed in accordance with the British Pharmacopoeia[27] procedure using an LS-200/Liquilaz AZ-E20 particle size analyzer with APSS-view software, version 3.4 (Particle Measuring Systems Europe, UK).

HPLC

The HPLC system comprised of a PU-2057 pump with vacuum degasser, an AS-2057 autosampler, a CO-2060 column oven, a MD-2010 UV diode array detector, and Chrompass version 1.7 software (Jasco, UK). A Waters Spherisorb® S5CN column, 5 μm particle size, 250×4.6 mm (HiCHROM, UK) was used at ambient temperature. Separation was achieved under isocratic conditions using a mobile phase of 0.005 M phosphate buffer, pH 6.5, with an injection volume of 20 μL, a flow-rate of 1 mL/min and UV detection at 200 nm. Carboplatin infusion was withdrawn from each bag, and using a previously calibrated automatic pipette, 0.5 mL was transferred to a 50 mL grade A volumetric flask and adjusted to volume with HPLC grade water. An external carboplatin standard solution (20 μg/mL) for a bracketing injection technique

was prepared from the carboplatin BPCRS reference standard.

HPLC method validation

An eight-point calibration plot of peak area versus concentration was prepared from duplicate injections over the concentration range 0.5–100 μg/mL. The plot was linear over the concentration range, with least-squares regression analysis giving the equation $y = 3.21x - 0.21$ ($R^2 \geq 0.999$).

The precision (relative standard deviation) of the HPLC system was determined as 0.67, 0.52, and 0.84%, respectively, for replicate injections ($n = 10$) of 5, 15, and 35 μg/mL carboplatin standard solutions. The intra-day precision of the method, as determined from replicate dilutions to concentrations of 5, 15, and 35 μg/mL, was 0.33, 0.40, and 0.23%, respectively. The corresponding values for the inter-day precision were 1.71, 1.71, and 1.18%, respectively. The accuracy of the HPLC assay was between 99 and 101% for the three concentrations.

Stability indication for the assay has previously been demonstrated and published with full validation data for this assay.[25]

Results and discussion

Chemical stability data for carboplatin 0.70 and 2.15 mg/mL infusions in 5% glucose are presented in Tables 1 and 2, while the physical stability data are shown in Tables 3 (pH-values), 4 (particle counts), and 5 (weight changes). The drug assay did not vary by more than ±4% for either concentration or infusion volume, and therefore remained within the normally accepted limits for cytotoxic drug infusions, of ±5% of the initial content.[28] Following 14 days at 4°C plus incubation at 25°C for 24 h, and after 28 days at 4°C and onwards, a minor degradation peak with a retention time concordant with that of cisplatin could be detected in some infusions. As hydrochloric acid is used by the manufacturer to adjust the pH of glucose infusion, it is possible that this actually was cisplatin formed by chloride ion nucleophilic attack of carboplatin. This theory can be supported by the fact that the degradation peaks did not increase with time, indicating that the reaction was limited by the additional chloride ions that were available for reaction.

Infusion pH-values varied slightly between measurements, but maximum deviations of 0.27 and 0.24 units from the initial values for the 0.70 and 2.15 mg/mL concentrations, respectively, were not considered significant. Firstly, the rate of hydrolysis of carboplatin appears similar between pH 4–7,[14] and secondly, the British Pharmacopoeia[27] permits a range of pH 3.5–6.5 for 5% glucose infusions, and the clinical influence of the observed pH fluctuations likely to be limited. The infusion solutions stayed clear with no visible particles, and

Table 1. Chemical stability of carboplatin (CAR): HPLC assay data for 100 mL infusions

