Cancer Chemother Pharmacol (1983) 10: 217–220

Cancer Chemotherapy and Pharmacology

Continuous Intravenous Infusion of Vinca Alkaloid Using a Subcutaneously Implanted Pump in a Canine Model

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Summary. *A major drawback of infusions of the vinca alkaloids is the lengthy period of hospitalization which is often required for this novel technique of cancer therapy. A potentially useful system to deliver outpatient therapy has been investigated in a preclinical study. A self-contained infusion pump powered by a self-charging fluorocarbon system has been implanted SC in three dogs. The performance of two pumps which had been factory-calibrated to deliver 2.5 and 4.5 ml/day, respectively, was evaluated during 22 infusions of the vinca alkaloids (vincristine, 7; vinblastine, 7; and vindesine, 8). Infusions were given over a 5- to 7-day period and were repeated at 3-week intervals. No malfunctioning of the pumps occurred in over 500 cumulative days of use. The flow rates of the pumps were quite stable except in one animal whose increased flow rate was probably a consequence of fever due to self-induced inflammation about the pump pocket. No local or distant tissue reactions to the pump were observed. Decompostion of vincristine and vinblastine in the infusate at the end of 5- or 7-day infusions was minimal as determined by high-pressure liquid chromatography. The amount of decomposition of vindesine in the infusate was variable. Steady-state concentrations of vincristine during infusion were always* $> 10^{-9}$ *M, and were similar to those previously determined in our clinical infusion trials using a dosage of 0.5 mg/m²/day. Clinical evaluation of this system for prolonged infusions of vincristine and other vinca alkaloids appears to be warranted.*

Introduction

The vinca alkaloids, vincristine, and vinblastine, have been widely employed in cancer chemotherapy for two decades. More recently, vindesine, a synthetic derivative of vinblastine, has been introduced into clinical practice [6]. These agents have generally been administered by rapid bolus injection. Their administration by prolonged continuous IV infusion has recently been evaluated in several cancer centers, including our own; preliminary results have been encouraging [1, 3, 8, 10, 12].

These clinical data prompted the search for a drug delivery system for continuous infusion of vinca alkaloids which might allow safe and reliable outpatient treatment. The Infusaid pump is a totally implantable, self-contained infusion device, powered by a self-charging fluorocarbon system. This pump has been demonstrated to deliver heparin [2], 5-fluorodeoxyuridine [2, 5], and methotrexate [4] safely and reliably to human patients. The current study is a preclinical evaluation of this device in the administration of the clinically useful vinca alkaloids by continuous IV infusion.

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Materials and Methods

Pump. Two Infusaid pumps (50-ml Model 100 and 35-ml Model 200) were provided by the Infusaid Corp., Norwood, MA. They were factory-calibrated to deliver flow rates of 4.5 and 2.5 ml/day at 37.0° C, respectively.

Animals and Pump Implantation. Three mongrel dogs (nos. 514, 87, and 1620) weighing 21.3–23.5 kg were anesthetized with a mixture of sodium amytal and enfluorane. An SC pocket was formed by blunt dissection over the posterolateral thorax, and the infusion pump was inserted. It was secured to the surrounding tissues with 2-0 prolene sutures passed through wire loops, which were spaced at regular intervals about the circumference of the device. The Silastic outflow catheter (0.092 inch external diameter × 0.015 inch internal diameter, Infusaid Corp., Norwood, MA, USA) was tunneled beneath the SC tissue and inserted into the internal jugular vein. Prior to drug-loading of the pump, catheter patency was maintained with a solution of saline and heparin (10,000 U/ml, Upjohn Co., Kalamazoo, MI, USA), with a final heparin concentration of 1,000 U/ml. Following surgery, the dogs were individually caged and the implantation site was partially protected by placing an inflatable tube around each dog's neck and wrapping elastic gauze around the thorax.

Drugs and Pump Loading/Refilling. Vincristine, vinblastine, and vindesine were generous gifts from Eli Lilly Co., Indianapolis, IN, USA. The infusate was prepared by sterilely combining the vinca alkaloid, normal saline, and heparin (final heparin concentration 1,000 U/ml); the concentrations of the vinca alkaloid were adjusted in this mixture to deliver the desired daily drug dose based on the known flow rate of the pump previously calibrated to deliver vincristine (see above). The drug concentration was further adjusted to take into account the known dead-space for each pump (5.9 and 3.9 ml, respectively).

