

Technical validation of a medical device for intrathecal injection of cytostatics in a closed system

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ABSTRACT

Background: Intrathecal (IT) injection of cytotoxic drugs is an important part of the management of acute lymphoblastic leukaemia (ALL) in children. This therapeutic procedure is associated with the risk of different medicines becoming mixed up, dose errors, exposure of nursing staff to cytotoxic drugs and septic risk.

Study objectives: The evaluation of a new version of a medical device designed to allow IT injection of cytostatics in a closed system – a Codan ramp – to control the iatrogenic risks of IT. The aim of the study, carried out at Nantes Teaching Hospital, was to validate the rinsing volume needed to administer the contents of three cytotoxic syringes pre-connected on a tap ramp (methotrexate, cytarabine and hydrocortisone hemisuccinate).

Methods: The study was carried out using hydrocortisone hemisuccinate as a marker assayed by absorption spectrophotometry in the ultraviolet range at 248 nm with extemporaneous calibration. A rinsing volume of 2.0 mL administered with a flush effect of about 0.5 mL was validated. This rinsing technique makes it possible to administer $98 \pm 4\%$, $93 \pm 5\%$ and $93 \pm 7\%$ respectively, of the volume of the three medication syringes.

Conclusion: This device requires operators and nursing staff to undergo special training and can therefore only be used in the context of centralised reconstitution with a clearly defined logistical circuit. It provides a temporary solution to a particularly delicate therapeutic procedure in paediatrics. The cost, estimated at around Euros 4,000 per year (i.e. for 1,000 devices), is negligible when compared with the predicted benefits and the overall cost of managing such cases.

KEYWORDS

Intrathecal injection, cytostatics, medical device, validation, closed system

INTRODUCTION

Prophylaxis and management of neuromeningeal disorders in children presenting with ALL is based on IT injection of cytotoxic drugs as an alternative to neuromeningeal irradiation and high doses of intravenous chemotherapy. IT injection consists of the sequential injection of cytotoxic drugs prepared in a syringe, usually methotrexate (MTX), cytarabine (AraC) and a corticosteroid [1, 2]. Many cases of errors leading to accidental fatal injection of vincristine by the IT route have been reported [3]. This procedure

also involves other risks such as exposure of nursing staff to cytotoxic drugs, dose errors and septic risk for the patient [4].

In order to control the iatrogenic risk linked to the practise of IT injection in paediatric oncology, a medical device designed to allow IT injection of cytotoxic drugs in a closed system, called a Codan ramp was evaluated in 2001 at Nantes Teaching Hospital by the oncology clinical pharmacy unit, which carries out centralised reconstitution of chemotherapeutic agents [5]. Following the technical and medical observations of the evaluators, Codan came up with a new version of this medical device in early 2006.

The aim of this study was to evaluate the necessary rinsing volume for administration of the cytotoxic doses prescribed with this version of the Codan ramp before its potential routine use.

METHODS

Medical device evaluation

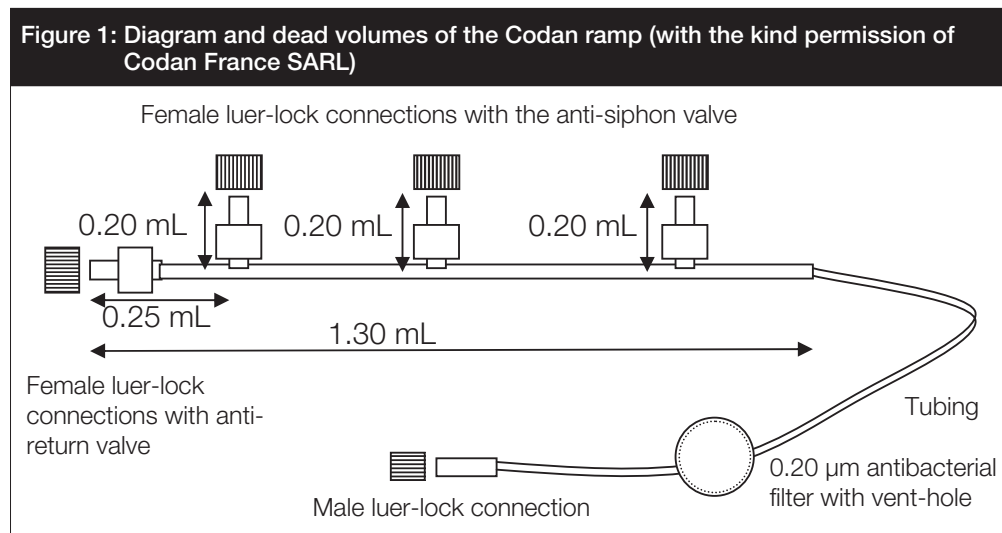
The medical device evaluated in this study was the four-valve multifold ramp sold by Codan and known as the Codan ramp, which carries EC labelling (class IIa). This is a tap ramp designed to allow IT injection of cytostatics

