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Stability of vincristine (Teva) in original vials after re-use, and in dilute infusions in polyolefin bags and in polypropylene syringes

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Abstract

Study objectives: To establish the stability of vincristine (Teva) in original vials with re-piercing over 28 days, and the stability of dilute infusions in polyolefin containers and polypropylene syringes at drug concentrations/storage condition combinations of relevance to 'standard' pharmaceutical practice that meet UK Department of Health National Patient Safety Agency guidance.

Methods: Original vials of vincristine injection (5 mg/5 mL, Teva) were stored under different conditions and subjected to re-piercing at intervals over 28 days. Samples taken at each interval were subjected to a stability-indicating LC assay for vincristine.

In separate studies, the stability of vincristine infusions (50 mL) in polyolefin bags (0.01 and 0.05 mg/mL) and in polypropylene syringes (0.5 mg in 20 mL and 2 mg in 20 mL), was determined under refrigerated and room temperature conditions.

Results: Vincristine injection (5 mg/5 mL) in original vials was chemically stable (> 95% of initial concentration remaining) when stored at refrigerated or room temperature, with and without light protection, and subjected to six piercings of the vial over 28 days. The very dilute 0.01 mg/mL vincristine infusions in polyolefin containers exhibited unpredictable chemical stability, although no infusion fell below 90% of initial concentration remaining over 84 days. The 0.05 mg/mL infusion in polyolefin containers and the 0.5 mg/20 mL and 2 mg/20 mL infusions in polypropylene syringes were all physically and chemically stable over 84 days under both refrigerated and room temperature storage.

Conclusion: Vials of vincristine injection (Teva) which are subject to repeat piercing, may be stored for up to 28 days with no loss of chemical potency. Vincristine infusions (0.05 mg/mL in polyolefin bags and either 0.5 or 2.0 mg/mL in 20 mL in polypropylene syringes) were physically and chemically stable for up to 84 days. Infusions of 0.01 mg/mL in polyolefin bags exhibited unpredictable drug assay values and cannot be considered stable. Microbiological considerations were not part of this study and must be established by individual compounding units.

Keywords: infusion, stability, vial, vincristine

Introduction

The vinca alkaloid vincristine is approved for the treatment of acute lymphocytic leukaemia, malignant lymphomas, multiple myeloma and various solid tumours [1]. Until recently, vincristine was administered as a small-volume IV bolus injection. However, the unintentional administration of vincristine by the intrathecal route, commonly after pre-filled syringes of vincristine and methotrexate injection were transposed, has resulted in 58 documented fatalities worldwide [2].

These fatalities prompted the WHO [3] and the UK National Patient Safety Agency [4] to issue directives that vinca alkaloids must be administered as minibag infusions in volumes of 50 mL or more to prevent inadvertent intrathecal administration. The manufacturer's recommended shelf life for vincristine infusions over the range 0.01–0.1 mg/mL is limited to 48 hours at 2°C–8°C and 24 hours at 15°C–25°C [1]. It was the aim of this study to determine the extended stability of dilute vincristine infusions to establish whether advanced preparation by pharmacy Central Intravenous Administration Service (CIVA) units would be possible. Given the occasional need to give low doses of vincristine, a concentration range of 0.01–0.05 mg/mL was considered adequate in this study to provide, in 50 mL infusions, a dose range of 0.5–2.5 mg. This would comfortably include the normal upper dose limit of 2 mg. The UK directive recognised that for paediatric use, administration of the dose in lower volumes using syringes would be required. The recommended syringe volume of 20 mL was still sufficient to prevent unintentional intrathecal administration. This study therefore included pre-filled polypropylene syringes containing 0.5 mg and 2.0 mg vincristine in 20 mL volumes, contained in polypropylene syringes. In both cases (infusions and pre-filled syringes), the study was carried out under both refrigerated and room temperature conditions, with light protection, over a period of 84 days.

The information provided by the manufacturer on stability of vincristine injection in the vial refers only to the unopened vial [1]. Unless drug vials are to be discarded after the first use, it is important to establish the stability of vincristine injection in the manufacturer's vials after repeated withdrawal and extended storage. This would enable pharmacy CIVA units to significantly reduce drug wastage. Therefore, additional studies considered the chemical stability of vincristine injection in the manufacturer's vials after repeat piercing of the vial septum, and storage of up to 28 days. Storage conditions of the vials included both refrigerated and room temperatures, with and without light protection of the vials.