After preparation of the skin by shaving and application of Betadine, the pump filling process was initiated by insertion of a 22-gauge Huber's point needle through the skin and the centralized silicone rubber septum of the pump until contact with the needle stop was achieved. Following removal of the drug-free, heparin-saline mixture by allowing the barrel of the

Table 1. Treatment characteristics of animals receiving continuous IV infusions of vinca alkaloids by pump

Dog no.	Pump no.	Drug[a]	Dosage (mg/m^2/day)	Duration (days)	Infusions no.
514	254	VCR	0.5	5	3
		VLB	0.5, 1.5	5, 5	3, 2
		VDS	0.5, 1.2	5, 5	3, 2
1620	563	VCR	0.5	7	2
		VLB	0.5, 1.5	7	1, 1
		VDS	1.2	7	3
87	563	VCR	0.5	7	2

[a] VCR, vincristine; VLB, vinblastine; VDS, vindesine

attached syringe to ascend freely, a second syringe containing the treatment solution was attached to the injection needle as it remained in the pump, and the drug chamber was filled.

The type of vinca alkaloid, dosage, and number and duration of infusions studied in each of the three dogs are listed in Table 1. Infusions of the vinca alkaloids were administered no more often than every 3 weeks from the start of the previous treatment cycle. After completion of the drug infusion, the pump was evacuated as outlined above, after which it was purged twice with 10 ml normal saline. The pump was then refilled between treatment cycles with a mixture of saline and heparin (final heparin concentration 1,000 U/ml) to maintain catheter patency. The intervals between pump refilling were generally 1 week for pump no. 254 and 2 weeks for pump no. 563, due to their present flow rates of 2.5 and 4.5 ml/day, respectively.

Study Parameters. The reliability of the pump was evaluated by determining the flow rate during drug administration (ml/day) and comparing it with the factory-calibrated rate. The actual flow rate was calculated by subtraction of the excess volume removed at the end of a 5- to 7-day infusion from the original loading volume divided by the number of infusion days. The data are reported as the mean flow rate ± SEM for each drug employed.

The safety of the pump was evaluated by observation of the following parameters: local tissue reaction (at the implantation pocket and transcutaneous injection site), mobility of the pump in the SC tissue, and systemic reactions such as fever, leukocytosis, and hepatic and/or renal dysfunction. Blood counts and SMA-12 multichannel serum biochemical analysis were obtained at the start and completion of each treatment cycle.

Stability of Infusates. Samples of the infusate obtained prior to filling of the pump and after removal of the excess treatment solution at the completion of infusion were frozen at −20° C until processed. The stability of the vinca alkaloids in these samples was estimated by high pressure liquid chromatography using a LiChrosorb ^{18}C reversed-phase column (E. Merck Co., Elmsford, NY). The details of this procedure have been reported previously [9].

Blood Concentrations. Serial serum samples for determination of vinca alkaloid concentrations were obtained by removal of 3 ml venous blood before, during, and after infusion of the vinca alkaloid. The blood samples were centrifuged and the resultant serum was stored at −20° C until processed. Serum concentrations of the vinca alkaloids were determined by radioimmunoassay with a lower limit of sensitivity to approximately 1×10^{-9} *M*; the details of the assay have been reported previously [11].

Table 2. Flow rates of pumps during infusions of the vinca alkaloids[a]

Dog no.	Vincristine	Vinblastine	Vindesine
514	4.60	4.14	4.40
	4.80	3.95	4.26
	4.40	4.14	4.20
	4.60 ± 0.20	3.87	4.26
		4.30	4.50
		4.08 ± 0.17	4.08
			4.28 ± 0.15
1620	2.48	2.50	2.17
	2.80	2.64	2.43
	2.64 ± 0.23	2.57 ± 0.10	2.30 ± 0.18
87	2.82	–	–
	3.29		
	3.06 ± 0.33		

[a] At the completion of a 5- or 7-day period of infusion, actual flow rates (ml/day) were determined by measurement of the discharged infusate and comparison with the loading volume. The data at the end of the columns represent the mean flow rates (ml/day) ± SEM for each of the vinca alkaloids investigated in each dog. Spillage of the infusate as it was being removed from the pump of dog 1620 precluded determination of the flow rate for one of the vindesine infusions

Results

A total of 22 infusions of vinca alkaloids delivered by the two Infusaid pumps have been evaluated in three dogs. The pumps were evaluated in these animals for 23, 5, and 1 months, respectively. No malfunctions have occurred during 543 cumulative days of use. Flow rates of the pumps (Table 2) were quite stable. Mean flow rates following infusion of each of the drugs were within 10% of the factory-calibrated flow rates with the exception of those observed in dog 87. The latter dog scratched the pump implantation site and caused wound dehiscence; fever probably accounted for an increase in flow rate.