Storage time = *x* days	CAR conc. (mg/mL)	CAR remaining after *x* days at 4°C [av. (SD)%]	CAR remaining after *x* days at 4°C + 24 h at 25°C [av. (SD)%]	CAR remaining after *x* days at 4°C + 24 h at 25°C + 3 days at 4°C [av. (SD)%]	CAR remaining after *x* days at 4°C + 24 h at 25°C + 7 days at 4°C [av. (SD)%]
0	0.70	0.673 mg/mL[a]	ND	ND	ND
	2.15	2.083 mg/mL[a]	ND	ND	ND
3	0.70	99 (1)	99 (0)	ND	ND
	2.15	101 (2)	100 (1)	ND	ND
7	0.70	100 (1)	99 (2)	ND	ND
	2.15	103 (2)	103 (1)	ND	ND
14	0.70	99 (2)	99 (1)	ND	ND
	2.15	101 (2)	103 (1)	ND	ND
28	0.70	101 (1)	101 (2)	102 (2)	100 (1)
	2.15	102 (2)	97 (1)	102 (2)	101 (2)
56	0.70	101 (2)	100 (1)	ND	ND
	2.15	103 (2)	102 (1)	ND	ND
84	0.70	102 (2)	102 (2)	102 (2)	102 (1)
	2.15	100 (1)	102 (0)	101 (1)	99 (1)

All values are averages (av.) from three infusion bags; HPLC = high performance liquid chromatography; SD = standard deviation; ND = not done. [a]*Initial concentrations for pooled infusion solutions prior to filling individual infusion bags.*

sub-visual particle counts also showed little change over the entire study period. The sub-visual particulate counts were expressed as counts per container for the 100 mL infusions and as counts per mL for 500 mL infusions, in accordance with British Pharmacopoeia requirements.[27] These remained well below the British Pharmacopoeial sub-visual particle limits of 6000 particles ≥10 μm and 600 particles ≥25 μm per container for the 100 mL infusions, and 25 particles ≥10 μm and 3 particles ≥25 μm per mL for the 500 mL infusions.[27] Additionally, changes in infusion bag weights did not exceeded 0.1% so carboplatin assay values were clearly not influenced by moisture transfer through the container wall.

The higher drug concentration in this article, 2.15 mg/mL, would have resulted from the highest dose in the dose-banding scheme being compounded in a 500 mL glucose infusion. However, for the purpose of this article and to contain costs, the infusion volume was scaled down to 100 mL. Therefore, to allow the comparison with the actual volume that would be used in clinical practice, the three 500 mL (2.15 mg/mL) infusions were prepared. The physical and chemical stability data for the 100 and 500 mL infusions were identical and the different plastic materials, PVC and polyolefin for the 500 and 100 mL bags, respectively, did not affect the physical or chemical stability of carboplatin infusion.

Table 2. Chemical stability of carboplatin (CAR): HPLC assay data for 500 mL infusions

Storage time = *x* days	CAR remaining after *x* days at 4°C [av. (SD)%]	CAR remaining after *x* days at 4°C + 24 h at 25°C [av. (SD)%]	CAR remaining after *x* days at 4°C + 24 h at 25°C + 3 days at 4°C [av. (SD)%]	CAR remaining after *x* days at 4°C + 24 h at 25°C + 7 days at 4°C [av. (SD)%]
0	2.13 (0.01) mg/mL[a]	ND	ND	ND
56	97 (1)	ND	ND	ND
84	96 (1)	99 (1)	96 (2)	98 (1)

All values are averages (av.) from three infusion bags; HPLC = high performance liquid chromatography; SD = standard deviation; ND = not done. [a]Initial mean concentration for infusions (n = 3).