Materials and methods

Stability in manufacturer's vials

Test vials

Two vials of each lot and for each storage condition were pooled by transferring the content of one vial with a Chemo-Aide Dispensing pin with Clearlink (Baxter Number Z1MC3490, estimated needle size 4 mm). This provides sufficient sample for testing the six measuring points for chemical stability. All this was performed under EU Class A environmental conditions and in accordance with the principles of Good Pharmaceutical Manufacturing Practice.

a) Vincristine Teva batch 09J20KD 1 mg/mL
b) Vincristine Teva batch 10A26MB 1 mg/mL

Storage conditions and sample times

One unit of each of the above (a–b) was stored, protected from light, at both of the test temperatures; 2°C–8°C (refrigerated temperature) and 25°C (room temperature) and without light protection at 25°C (room temperature). Samples were taken for analysis at the sfollowing time points: 0 (initial), 1, 7, 14, 21 and 28 days.

Analytical methods

Vincristine assay: Samples were taken for assay at all above sample times, using fully validated stability-indicating LC assay. The assay was validated to include accuracy, precision, linearity of response, stress-degradation and stability-indication. An external standard technique with bracketing was used.

Chromatographic conditions: The system comprised a model K1001 Wellchrom HPLC-Pump with Solvent Organizer K-1500, a Degasser, a model K2700 diode array detector (all from Knauer, Berlin, Germany), a model SIL-10ADvp Autosampler (Shimadzu, Columbia, USA), a model Jetstream II column oven, and EuroChrom (version 3.05 P5) software (Knauer, Berlin, Germany). Mobile phase comprised 50% phosphate buffer (pH 6.5) containing 0.2% triethylamine: 50% acetonitrile. A Macherey Nagel MN CC125/4 Nucleodur C18 5µ column was used, with a flow rate of 1.0 mL/minute and detection wavelength of 230 nm. The acquisition run-time was 10.0 minutes for each injection. Samples were injected without dilution and 'bracketed' by an injection of a freshly opened vincristine standard (1 mg/mL).

HPLC method validation: Validation as described in the following section 'Stability of vincristine infusions and pre-filled syringes'.

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

Stability of vincristine infusions and pre-filled syringes

Infusion components

Vincristine injection, Teva, batch 08J17TC, expiry 10/2010
Sodium chloride 0.9% infusion, Maco Pharma, batch 08112G, expiry 09/2010
50 mL polyolefin Freeflex infusion bags, Fresenius Kabi, batch 13BIS092, expiry 09/2010
20 mL Luer-lok polypropylene syringes, Becton-Dickinson, batch 0812226, expiry 11/2013

Test infusions

Four infusions of each drug concentration/container combination were prepared under EU Class A environmental conditions and in accordance with the principles of Good Pharmaceutical Manufacturing Practice:

a) Vincristine 0.01 mg/mL in 0.9% sodium chloride (50 mL) in polyolefin bag
b) Vincristine 0.05 mg/mL in 0.9% sodium chloride (50 mL) in polyolefin bag
c) Vincristine 0.5 mg in 20 mL 0.9% sodium chloride in polypropylene syringe (0.025 mg/mL)
d) Vincristine 2 mg in 20 mL 0.9% sodium chloride in polypropylene syringe (0.1 mg/mL)

Storage conditions and sample times

Four units of each of the above (a–d) were stored, protected from light, at both of the test temperatures; 2°C–8°C (refrigerated

Table 1: Chemical stability of vincristine in manufacturer's vials after storage and repeat piercing of vial septum

Storage conditions	Time (days)	Vincristine (% of initial)	
		Vial (a)	Vial (b)
22°C, light protection	0	100.0 (1.03 mg/mL)	100.0 (1.07 mg/mL)
	1	99.7	99.4
	7	98.4	98.3
	14	100.4	98.4
	21	102.0	99.1
	28	100.3	99.4
22°C, no light protection	0	100.0 (1.04 mg/mL)	100.0 (1.05 mg/mL)
	1	100.9	100.6
	7	99.5	99.1
	14	98.3	100.8
	21	97.9	97.6
	28	97.5	98.7
2°C–8°C, no light protection	0	100.0 (1.03 mg/mL)	100.0 (1.05 mg/mL)
	1	100.8	98.2
	7	98.5	98.1
	14	99.4	100.1
	21	99.6	100.5
	28	98.4	98.3