A seroma consistently developed in the SC pocket following implantation, which resolved over a period of 5–7 days before the drug infusions were started. However, during and after infusions of the vinca alkaloids no evidence of local tissue reaction to the pump was observed, with the exception noted above which was secondary to self-induced trauma. Neither erythema nor ulceration of the skin at the injection site occurred. No special precautions were used when removing the injection needle; it was not necessary to inject saline just prior to removal of the needle to prevent tracking of potentially caustic drug along the needle path. Despite the mobility of the overlying skin, the pumps appeared to remain fixed in their original site of implantation; no inflammation around the pump pocket was observed. There were no unexpected distant tissue reactions to the pump or its infusates as determined by comparison of the white blood cell count, total bilirubin, alkaline phosphatase, transaminase (SGOT), and creatinine before and after infusions.

Table 3. High-pressure liquid chromatographic analysis of infusate evacuated from the pumps at the completion of infusion[a]

Dog no.	Vincristine		Vinblastine		Vindesine	
	μg/ml	Decomposition (%)	μg/ml	Decomposition (%)	μg/ml	Decomposition (%)
514	90	< 1	100	< 1	100	< 1
	100	< 1	100	< 1	100	10–15
	100	< 1	100	< 1	100	< 1
			330	1–2	100	15
			330	2–4	260	< 1
					260	40–45
1620	159	ND	159	< 1	334	4– 5
	159	ND	418	< 1	334	1– 3
					334	1– 3
87	129	< 1				
	129	1–2				

[a] At the completion of infusions, the solution remaining in the pump was evacuated and subsequently analyzed by high-pressure liquid chromatography (except when indicated as ND, not done). The vinca alkaloid concentration (μg/ml) given is that expected following preparation of the infusate

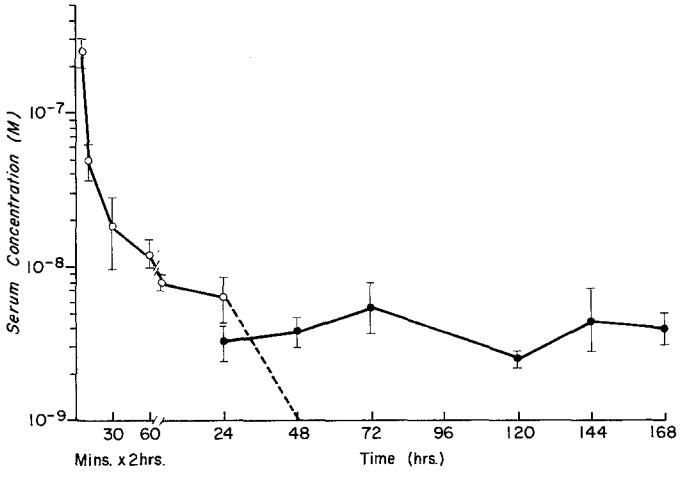

Fig. 1. Serum concentrations of vincristine were determined by radioimmunoassay at various time points following continuous IV infusion (●———●) or rapid bolus injection (○———○). Subcutaneously implanted pumps (Infusaid) were used to deliver continuous infusions; the *points* on the *curve* represent the mean serum concentrations ± SEM obtained during seven infusions of vincristine 0.5 mg/m^2/day for 5–7 days in three dogs. For comparison with serum levels achieved by conventional administration of vincristine, two 2-mg IV rapid bolus injections of vincristine were given to one of the dogs (no. 514) that had previously received infusion treatment; the *points* on the *curve* represent the mean serum concentration ± SEM. In this animal the concentrations of vincristine attained in the serum were at or below the lower limits of sensitivity of the assay (~1 × 10^{-9} *M*) by 48–72 h after IV bolus injection (– – –)

The stability of vincristine, vinblastine, and vindesine in the infusate as determined by high-pressure liquid chromatographic analysis of the evacuated solution obtained at the completion of the period of infusion is displayed in Table 3. Decomposition products were usually less than 5% in infusates containing vincristine and vinblastine. However, the amount of decomposition products in infusates containing vindesine varied from < 1% to 40%–45%. This may be due, in part, to handling of the samples after their removal from the pump, since there were large variations in the amount of decomposition products in the vindesine infusates obtained from the same pump during different infusions containing the same drug concentration.