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Received: 19 July 2007; revised manuscript received: 9 May 2008; accepted: 30 May 2008



volume evaluated was fixed at 2.0 mL.

The MTX, AraC and hydrocortisone hemisuccinate (HCHS, the corticosteroid used in paediatric IT injections at Nantes Teaching Hospital) doses administered depend on the chemotherapy protocol and patient age. The minimum and maximum volumes to be administered were determined for each syringe as a function of the concentration of cytotoxic solution used, with the total injected volume of cytotoxic ranging

in a closed system using four pre-connected syringes including three anti-siphon valves, an anti-return valve and a 0.20 µm antibacterial filter with a vent-hole along the tubing (Figure 1).

Determination of rinsing volume

The overall dead volume of the Codan ramp is 1.90 mL, apart from the tubing (0.20 mL for each cytotoxic syringe fitting, 0.25 mL for the fitting of the fourth syringe and 1.05 mL for the body of the ramp). The information in the packaging of the medical device states that the tubing represents a dead volume of around 0.30 mL (Figure 1) and the rinsing volume corresponds to about 1.35 mL (body of ramp and tubing). Taking into account the dead volume of the luer-lock connection of the rinsing syringe, the total dead volume is thus estimated to be 1.60 mL. As a result of variations between devices and the surplus volume required to obtain satisfactory rinsing, the rinsing

from 1.27 to 2.90 mL (Table 1) [6].

Evaluation methodology

Evaluation of the rinsing volume was carried out twice for minimum and maximum volumes for each syringe, i.e. four tests per syringe. The marker retained was HCHS as it is easy to handle and is compatible with the medical device, making it simple to carry out ultraviolet absorption spectrophotometry. This marker was used in the syringe to be evaluated while the other syringes were filled with physiological serum (sodium chloride [NaCl] at 0.9%).

In the course of preparing each syringe, a surplus volume of 0.20 mL was added because of the dead volume of the luer lock. After connecting the syringes to the device (the first one containing the marker and two others NaCl at 0.9%), the luer-lock connections were filled by dripping the liquid into the ramp ('pearlising drop'). The fourth

Table 1: Minimum and maximum volumes to be administered with the Codan ramp for each syringe, as a function of the concentration of cytotoxic solution used and prescribed dose

	AraC (syringe 1)	MTX (syringe 2)	HCHS (syringe 3)	Total therapeutic volume (mL)	Rinsing volume (mL) (syringe 4)
Preparation used	Cytarabine 100 mg/5 mL	Methotrexate 25 mg/1 mL	Hydrocortisone hemisuccinate 100 mg/2 mL		
Dose and minimum volume prescribed*	15 mg 0.75 mL	8 mg 0.32 mL	10 mg 0.20 mL	1.27 mL	2.00 mL
Dose and maximum volume prescribed*	30 mg 1.50 mL	15 mg 0.60 mL	40 mg 0.80 mL	2.90 mL	2.00 mL

* As a function of each protocol and stratified according to patient's age.

