International Journal of Pharmaceutics, 77 (1991) 279–285

IJP 02590

Stability and compatibility studies of vinblastine, vincristine, vindesine and vinorelbine with PVC infusion bags

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(Received 27 June 1991)
(Accepted 18 July 1991)

Key words: Stability; Compatibility; Vinca alkaloid; Intravenous infusion; PVC bag; Administration set; HPLC

Summary

A rapid isocratic technique was developed for the analysis of vinca alkaloids (vinblastine, vincristine, vindesine and vinorelbine) in parenteral solutions using high-performance liquid chromatography (HPLC) with UV detection and an Intersphere CN column. The availability and compatibility of drugs from solutions infused via plastic infusion bags through plastic administration sets have been examined. No significant drug loss was observed during simulated infusions ($n = 4$) for 2 h using PVC infusion bags and administration sets. No significant difference was found between infusion solutions (5% glucose or 0.9% NaCl). The stability of drugs was also studied in solution in PVC bags after storage at 4 °C with protection from light. The results show the stability of vinblastine, vincristine and vindesine during 7 days of storage to be satisfactory, irrespective of the infusion solution (5% glucose or 0.9% NaCl). In the case of vinorelbine, the stability of the drug was greater in 5% glucose (7 days) than in 0.9% NaCl (3 days).

Introduction

The vinca alkaloids (Fig. 1), vinblastine (**A**), vincristine (**B**), vindesine (**C**) and vinorelbine (**D**), are antitumor drugs widely used for the treatment of neoplastic diseases (leukemias, lymphomas) (Carlson and Sikic, 1983; Liso et al., 1990). Conventionally, the vinca alkaloids have been administered by intravenous bolus injections, however, because of their phase specificity, continuous infusion therapy has been studied (Weber et al., 1979; Bodey et al., 1980; Tannock et al., 1982). Hence, the therapeutic advantages of continuous infusion vs intermittent small-volume infusion or intravenous (i.v.) push have been suggested (Carlson and Sikic, 1983). Therefore, with the increasing use of continuous i.v. infusion and intermittent small-volume i.v. infusion modes of administration, it is imperative that the stability and compatibility of vinca alkaloids in administration vehicles and PVC containers be investigated. Consequently, when drugs are administered by continuous i.v. infusion with PVC

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material, knowledge of the rate of drug delivery to the patient is essential (D'Arcy, 1983).

Previous studies (Moorhatch and Chiou, 1974; Kowaluk et al., 1981; Illum and Bundgaard, 1982) have reported the loss of certain drugs from aqueous solutions stored in plastic infusion bags for various periods of time. Generally, these losses have been attributed to interaction (adsorption or absorption) between the drug and the plastic infusion bag, and in some cases, may diminish the therapeutic response due to reduced drug delivery to the patient. Documentation of the compatibility of vinca alkaloids (Benvenuto et al., 1981; Magnam and Martin, 1988) administered by plastic infusion bags and intravenous administration sets is limited.

The present study was undertaken with the following objectives: (i) to survey a range of drugs (vinca alkaloids), including those presently being administered by i.v. infusion, for possible interactions with plastic infusion bags; (ii) to study the behaviour of these drugs in simulated infusion using PVC containers and administration sets; (iii) to conform with the conditions of infusion