Concentrations of the vinca alkaloids attained in serum samples during treatment varied according to the type of drug infused and its dosage. Serum vincristine concentrations were always in excess of 1 × 10^{-9} *M* during administration of vincristine using a dosage of 0.5 mg/m^2/day. Mean blood concentrations attained during the infusions are shown graphically in Fig. 1; the blood decay curve inscribed following conventional bolus injection of vincristine is shown for comparison. Infusion doses of 0.5 mg/m^2/day vinblastine and vindesine were generally associated with serum concentrations below the range of detectability (< 1 × 10^{-9} *M*). Serum concentrations of vinblastine during 1.5 mg/m^2/day infusions varied between 7.2 × 10^{-9} *M* and undetectable. Serum concentrations of vindesine during 1.2 mg/m^2/day infusions were usually greater than 3.7 × 10^{-9} *M* (range, < 1 × 10^{-9} to 9.4 × 10^{-9} *M*).

Discussion

The initiation of this project stems from our interest in vincristine, a chemotherapeutic agent which is rather unique in cancer chemotherapy due to its relative lack of myelosuppression. The cytotoxicity of this agent has been found to be critically dependent upon both drug concentration and exposure time for mammalian tumor cells in vitro [7]. Whereas a 50% cell kill has been found to occur in L-1210 murine leukemia following exposure to 10^{-7} *M* vincristine for a period of 3–6 h in a soft agar cloning system, 6–12 h exposure is required to achieve this degree of cytotoxicity with a concentration of 10^{-8} *M*. Furthermore, vincristine concentrations of < 1 × 10^{-9} *M* resulted in no evidence of cytotoxicity in this in vitro system [7]. Application of these data led to the development of a phase I trial in our center, in which a 5-day continuous infusion of vincristine was administered in an attempt to sustain potentially cytotoxic concentration of vincristine [8]. Objective antitumor responses in patients previously refractory to conventional IV bolus injection of this agent were observed during the latter trial. This suggested the possibility of increasing the therapeutic efficacy of vincristine by the use of infusion techniques. However, a major drawback

to the prolonged use of continuous IV infusions of vinca alkaloids is the lengthy period of hospitalization, with its attendant costs and patient inconvenience.

The drug delivery system evaluated in the current trial seems ideal for use in the administration of prolonged IV infusions of vincristine. In the current dog model, the Infusaid pump has been found to be both reliable and safe; local tissue reactions and systemic reactions were distinctly lacking. Decomposition of vincristine within the pump infusate has been quite minimal over prolonged periods of infusion. Evaluation of serum concentrations attained by infusion of vincristine 0.5 mg/m^2/day (the maximum tolerated phase I dosage [8]) by the Infusaid pump reveals similar steady-state concentrations observed in the clinic at this dose level [9]. Further data obtained during this investigation would suggest applicability of this infusion pump for the administration of the other clinically useful vinca alkaloids, vinblastine and vindesine, in the treatment of a variety of malignancies previously found to be responsive to this technique [1, 3, 10, 12].

It is apparent that a limited number of clinically useful chemotherapeutic agents is available to the practicing oncologist, and therefore optimal use of established cytotoxic agents is exceedingly important. Preliminary data from several trials using prolonged infusions of the vinca alkaloids have demonstrated responsiveness of malignancies previously refractory to conventional bolus injection; this suggests the possibility of enhancing the therapeutic efficacy of the vinca alkaloids by the technique of infusion. However, methods to decrease the duration of hospitalization for infusions are needed. The current study demonstrates the ability of the Infusaid pump to administer infusion of vincristine, vinblastine, and vindesine safely, reliably and conveniently in a canine model. Clinical trials of this infusion device for outpatient administration of prolonged infusions of the vinca alkaloids appear to be warranted.

Acknowledgements. This work was supported in part by National Cancer Institute grant no. CA-12197.

The authors appreciate the technical assistance of Diana Brown, Nancy Parce, Lori Carlisle, Paulette Surratt, and Julie Gee, and manuscript preparation by Denise James.

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