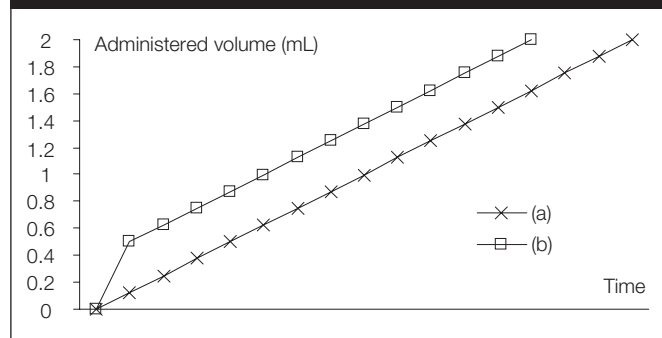
syringe (NaCl at 0.9%) was then put in place to fill and purge the body of the ramp and the tubing. Finally, this fourth syringe was removed, filled with 2.0 mL of NaCl 0.9% and re-attached to the ramp.

The three syringes were administered factitiously as they would be at the clinical unit, then the ramp was rinsed with the fourth one. Two rinsing methods were tested: the first tests were carried out by forced continuous rinsing over 2.00 mL of 0.9% NaCl, and the second series of tests using a 0.50 mL flush, rinsing before continuous forcing of the remaining 1.50 mL of 0.9% NaCl (Figure 2).

All effluents (administration and rinsing) were collected in a dry tared beaker. The volume of liquid was determined immediately by weighing, and the absorbance of the solution was measured in order to calculate percentage recovery. The rinsing volume was considered to be sufficient if at least 90% of the theoretical dose was administered for the evaluated syringe, with the objective being correct administration of the three syringes.

An absorption spectrum in the ultraviolet range and a calibration graph were realised extemporaneously (from 0.005 to 0.05 mg/mL, by dilution in a commercial solution of HCHS in sterile water). The working solution of 0.06 mg/mL was prepared extemporaneously by dilution in the same commercial solution. The densities of the various diluted HCHS solutions were determined. All absorbance measurements were performed on a UV-visible spectrophotometer 1605; Shimadzu Europa GMBH. BD 3.0 mL syringes (0.2 mL graduations) and Medallion 1.00 mL syringes (0.01 mL graduations) were used.

Figure 2: Schematic flow diagram for the administration of the rinsing syringe: forced continuous rinsing for the first tests (a) and 0.50 mL flush rinsing before continuous forcing of the remaining 1.50 mL for the second series of tests (b)



RESULTS

General points

The volumes administered were 3.35 ± 0.03 mL for the lowest doses and 5.00 ± 0.04 mL for the highest doses ($n = 8$), the volume of cytotoxic drugs representing about 38% (1.27 mL) and 58% (2.90 mL) of the total volume. The different densities of the diluted HCHS were equal to 1.

First series of tests: forced continuous rinsing

After making up HCHS dilutions, the absorption maximum was determined at 248 nm for a 0.025 mg/mL solution (theoretical 242 nm).

The calibration graph equation was “concentration = $0.0240 \times \text{absorbance} - 0.0007$ ” (r^2 , the square of Pearson’s correlation coefficient, = 0.9984). The percentage recovery, taking all volumes together, was $98 \pm 4\%$ for the first syringe, $93 \pm 5\%$ for the second syringe and $75 \pm 8\%$ for the third syringe (Table 2).

Second series of tests: flush rinsing over 0.50 mL

Only the third syringe was evaluated because it posed a problem in the first series of tests. After making up HCHS dilutions, the absorption maximum was determined at 248 nm for a 0.025 mg/mL solution (theoretical 242 nm). The calibration graph equation was “concentration = $0.0254 \times \text{absorbance}$ ” ($r^2 = 0.9999$). Percentage recovery taking all volumes together was $93 \pm 7\%$ for the third syringe (Table 3).

DISCUSSION

IT injections of cytotoxic drugs, indicated for the prevention and treatment of neuromeningeal disorders in ALL in children, carries a high iatrogenic risk [1, 2]. After lumbar puncture, the cytotoxic syringes are connected sequentially to the puncture needle. This procedure, a relatively long and delicate one in paediatrics, exposes nursing staff to anti-cancer agents and carries the risk of dose errors as a result of reflux on changing the syringes. Because most IT injections are carried out at the patient’s bedside, there is also a theoretical risk of sepsis [5, 7]. These injections, most often associated with intravenous chemotherapy, also carry the risk of medicines being confused. In spite of an awareness of these risks and the prevention methods put in place, fatal accidents continue to be reported after accidental IT injection of vincristine intended for the intravenous route [3, 8-13]. In France, recommendations outlining safety measures for vincristine injections were recently published [14]. Moreover, while the preparation of anti-cancer agents is centralised within the oncology clinical pharmacy unit, corticosteroid injections for the IT route are prepared