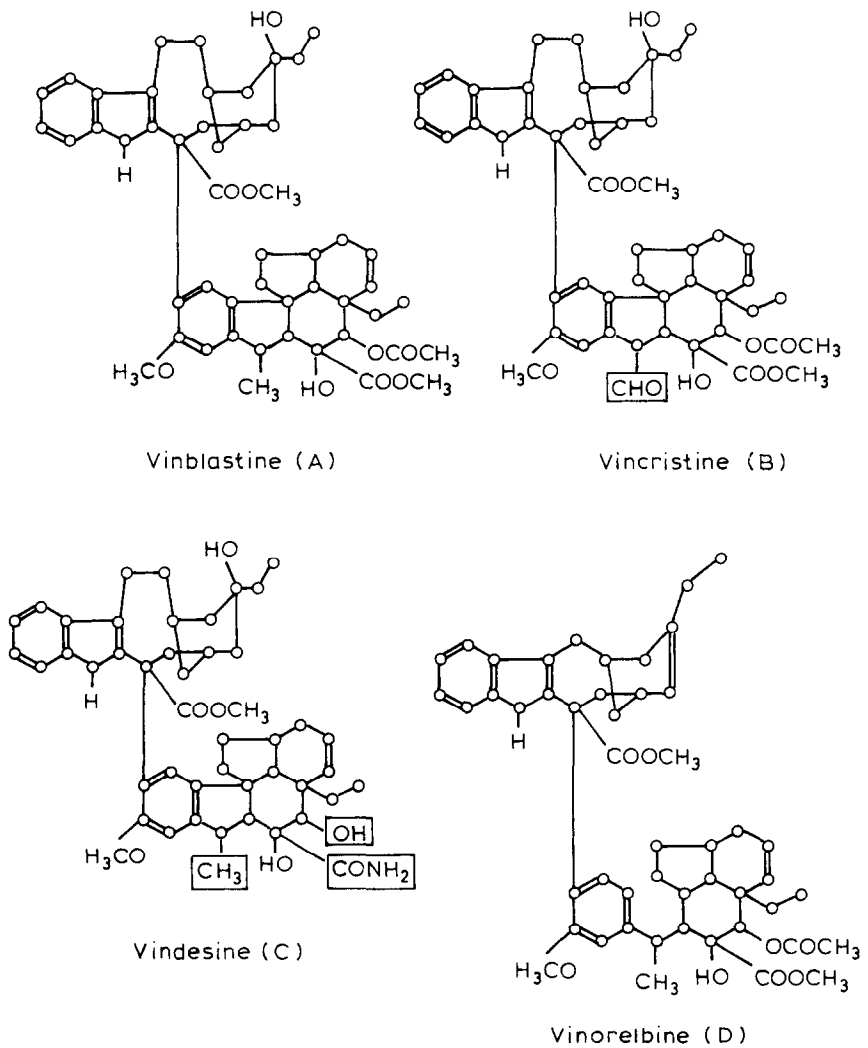

Fig. 1. Structures of vinblastine (**A**), vincristine (**B**), vindesine (**C**) and vinorelbine (**D**).

routinely used in hospitals (infusion flow rate, dose, volume, temperature and light); and (iv) to determine the differences in possible interactions between PVC containers and administration sets, as well as the differences in stability of the drugs in 0.9% NaCl and 5% glucose.

The high-performance liquid chromatography (HPLC) method used in the present study has previously been reported by De Smet et al. (1985) for the determination of vinca alkaloids (**A–C**) in biological fluids. Our method allowed the rapid determination not only of drugs **A–C**, but also of **D**, a new semisynthetic vinca alkaloid, in infusion solutions (5% glucose and 0.9% NaCl) using a suitable chromatographic column and mobile phase.

We have used this analytical technique to investigate the compatibility of the drugs with PVC containers and PVC infusion sets both during simulated infusions, and during storage at 4 °C in PVC bags used in a hospital pharmacy department where the reconstitution of cytostatics is centralized.

Experimental

Chemicals

A–C were obtained from Lilly France Laboratories (Saint-Cloud, France). Each drug was received in vials of sterile powder for injection: **A**, 10 mg vinblastine sulfate; **B**, 1 mg vincristine sulfate; **C**, 1 mg vindesine sulfate. **D** was obtained from Pierre Fabre Laboratories (Paris, France) in vials of 50 mg/5 ml water. Methanol (analytical grade), acetonitrile (HPLC grade) and NaH_2PO_4 (Rectapur) were obtained from Prolabo (Paris, France). Injectable preparation water (sterile and apyrogenic) obtained from Macopharma Laboratories (Tourcoing, France) was used for buffers, dilutions and standard solutions.

Chromatographic conditions and instrumentation

Chromatographic analysis was performed with an HP 1090 high performance liquid chromatograph (Hewlett Packard, Orsay, France), equipped with a variable-volume injector, an automatic sampling system and an HP 79994A UV diode array detector operating at 220 nm. The output from the detector was connected to a Hewlett Packard 9000 model integrator and the data recorded on an HP Thinkjet terminal printer.