Two vials (a and b) were sampled at each time interval for each storage condition
Vials were pierced at each sample time

Table 2a: Physical stability of vincristine infusions at 2°C–8°C

Concentration (mg/mL)	Container	Time (days)	pH	Visual appearance	Sub-visual particles /mL ≥ 10 µ	≥ 25 µ	Weight change %
0.01	Polyolefin bag	0	6.23	Pass	26.4	0.6	< 0.2
		7	6.05	Pass	-	-	< 0.2
		28	6.86	Pass	-	-	< 0.2
		56	6.14	Pass	-	-	< 0.2
		84	5.6	Pass	40.2	1.2	< 0.2
0.05	Polyolefin bag	0	5.51	Pass	16.3	0.7	< 0.2
		7	5.48	Pass	-	-	< 0.2
		28	6.56	Pass	-	-	< 0.2
		56	6.15	Pass	-	-	< 0.2
		84	5.59	Pass	34.1	1.0	< 0.2
0.025	Polypropylene syringe	0	4.44	Pass	26.8	0.2	< 0.2
		7	4.33	Pass	-	-	< 0.2
		28	5.25	Pass	-	-	< 0.2
		56	5.12	Pass	-	-	< 0.2
		84	5.06	Pass	48.2	0.8	< 0.2
0.1	Polypropylene syringe	0	4.50	Pass	9.7	0.2	< 0.2
		7	4.38	Pass	-	-	< 0.2
		28	4.96	Pass	-	-	< 0.2
		56	5.03	Pass	-	-	< 0.2
		84	4.83	Pass	17.5	0.7	< 0.2

All data are means of determinations on duplicate containers

temperature) and 25°C (room temperature). This provides sufficient sample for testing duplicate containers for chemical stability and duplicates for physical stability. Samples were taken for analysis at the following time points: 0 (initial), 7, 28, 56 and 84 days.

Analytical methods

Vincristine assay: Samples were taken for assay at all above sample times, using fully validated stability-indicating LC assay. The assay was validated to include accuracy, precision, linearity of response, stress-degradation and stability-indication. An external standard technique with bracketing was used.

Chromatographic conditions: The system comprised a model PU-2089 Plus pump, a model AS-2057 Plus auto-sampler with in-line degasser, a model CO-2060 Plus column oven, a model MD-2010 Plus diode array detector, and ChromPass (version 1.7403.1) software (all from Jasco Ltd, Essex, UK). Mobile phase comprised 50% phosphate buffer (pH 6.5) containing 0.2% triethylamine: 50% acetonitrile. A Luna 5µ C18(2) column, 250 x 4.6 mm was used, with a flow rate of 1.0 mL/minute and detection wavelength of 230 nm. The acquisition run-time was 12.5 minutes for each injection. Samples were injected following dilution to approximately 0.01 mg/mL in duplicate and 'bracketed' by an injection of a freshly-prepared vincristine standard (0.01 mg/mL).

HPLC method validation:
Linearity of response: Range 0.005–0.1 mg/mL, r = 0.998, intercept = not significant, (n = 6)
Intra-day precision: At 0.01 mg/mL, CV = 1.9%, n = 6
Inter-day precision: At 0.01 mg/mL, CV = 1.4%, n = 5 (consecutive days)
Stability-indication: The HPLC analytical method was validated to be stability-indicating by accelerated degradation studies. Vincristine sulphate eluted at about 8.6 minutes. Vincristine sulphate 0.05 mg/mL sample solution was exposed to each of the following treatments, at 60°C, for 30 minutes: 0.1 N sodium hydroxide, 0.1 N hydrochloric acid, 6vol hydrogen peroxide, and heating only. The vincristine peak decreased with respect to an untreated control sample and the formation of new peaks was observed at about 3.1, 5.9, and 11.2 minutes. There was no interference of the vincristine peak by degradation product peaks and peak purity of the vincristine peak was > 0.95 (by photodiode array detection) after all treatments. It was concluded that the assay was stability-indicating with respect to non-specific degradation of vincristine, and was suitable for this study.