Table 2: First series of tests, with forced continuous rinsing over 2.00 mL of 0.9% NaCl, showing the percentage recovery of the marker

Position of syringes tested	Volume prescribed (mL)*			Amount of marker injected (mg)	Volume recovered (mL)	Measured absorbance	Percentage recovery	Mean	Standard deviation
	Syringe 1	Syringe 2	Syringe 3						
1	0.75 mL	0.32 mL	0.2 mL	0.0450	3.275	0.610	101%	98%	4%
1	0.75 mL	0.32 mL	0.2 mL	0.0450	3.314	0.575	96%		
1	1.5 mL	0.6 mL	0.8 mL	0.0900	5.088	0.750	98%		
1	1.5 mL	0.6 mL	0.8 mL	0.0900	4.991	0.757	97%		
2	0.75 mL	0.32 mL	0.2 mL	0.0192	3.335	0.253	93%	93%	5%
2	0.75 mL	0.32 mL	0.2 mL	0.0192	3.350	0.240	88%		
2	1.5 mL	0.6 mL	0.8 mL	0.0360	4.971	0.312	94%		
2	1.5 mL	0.6 mL	0.8 mL	0.0360	4.946	0.318	95%		
3	0.75 mL	0.32 mL	0.2 mL	0.0120	3.384	0.135	71%	75%	8%
3	0.75 mL	0.32 mL	0.2 mL	0.0120	3.371	0.134	71%		
3	1.5 mL	0.6 mL	0.8 mL	0.0480	5.014	0.352	81%		
3	1.5 mL	0.6 mL	0.8 mL	0.0480	4.988	0.343	78%		

Marker: HCHS solution at 0.06 mg/mL, density = 1, in the syringe tested. Other syringes filled with physiological serum. Evaluation carried out twice for minimum and maximum volumes for each syringe.
 Calibration curve: concentration = 0.0240 × absorbance – 0.0007, r² = 0.9984
 *prepared volume = prescribed volume + 0.20 mL

extemporaneously in the paediatric unit; this means that there is a higher risk of error than in the pharmaceutical unit dedicated to such preparation, and where there is an operational quality control system [5].

This is the framework within which an initial version of a Codan ramp medical device intended for intrathecal injection of cytotoxic drugs in a closed system was evaluated in 2001 [5]. Medically, nursing staff show greater control of

the iatrogenic risk with a ready-to-use system and comply fully with the protocol doses. They also note that the procedure is faster, which is better for patient comfort, with a reduced risk of sepsis and exposure to cytotoxic drugs. Nevertheless, the presence of a significant dead volume could present an obstacle to the use of this device. Technically, this device is harder to handle than the current system of separate syringes: special training is needed for its assembly, it is cumbersome and its storage and

Table 3: Second series of tests, using 0.50 mL flush rinsing before continuous forcing of the remaining 1.50 mL of 0.9% NaCl, showing percentage recovery of the marker

Position of syringes tested	Volume prescribed (mL)*			Amount of marker injected (mg)	Volume recovered (mL)	Measured absorbance	Percentage recovery	Mean	Standard deviation
	Syringe 1	Syringe 2	Syringe 3						
3	0.75 mL	0.32 mL	0.2 mL	0.0120	3.399	0.123	88%	93%	7%
3	0.75 mL	0.32 mL	0.2 mL	0.0120	3.374	0.141	100%		
3	1.5 mL	0.6 mL	0.8 mL	0.0480	4.952	0.347	91%		
3	1.5 mL	0.6 mL	0.8 mL	0.0480	5.010	0.352	93%		

Marker: HCHS solution at 0.06 mg/mL, density = 1, in the syringe tested. Other syringes filled with physiological serum. Evaluation carried out twice for minimum and maximum volumes for each syringe.
 Calibration curve: concentration = 0.0254 × absorbance, r² = 0.9999
 *prepared volume = prescribed volume + 0.20 mL

transport require a protection system to prevent any leaks resulting from the syringes being moved. As a result of this evaluation, several improvements were suggested [5].