Analyses were performed on a 5 μm CN Intersphere column (150 × 4.6 mm i.d.) (Interchim, Montluçon) operating at room temperature. During assay development, compounds were eluted isocratically with a mobile phase consisting of acetonitrile and phosphate buffer mixture (60 : 40, v/v) at a flow rate of 1.5 ml/min. The phosphate buffer was prepared in water with 0.1 N NaH_2PO_4 adjusted to pH 3 with 85% phosphoric acid.

For simulated infusions, we used a volumetric infusion pump (ref. VIP II) and plastic infusion sets (ref. Perfecran 781547) obtained from Becton Dickinson Laboratories, Division Vial Medical (Saint-Etienne de Saint-Geoirs, France) and Fandre Laboratories (Ludres, France), respectively. Macoflex® plastic infusion bags containing either 5% glucose or 0.9% NaCl in water (100 and 250 ml) were provided by Macopharma Laboratories (Tourcoing, France).

Preparation of standard solutions

To obtain standard stock solutions, **A–C** were reconstituted with distilled water while **D** was diluted with distilled water to give a drug concentration of 1 mg/ml in all four cases, followed by protection from light. Working solutions were prepared from the standard solutions of **A–D** by suitable dilutions with distilled water in polypropylene tubes. Calibration curves were constructed between 15 and 25 μg/ml for **A**, between 4 and 8 μg/ml for **B** and **C**, and between 6.25 and 25 μg/ml for **D**.

For quantification of drugs, an internal standard (I.S.) was employed. The peak ratio (drug peak area/I.S. peak area) was calculated and the amount of drug determined by reference to the calibration curve. The internal standard used to quantify **A** was **C**, while **A** was employed in the cases of **B–D**.

Simulated infusions

Infusion of **A–D** to patients was carried out under laboratory conditions simulating those routinely used in hospitals. For this purpose, we used

an infusion pump and plastic administration sets. The respective drug concentrations in solution were 10 mg/250 ml (40 μg/ml) for **A**, 2 mg/250 ml (8 μg/ml) for **B**, 4 mg/250 ml (16 μg/ml) for **C** and 50 mg/250 ml (200 μg/ml) for **D**. The simulated infusions were carried out over a period of 2 h at a flow rate of 2.08 ml/min.

Infusion solutions of drug were prepared in PVC infusion bags containing 250 ml of 5% glucose or 0.9% NaCl immediately before infusion. The bag containing drug was then attached to an administration set connected to the infusion pump that allowed the solution to flow through at a constant rate. At specified times of infusion, samples (1 ml) were withdrawn at regular intervals into the PVC bags, and at the same time, an aliquot of effluent (1 ml) was collected from the administration set. Samples were kept frozen in polypropylene tubes at −20 °C until analysis by HPLC.

All simulated infusions were carried out at least in duplicate (two infusions in 0.9% NaCl and two infusions in 5% glucose) at ambient temperature (20–24 °C) with protection from light.

Storage in infusion bags

Insofar as it was possible, we employed conditions in conformity with the drug concentrations normally used in hospital pharmacy departments for the storage of drugs in infusion bags. To infusion bags containing 100 ml of 0.9% NaCl or 5% glucose solution, a known amount of drug was added to achieve the following concentrations which are most often used in hospitals: **A**, 100 μg/ml; **B** and **C**, 20 μg/ml; **D**, 500 μg/ml in the bags.

After mixing the drug in the bag by rapid shaking, samples (1 ml) were withdrawn at regular intervals and stored in polypropylene tubes at −20 °C until HPLC analysis. Infusion bags containing the drug were stored at +4 °C for a period of 7 days with protection from light. Drug storage in these bags was carried out in 0.9% NaCl and 5% glucose.