Table 3. Carboplatin (CAR) infusion pH during storage

	x days at 4°C		*x* days at 4°C + 24 h at 25°C		*x* days at 4°C + 24 h at 25°C + 3 days at 4°C		*x* days at 4°C + 24 h at 25°C + 7 days at 4°C		
Storage time = *x* days	CAR conc. (mg/mL)	pH	Change from initial (%)	pH	Change from initial (%)	pH	Change from initial (%)	pH	Change from initial (%)
0 100 mL infusions	0.70	4.16	–	ND	–	ND	–	ND	–
	2.15	4.52	–	ND	–	ND	–	ND	–
3	0.70	4.25	2.2	4.43	6.5	ND	–	ND	–
	2.15	4.67	3.3	4.75	5.1	ND	–	ND	–
7	0.70	4.30	3.4	4.31	3.6	ND	–	ND	–
	2.15	4.61	2.0	4.60	1.8	ND	–	ND	–
14	0.70	4.33	4.1	4.25	2.2	ND	–	ND	–
	2.15	4.61	2.0	4.56	0.9	ND	–	ND	–
28	0.70	4.28	2.9	4.31	3.6	4.29	3.1	4.26	2.4
	2.15	4.59	1.5	4.59	1.5	4.59	1.5	4.54	0.4
56	0.70	4.19	0.7	4.18	0.5	ND	–	ND	–
	2.15	4.49	−0.7	4.45	−1.5	ND	–	ND	–
84	0.70	4.17	0.2	4.20	0.2	4.20	1.0	4.17	0.2
	2.15	4.47	−1.1	4.46	−1.3	4.39	−2.8	4.45	−1.5
0 500 mL infusions	2.15	4.48	–	ND	–	ND	–	ND	–
56		4.30	−4.0	ND	–	ND	–	ND	–
84		4.31	−3.8	4.31	−3.8	4.24	−5.4	4.28	−4.5

Average values from three infusion bags, except for x = 0, when the pH of the pooled initial solution was measured; ND, not done.

Table 4. Sub-visual particle counts for carboplatin infusions

	100 mL bags (particles/container)					
	0.7 mg/mL		2.15 mg/mL		500 mL bags, 2.15 mg/mL (particles/mL)	
Sample time	>10 μm	>25 μm	>10 μm	>25 μm	>10 μm	>25 μm
T0	30	0	10	0	3.7	0.1
3 d	140	10	40	24	ND	ND
3 d + 24 h[a]	87	14	40	7	ND	ND
7 d	24	7	30	27	ND	ND
7 d + 24 h	77	27	34	7	ND	ND
14 d	90	57	34	27	ND	ND
14 d + 24 h	77	60	67	20	ND	ND
28 d	14	4	34	4	ND	ND
28 d + 24 h	54	7	64	14	ND	ND
28 d + 24 h + 3 d[b]	44	14	44	0	ND	ND
28 d + 24 h + 7 d[c]	34	10	37	10	ND	ND
56 d	14	4	54	34	0.5	0.1
56 d + 24 h	27	10	30	7	ND	ND
84 d	64	30	24	14	1.0	0.1
84 d + 24 h	47	7	30	7	0.5	0.1
84 d + 24 h + 3 d	4	0	10	0	0.4	0.1
84 d + 24 h + 7 d	47	0	20	0	0.9	0.5

[a]Xd + 24 h = x days at 4°C + 24 h incubation at 25°C. [b]Xd + 24 h + 3 d = x days at 4°C + 24 h incubation at 25°C + 3 days at 4°C. [c]Xd + 24 h + 3 d = x days at 4°C + 24 h incubation at 25°C + 7 days at 4°C. ND, not done.

Table 5. Weight change of carboplatin (CAR) infusions over 84 days

Storage time = x days	CAR conc. (mg/mL)	Weight change after x days at 4°C (%)	Cumulative weight change after x days at 4°C + 24 h at 25°C (%)	Cumulative weight change after x days at 4°C + 24 h at 25°C + 3 days at 4°C (%)	Cumulative weight change after x days at 4°C + 24 h at 25°C + 7 days at 4°C (%)	
0	100 mL infusions	0.70	–	ND	ND	ND
		2.15	–	ND	ND	ND
3		0.70	<0.01	<−0.02	ND	ND
		2.15	<0.01	<−0.02	ND	ND
7		0.70	<0.02	<−0.01	ND	ND
		2.15	<−0.01	<−0.01	ND	ND
14		0.70	<−0.01	<−0.01	ND	ND
		2.15	<0.01	<−0.01	ND	ND
28		0.70	<0.01	<−0.02	<0.02	<0.06
		2.15	<−0.01	<−0.01	<0.04	<0.08
56		0.70	<−0.06	<−0.06	ND	ND
		2.15	<−0.04	<−0.04	ND	ND
84		0.70	<−0.06	<−0.06	<−0.05	<−0.02
		2.15	<−0.04	<−0.04	<−0.02	<0.04
0	500 mL infusions	2.15	–	ND	ND	ND
56			<−0.10	ND	ND	ND
84			<−0.05	<−0.06	<−0.05	<−0.05

Average values from three infusion bags; ND, not done.