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 at pH 4.0 and 7.0.

Weight change: Recorded at all above sample times using a 4-figure analytical balance (Sartorius Ltd).

Sub-visual particulates: Measured at sample times 0 and 84 days, using light-blocking counting system, in accordance with the method described in the *British Pharmacopoeia*, 2009, for particles ≥ 10 µm and 25 µm/mL. A LiQuilaz LS200 Particle Counter (Particle Measuring Technique GB Ltd, Malvern, UK) was used and average cumulative counts of 5 x 1 mL samples

Table 2b: Physical stability of vincristine infusions at 25°C

Concentration (mg/mL)	Container	Time (days)	pH	Visual appearance	Sub-visual particles/mL ≥ 10 µ	≥ 25 µ	Weight change %
0.01	Polyolefin bag	0	6.11	Pass	36.2	1.2	< 0.2
		7	5.94	Pass	-	-	< 0.2
		28	6.88	Pass	-	-	< 0.2
		56	6.37	Pass	-	-	< 0.2
		84	5.98	Pass	52.2	0.8	< 0.2
0.05	Polyolefin bag	0	5.49	Pass	17.4	0.8	< 0.2
		7	5.34	Pass	-	-	< 0.2
		28	6.47	Pass	-	-	< 0.2
		56	6.29	Pass	-	-	< 0.2
		84	5.98	Pass	43.8	0.6	< 0.2
0.025	Polypropylene syringe	0	4.42	Pass	8.4	0.2	< 0.2
		7	4.38	Pass	-	-	< 0.2
		28	5.10	Pass	-	-	< 0.2
		56	5.38	Pass	-	-	< 0.2
		84	5.51	Pass	25.6	0.6	< 0.2
0.1	Polypropylene syringe	0	4.50	Pass	15.8	0.7	< 0.2
		7	4.46	Pass	-	-	< 0.2
		28	4.99	Pass	-	-	< 0.2
		56	5.14	Pass	-	-	< 0.2
		84	5.32	Pass	23.5	0.6	< 0.2

All data are means of determinations on duplicate containers

Table 3: Chemical stability of vincristine infusions at 2°C–8°C and at 25°C

Concentration (mg/mL)	Container	Time (days)	2°C–8°C vincristine: % of initial[a]	25°C vincristine: % of initial[a]
0.01	Polyolefin bag	0	100 (0.012 mg/mL)	100.0 (0.0099 mg/mL)
		7	93.8	96.0
		28	95.1	97.0
		56	90.7	93.1
		84	98.9	98.6
0.05	Polyolefin bag	0	100 (0.046 mg/mL)	100.0 (0.045 mg/mL)
		7	98.1	100.4
		28	96.7	99.6
		56	97.5	99.1
		84	101.3	103.8
0.025	Polypropylene syringe	0	100 (0.0254 mg/mL)	100.0 (0.0269 mg/mL)
		7	99.9	97.5
		28	100.5	97.6
		56	98.7	96.2
		84	102.4	97.0
0.1	Polypropylene syringe	0	100 (0.093 mg/mL)	100.0 (0.092 mg/mL)
		7	104.0	102.1
		28	102.1	99.9
		56	104.9	103.1
		84	103.6	103.2

All data are means of determinations on duplicate containers

from duplicate infusions were recorded. The instrument was calibrated externally.

Data analysis

All measurements (drug assay, pH, weight change, sub-visual particulates) were determined in duplicate and the arithmetic mean reported.

Acceptance criteria

Stability of infusions at a given sampling point was confirmed if the following conditions were met:

Assay for vincristine: Within the range 95–105% of initial concentration.

pH: Within ± 1.0 pH unit of initial value

Visual appearance: Solution remains clear, colourless and free of visible particulates

Weight change: < 0.2% w/w variation from infusion weight at previous sample point

Sub-visual particulates: No significant change between samples measured at day 0 and at day 84.

Results

Chemical stability data for vincristine injection in the manufacturer's vials, under different storage conditions and after repeat piercing, are shown in Table 1.