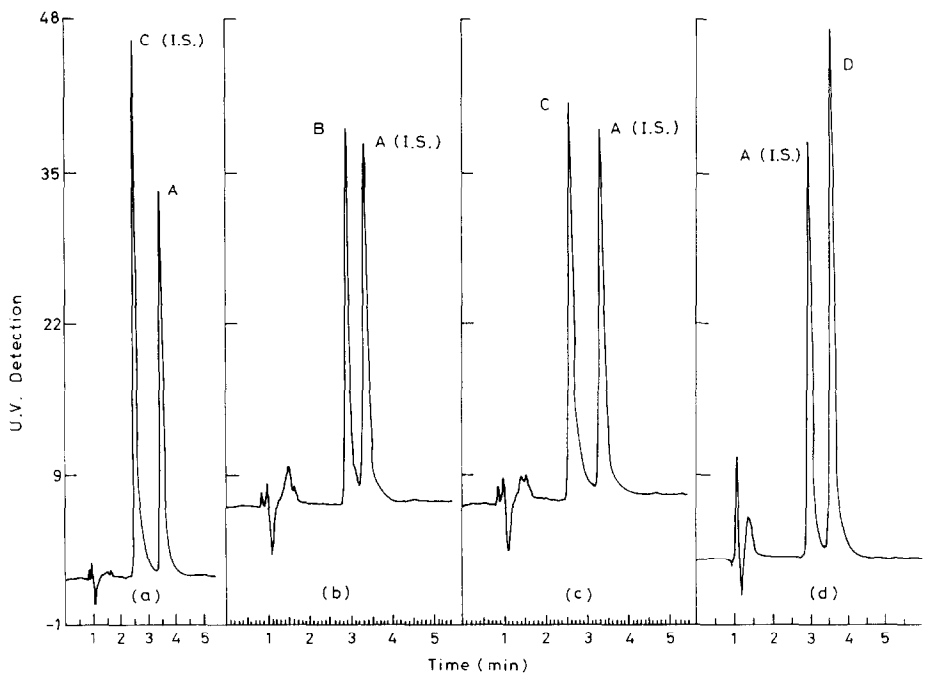

Fig. 2. Chromatographs of: (a) **A** with **C** (I.S.); (b) **B** with **A** (I.S.); (c) **C** with **A** (I.S.); (d) **D** with **A** (I.S.).

Results and Discussion

HPLC

The chromatographs of the four drugs with the respective internal standard in solution obtained immediately after mixing are illustrated in Fig. 2 [(a) vinblastine and vindesine (I.S.); (b) vincristine and vinblastine (I.S.); (c) vindesine and vinblastine (I.S.); (d) vinorelbine and vinblastine (I.S.)]. Drugs were simultaneously and rapidly well separated, identified and quantified. The components were satisfactorily resolved by this HPLC method and had retention times of 3.39, 2.94, 2.65 and 3.61 min (**A–D**, respectively).

Table 1 summarises the validation data of the assay procedure for each drug. We observed good linearity between peak area ratios and concentrations. The calibration curves were fitted by the least-square method for the peak area ratio of the sample substance and the internal standard (y) vs the concentration of the analysed product (x). The correlation coefficients were all above 0.994 and no significant differences were observed between the equation parameters.

To assess reproducibility, the same concentration was analysed five times for each point of the calibration curves. The results demonstrate that this analytical method had acceptable accuracy and precision in every case.

Stability of vinca alkaloids during simulated infusions using plastic infusion bags and sets

The analysis of each sample was performed by HPLC after suitable dilutions in the mobile phase in order to fit the calibration curves. Fig. 3 depicts the concentration kinetics of all four drugs during simulated infusions ($n = 4$), using plastic infusion bags and sets. When solutions of **A–D** were infused through plastic infusion sets from PVC infusion bags over a period of 2 h, the variation in drug concentration in both the PVC bags and effluent in no case exceeded 10%. This demonstrates that the drugs, **A–D**, were not sorbed by the plastic infusion bags and sets during infusion at ambient temperature. No significant difference was observed with respect to drug stability during simulated infusions using 5% glucose or 0.9% NaCl.

Stability of vinca alkaloids in infusion bags during storage at 4 °C with protection from light

The analysis of each sample was performed by HPLC after suitable dilution in the mobile phase in order to fit the calibration curves. The concen-

TABLE 1

Validation data of the HPLC assay procedure ($n = 5$)