The second version of the Codan ramp, presented in 2006, includes various modifications: a round ramp and longer tubing to facilitate handling during injection and to limit needle movement during puncture. The filter, added to the tubing, facilitates purging and reduces the risk of small air bubbles being injected. Various industrial aspects of the assembly process have been modified to ensure reproducibility of the technical features. Moreover, the compatibility of the cytotoxic drugs used (AraC, MTX and HCHS) has been tested with the various ramp constituents. However, these modifications lead to an increased dead volume, and a kit form, with syringes to make the assembly procedure easier, is still not a reality.

During our evaluation, a continuously forced rinsing volume of 2.0 mL led to satisfactory administration of the contents of the first two syringes (98% and 93% recovery respectively). On the other hand, only 75% of the contents of the third syringe were administered, probably as a result of reflux in the course of administration of the contents of this third syringe. The rinsing volume could therefore not be validated as such. Because the Codan laboratories do not want to make further modifications to this device, we evaluated the rinsing mechanism for the third syringe using a rinsing mechanism inspired by rinsing in chamber implants with a "flush" effect of about 0.5 mL aimed at limiting the adherence of molecules to the ramp. With this rinsing technique, administration of the contents of a third syringe was found to be satisfactory (recovery: 93%). By extension, administration of the contents of the first two syringes was also validated because forced continuous rinsing had already been shown to be sufficient. These results were presented to paediatric oncologists who, in spite of the increase in dead volume, approved of this administration system because the procedure had been made safer and there was better control of the iatrogenic risk. Technically speaking, the Codan ramp medical device could therefore be used when rinsing with 2.0 mL of physiological serum with a flush effect of about 0.5 mL.

However, considerable difficulties remain before routine use of this device can be envisaged. The assembly technique takes a long time and is delicate, requires special training for operators and a longer operator time than the current system, using separate syringes. For the same reasons, preparation outside the centralised reconstitution unit is not an option. Preparation times are therefore longer, especially so because the transport and storage

conditions have to be such that assembly remains intact until reaching the patient's bedside, with clear labelling of the different syringes. Nursing staff also have to be trained to ensure the Codan ramp is used correctly and that they comply with the rinsing protocols.

Assembly of the device was carried out in the oncology clinical pharmacy unit no more than 24 hours in advance because of the decreased stability of HCHS solutions compared with AraC and MTX [15, 16]. During the evaluation in 2006, the extra cost was estimated at Euros 4,000 per year (for around 1,000 devices); this is negligible compared with the overall cost of treatment. However, the cost of syringes (1 mL luer lock) and preparation time have to be added to this. For various reasons, this device appears to us to be a temporary solution, allowing the iatrogenic risk associated with carrying out IT injection to be limited, until new recommendations and materials appear.

CONCLUSION

Technical evaluation of the second version of the Codan ramp medical device made it possible to validate a rinsing volume of 2.0 mL administered with a flush effect of about 0.5 mL. This enabled the administration of the total dose of AraC, MTX and HCHS, pre-connected to a ramp.

This new device would confer considerable security of use in the paediatric oncology department. In fact, it eliminates the risk of: confusion occurring between medicines intended for the IT route and those using other routes of administration, dose errors during preparation of the corticosteroid at the patient's bedside, and of exposing nursing staff to cytotoxic drugs when changing the syringes. Moreover, the availability of this pre-connected system reduces the duration of the therapeutic procedure and is therefore more comfortable for patients. Nonetheless, it presents a number of technical limitations because it has to be prepared by a centralised reconstitution unit and operators and nursing staff have to be specially trained.

Our method is an interesting temporary solution, at a time when there are many suggestions to make the administration of cytotoxic drugs by the intravenous route safer. The cost of this new device is negligible, given the control it provides over iatrogenic risk, and in view of the overall cost of treatment.

ACKNOWLEDGEMENTS

The authors thank the International Codan Group, and especially Dr Marie-Hélène Pauvert and Dr Marie-Jeanne Mennesson, for their technical assistance.

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