Data for the physical stability of vincristine infusions at 2°C–8°C and 25°C are presented in Tables 2a and 2b, respectively. Data for the chemical stability of vincristine infusions at both storage temperatures are presented in Table 3.

Discussion

The data presented in Table 1 show that the stability of vincristine injection in the manufacturer's vials was demonstrated over 28 days and with six piercings of the vial septum. Stability was not influenced by the storage temperature (refrigerated or room temperature) or by the presence or absence of light protection.

Vincristine infusions at a concentration of 0.05 mg/mL in infusion bags, and at 0.025 mg/mL and 0.1 mg/mL in syringes were physically and chemically stable for up to 84 days, at both 2°C–8°C and 25°C, see Tables 2a, 2b and 3. All physical and chemical test data for these infusions were within the stated acceptance criteria. The acceptance criteria for pH change (± 1 unit)

was larger than that usually applied (± 0.5 unit) to reflect the low drug concentration and minimal buffer capacity of the test infusions. This is recognised in the wide pH range (3.5–5.5) permitted for the 1 mg/mL injection concentrate [1]. In such cases, small variations in dissolved CO_2 in the infusion can exert significant effects on pH values.

From Table 3 it can be seen that the assay value for vincristine 0.01 mg/mL in the polyolefin infusion bags stored at 2°C–8°C, was below the acceptance criteria (95–105% of initial concentration) on days 7 and 56, but the samples at day 28 were within limits. This may reflect limited adsorption of vincristine onto the surface of the bag and the fact that loss from the infusion was more significant (as % loss) at low drug concentrations. The vincristine assay of the 0.01 mg/mL infusion stored at room temperature also fell below the acceptance criteria on day 56, possibly for the same reason. Such fluctuations and generally lower assay values suggest that infusions with very low vincristine concentrations have a more limited shelf life and, where possible, should be avoided. If unpredictable sorption is responsible for these observations, this would be a characteristic of the vincristine molecule and not related to any particular formulation or brand of vincristine. Rigorous drug assay acceptance criteria of 95–105% of initial concentration were applied in this study. However all assay values in this study, even for the 0.01 mg/mL vincristine infusions, were above the lower limit of 90% of initial assay value advocated by other experts [5], and would have been considered acceptable by other researchers.

Although we recommend that the shelf life of the lowest concentration (0.01 mg/mL) infusion in polyolefin should be restricted to 28 days, the 84 day shelf life obtained for the 0.05 mg/mL infusions in polyolefin containers and for 0.025 mg/mL and 0.1 mg/mL infusions in polypropylene syringes comfortably exceed those of 21 and 7 days previously reported for dilute infusions of this drug in polypropylene [6] and PVC [7] containers, respectively. These new data support the advanced preparation of dilute vincristine infusions by pharmacy CIVA units and also permit the incorporation of vincristine infusion into dose-banding systems where extended expiry dates are required [8].

Conclusion

Manufacturer's vials opened and pierced six times with Chemo-Aide Dispensing pins were physically and chemically stable for a minimum of 28 days at room temperature (25°C) or under refrigerated storage at 2°C–8°C. Stability was not influenced by the storage temperature or by the presence or absence of light protection.

Vincristine sulphate infusions (Teva), 0.05 mg/mL, prepared in 50 mL polyolefin infusion bags containing 0.9% sodium chloride, were physically and chemically stable for 84 days at room temperature (25°C) or under refrigerated storage at 2°C–8°C when protected from light. Under similar conditions, the shelf life of vincristine infusions at the lower concentration of 0.01 mg/mL should be restricted to 28 days.

Vincristine infusions (Teva), diluted in 0.9% sodium chloride to concentrations of 0.025 mg/mL and 0.1 mg/mL in polypropylene syringes, were physically and chemically stable for 84 days, at either room temperature (25°C) or refrigerated at 2°C–8°C when protected from light.

As with all aseptically prepared medicines, it is the responsibility of the compounding unit to establish and validate aseptic procedures and to ensure the sterility and microbiological integrity of drug vials subjected to multiple piercing and of aseptically prepared infusions. Also, the maximum shelf life supported by this study should only be assigned where absolutely necessary.

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