Sample substance	Internal standard	Concentrations (μg/ml)	Average concentrations found ($\pm$SD) (μg/ml)	C.V. Intra-assay (%)	C.V. Inter-assay (%)	Accuracy (%)	Linear regression equation ($y = ax + b$)	Correlation coefficient (r)
A	Vindesine	15	15.29 ± 0.08	0.24	0.52	101.93		
		20	19.42 ± 0.13	0.42	0.67	97.10	$y = 0.053x - 0.205$	0.994
		25	25.29 ± 0.35	0.92	1.38	101.16		
B	Vinblastine	4	4.00 ± 0.04	0.34	1.00	100.00		
		6	5.92 ± 0.11	0.41	1.86	98.66	$y = 0.101x + 0.052$	0.998
		8	8.00 ± 0.19	0.32	2.37	100.00		
C	Vinblastine	4	3.99 ± 0.10	0.98	2.50	99.75		
		6	5.96 ± 0.09	0.88	1.51	99.33	$y = 0.136x - 0.069$	0.998
		8	8.00 ± 0.09	0.69	1.13	100.00		
D	Vinblastine	6.25	6.29 ± 0.02	0.22	0.32	100.64		
		12.5	12.37 ± 0.05	0.26	0.40	98.96	$y = 0.136x - 0.179$	0.999
		25	24.94 ± 0.20	0.30	0.80	99.76		

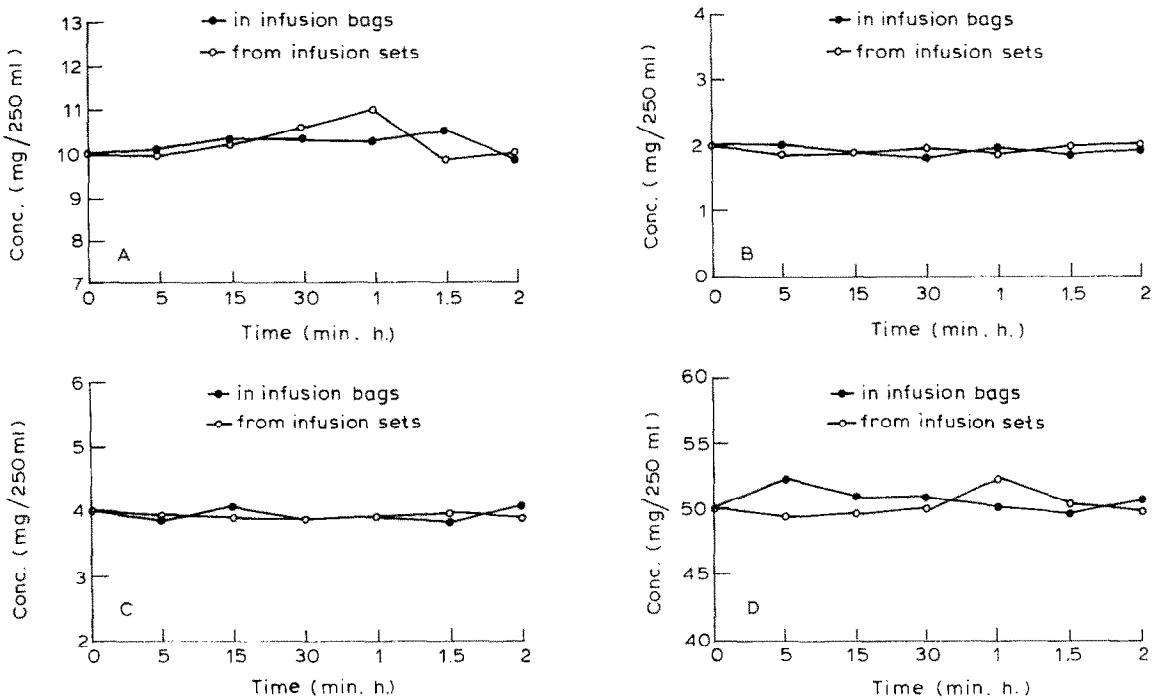

Fig. 3. Concentration kinetics of **A–D** during simulated infusions ($n = 4$) using plastic infusion bags and sets.

trations of **A–D** present in solution after various periods of storage in plastic infusion bags at 4 °C with protection from light are listed in Table 2. No significant disappearance of drug was observed in plastic infusion bags for **A–C**.

In contrast, with **D** we did note a significant difference subsequent to storage of the drug between 5% glucose and 0.9% NaCl. Indeed, **D** appeared to be more stable in the former (7 days) than in the latter (3 days). In 0.9% NaCl, we determined the loss of drug to exceed 10% following 3 days of storage.