Control of humidity was not considered appropriate for this article. This was justified by the fact that the applicable ICH guidelines[29] do not require humidity control for drug substances intended for refrigerated storage and that, in the hospital setting, the humidity of wards and clinics is not controlled.[29] That only minor weight changes of infusions occurred during storage (Table 5) suggests moisture

transfer across container walls was not an issue in this article. The application of extended shelf-lives to aseptically-prepared infusions is dependent upon the microbiological validation of the aseptic process and appropriate environmental and microbiological monitoring of the preparation unit.

In the UK, preparation of aseptic pharmaceuticals with a shelf-life exceeding 7 days is restricted to hospital and commercial units that carry a 'Specials' manufacturing licence issued by the Medicines and Healthcare Regulatory Agency.[30] This level of accreditation requires full compliance with the European guidelines on good pharmaceutical manufacturing,[26] which includes extensive validation of all production staff and procedures, together with rigorous quality assurance of the production environment. Preparation of carboplatin infusions in this type of facility is a pre-requisite for the application of the extended stability data described in this report and the assignment of expiration dates of up to 84 days. Furthermore, the re-issue of infusions returned unused from clinics would be dependent upon secure knowledge that infusions were stored appropriately. With the introduction of medicines management schemes in the UK, where pharmacy technicians monitor drug storage refrigerators in clinical areas either continuously with data-logging devices or by daily recording of temperatures, some institutions would feel comfortable with recycling returned stock. This would also require careful monitoring and management of transportation services between pharmacy and clinical areas and full recording of all infusion movements. Where such control cannot be enforced, only infusions which have been removed from refrigerators but have not physically left the pharmacy preparation area could be considered for re-issue.

CONCLUSION

This study has shown that 0.70–2.15 mg/mL carboplatin infusions in 5% w/v glucose have sufficient chemical and physical stability, when protected from light, to be stored refrigerated for 84 days, followed by a further 24 h under 'in-use' conditions at 25°C. The application of extended stability data of this type is dependent upon the preparation of infusions in rigorously controlled and accredited pharmacy aseptic units. This article has also shown that if the infusion was unused, it may be returned to refrigerated storage again for at least 7 days before use, providing that appropriate storage conditions can be assured. Infusion volume and the material from which containers were constructed (polyolefin or PVC) did not appear to influence infusion stability. Potentially, carboplatin could therefore be batch-manufactured for use in a dose-banding scheme.

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REFERENCES

1 Perry MC. *The Chemotherapy Source Book* 1996, second edition. Baltimore, Williams & Wilkins, 1996.

2 *Martindale: The Complete Drug Reference*, thirty fifth edition. Pharmaceutical Press, 2007.

3 *Carboplatin: Summary of Product Characteristics*. Mijdrecht, The Netherlands: Teva Pharma BV, 2003.

4 Schwartz GN, Pendyala L, Kindler H *et al.* The clinical development of paclitaxel and the paclitaxel/carboplatin combination. *Eur J Cancer* 1998; 34: 1543–48.

5 Soo RA, Lim HL, Wang LZ *et al.* Phase I trial of fixed dose-rate gemcitabine in combination with carboplatin in chemonaive advanced non-small-cell lung cancer: a Cancer Therapeutics Research Group study. *Cancer Chemother Pharmacol* 2003; 52: 153–58.

6 Obasaju CK, Johnson SW, Rogatko A *et al.* Evaluation of carboplatin pharmacokinetics in the absence and presence of paclitaxel. *Clin Cancer Res* 1996; 2: 549–52.

7 Siddiqui N, Boddy AV, Thomas HD *et al.* A clinical and pharmacokinetic study of the combination of carboplatin and paclitaxel for epithelial ovarian cancer. *Br J Cancer* 1997; 75: 287–94.

8 Martin M. Platinum compounds in the treatment of advanced breast cancer. *Clin Breast Cancer* 2001; 2: 190–208.

9 Perez EA, Hartmann LC. Paclitaxel and carboplatin for advanced breast cancer. *Semin Oncol* 1996; 23: 41–45.

10 Calvert AH, Newell DR, Gumbrell LA *et al.* Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol* 1989; 7: 1748–56.

11 Allsopp MA, Sewell GJ. A pharmacokinetic-pharmacodynamic study on carboplatin administered in prolonged continous infusion regimens with synchronous radiotherapy. *J Oncol Pharm Pract* 1995; 1: 25–32.

12 Lebwohl D, Canetta R. Clinical development of platinum complexes in cancer therapy: an historical perspective and an update. *Eur J Cancer* 1998; 34: 1522–34.

13 Polee MB. A phase I and pharmacokinetic study of weekly paclitaxel and carboplatin in patients with metastatic esophageal cancer. *Clin Cancer Res* 2004; 10: 1928–34.

14 Allsopp M, Sewell G, Rowland C, Riley C, Schowen R. The degradation of carboplatin in aqueous solutions containing chloride or other selected nucleophiles. *Int J Pharm* 1991; 69: 197–210.

15 Desoize B, Madoulet C. Particular aspects of platinum compounds used at present in cancer treatment. *Crit Rev Oncol Hematol* 2002; 42: 317–25.

16 Gust R, Schnurr B. Investigations on the stability of carboplatin infusion solutions. *Monatsh Chem* 1999; 130: 637–44.

17 Plumridge R, Sewell GJ. Dose-banding of cytotoxic drugs: a new concept in cancer chemotherapy. *Am J Health-Syst Pharm* 2001; 58: 1760–64.

18 Kaestner S, Sewell G. Pharmacoeconomic aspects of dose-banding. *Hospital Pharmacy Europe* 2006; 26: 33–34.

19 Baker JP, Jones SE. Rationalisation of chemotherapy services in the University Hospital Birmingham NHS Trust. *J Oncol Pharm Pract* 1998; 4: 10–14.

20 So J. Improving the lives of patients with cancer. *Pharm Manage* 2002; 18: 27–29.

21 MacLean F, MacIntyre J, McDade J, Moyes D. Dose banding of chemotherapy in the Edinburgh Cancer Centre. *Pharm J* 2003; 270: 691–93.

22 Allwood M, Stanley A, Wright P eds. *The Cytotoxics Handbook*, fourth edition. Radcliffe Medical Press, 2002: 276–81 and 286–90.

23 Sewell GJ, Rigby-Jones AE, Priston MJ. Stability of intravesical epirubicin infusion: a sequential temperature study. *J Clin Pharm Ther* 2003; 28: 349–53.

24 Kaestner S, Sewell G. Dose-banding of carboplatin: rationale and proposed banding scheme. *J Oncol Pharm Pract* 2007; 13: 109–17.

25 Kaestner SA. Studies on dose-banding of cancer chemotherapy. Thesis. University of Bath, 2007.

26 *Rules and Guidance for Pharmaceutical Manufacturers and Distributors* 2007 – the 'Orange Guide'. Pharmaceutical Press, 2007.

27 *British Pharmacopoeia*. The Stationery Office, 2006.

28 Sewell G, Allsopp M, Collinson M, Tyrrell C, Prentice A, Copplestone J. Stability studies on admixtures of 5-fluorouracil with carboplatin and 5-fluorouracil with heparin for administration in continuous infusion regimens. *J Clin Pharm Ther* 1994; 19: 127–33.

29 *Notes for Guidance on Stability Testing*: *Stability Testing of New Drug Substances and Products* 2003, CPMP/ICH/2736/99 European Medicines Evaluation Agency, London.

30 Sewell GJ. Drugs prescribed: licensing and registration. In Payne J, James J, Byard RW, Corey TS, Henderson C eds. *Encyclopaedia of Forensic and Legal Medicine* 2005. Elsevier, 2005: 239–42.