In conclusion, the HPLC procedure described in this paper is rapid and reproducible for the determination of vinca alkaloids in parenteral solutions. The present study has examined the

TABLE 2

*Concentrations (mg / 100 ml) of **A–D** present in solution after storage in plastic bags at 4 °C*

Infusion solution	Drug							
	A		**B**		**C**		**D**	
	NaCl (0.9%)	Glucose (5%)	NaCl (0.9%)	Glucose (5%)	NaCl (0.9%)	Glucose (5%)	NaCl (0.9%)	Glucose (5%)
T_0	10.00	10.00	2.00	2.00	2.00	2.00	50.00	50.00
24 h	10.20	9.55	1.87	1.95	2.08	1.91	49.27	48.91
3 days	9.72	9.47	1.99	1.91	2.09	1.95	48.20	47.94
5 days	9.85	9.23	1.84	1.93	2.07	1.95	44.50	48.50
7 days	10.57	9.41	1.95	1.94	2.09	2.00	43.08	49.06

kinetics of vinblastine, vincristine, vindesine and vinorelbine concentration during simulated infusion using plastic infusion bags and administration sets. The results demonstrate satisfactory compatibility of vinca alkaloids with PVC infusion material over a 2 h infusion period. It is likely that other drugs interact with plastic infusion bags and administration sets, leading to a reduction in the clinical effectiveness of the drug. This type of study is important concerning the packaging of pharmaceuticals in plastic containers in general, and might be carried out for all drugs administered in PVC infusion bags.

Acknowledgements

This work was supported by grants of the Comité du Nord de la Ligue Nationale Française Contre le Cancer and the Conseil Régional du Nord-Pas de Calais. The authors also wish to thank Macopharma, Lilly France and Pierre Fabre Laboratories for cooperation in this study.

References

Benvenuto, J.A., Anderson, R.W., Kerkof, K., Smith, R.G. and Loo, T.L., Stability and compatibility of antitumor agents in glass and plastic containers. *Am. J. Hosp. Pharm.*, 38 (1981) 1914–1918.

Bodey, G.P., Yap, H.Y., Yap, B.S. and Valdivieso, M., Continuous infusion vindesine in solid tumors. *Cancer Treat. Rev.*, 7 (1980) 39–45.

Carlson, R.W. and Sikic, B.I., Continuous infusion or bolus injection in cancer chemotherapy. *Ann. Int. Med.*, 99 (1983) 823–833.

D'Arcy, P.F., Drug interactions and reactions update. *Drugs Intell. Clin. Pharm.*, 17 (1983) 726–731.

De Smet, M., Van Belle, S.J.P., Storme, G.A. and Massart, D.L., High performance liquid chromatographic determinations of vinca alkaloids in plasma and urine. *J. Chromatogr.*, 345 (1985) 309–321.

Illum, L. and Bundgaard, H., Sorption of drugs by plastic infusion bags. *Int. J. Pharm.*, 10 (1982) 339–351.

Kowaluk, E.A., Roberts, M.S., Blackburn, H.D. and Polack, A.E., Interactions between drugs and polyvinyl chloride infusion bags. *Am. J. Hosp. Pharm.*, 38 (1981) 1308–1314.

Liso, V., Specchia, G., Pavone, V., Capalbo, S. and Dione, R., Continuous infusion chemotherapy with epirubicin and vincristine in relapsed and refractory acute leukemia. *Acta Haematol.*, 83 (1990) 116–119.

Magnam, J. and Martin, J.P., Les anticancéreux sont-ils compatibles avec les matières plastiques? *Lett. QS Cancérol.*, 72 (1988) 1–6.

Moorhatch, P. and Chiou, W.L., Interactions between drugs and plastic intravenous fluid bags. I: Sorption studies on 17 drugs. *Am. J. Hosp. Pharm.*, 31 (1974) 72–78.

Tannock, I., Erlichman, C., Perrault, D., Quirt, I. and King, M., Failure of 5-days vinblastine infusion in the treatment of patients with advanced refractory breast cancer. *Cancer Treat. Rep.*, 66 (1982) 1783–1784.

Weber, W., Nagel, G.A., Nagel-Studer, E. and Albrecht R., Vincristine infusion: a phase I study. *Cancer Chemother Pharmacol.*, 3 (1979) 49–55.