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Evaluation of the dead volume in intravenous short-term infusion

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Abstract

Study objectives: To evaluate the extent of the dead volume in IV short-term infusions.

Methods: Literature data were screened by a Medline search using the keywords: intravenous therapy, infusion, short infusion, infusion system, dead volume and dead space. Short-term infusion solutions that are mainly used and the wards which frequently order these products from the hospital pharmacy were identified. A survey was performed on six wards in order to get information about the handling of short-term infusions on the ward. The dead volume was analysed under laboratory conditions as well as on two wards after administration to the patient.

Results: Depending on the volume of infusion and the manufacturer of the infusion fluid, the dead volume varied in the laboratory tests between 47% and 24% when the drip chamber was filled to the mark and between 32% and 15% when the drip chamber was empty. The results of the tests on the ward ranged between 14% and 20% for 100 mL Miniflac bottles and between 24% and 32% for 50 mL Miniflac bottles.

Conclusion: A considerable amount of the infusion volume and therefore of the active compound is lost at the end of short-term infusion because of dead volume. The loss of a potential amount of drug can be a problem in regard to patient safety and effectiveness of the therapy, especially for those drugs where dosage is adjusted to body weight. The nursing guidelines at University Hospital Basel (USB) concerning the handling of infusions were adapted in line with the results of this study.

Keywords

Dead volume, hospital pharmacy, intravenous (IV) administration system, medication safety, short-term infusion

Introduction

Parenteral administration of drugs plays an important role in the hospital setting; they are frequently administered by intermittent infusion over a short time. A short infusion is defined as an IV infusion of a small volume (usually 50 mL to 100 mL), which is administered over a period of, at most, three hours, usually 30 to 60 minutes [1, 2]. In particular, antibiotics, cytotoxic drugs and analgesics are administered via short infusion [2].

It is well known that a certain quantity of the drug remains at the end of the infusion and is not administered to the patient because of the dead volume [3], which is defined as the total volume of the intravascular catheter and IV tubing [4].

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Furthermore, a residual volume remains in the infusion bottle at the end of each infusion. In this paper, the term 'dead volume' describes the total infusion volume remaining in the IV administration set and the bottle at the end of the infusion. No literature data were found on research aiming at quantifying this problem. Internal nursing guidelines at University Hospital Basel (USB) concerning the handling of IV infusions did not deal with the administration of short infusions and therefore gave no advice. Furthermore, the hospital pharmacy had no detailed information about the handling of short infusions on the wards, e.g. whether the infusion system was flushed after the application or which infusion volume was preferred. It has been discovered that nursing staff are using web forums to discuss whether the IV administration set has to be flushed with the vehicle after the end of the short infusion or not [5]; no information is routinely available about the dead volume in infusion bottles or bags.

The question whether lyophilised drugs, which have to be reconstituted in 50 mL or 100 mL of a vehicle, are overfilled by the manufacturers to address the problem of a loss of the drug because of the dead volume is also controversially discussed by nursing staff [5]. Eleven manufacturers of drugs in powder form to be reconstituted for parenteral administration were asked for information. The replies were inconsistent; the amount of powder varies between

95% and 110% of that stated on the label. Seven of the 11 manufacturers indicated that the amount of powder varies between 100% and 103%. Thus, it cannot be assumed that powders for infusion are generally overfilled.

Methods

Literature was searched on Medline, for the period 1990–2009, using the keywords: intravenous therapy, infusion, short infusion, infusion system and dead volume. There are several papers focusing on IV medication errors [6-8], but dead volumes were not analysed. Other authors addressed the phenomenon of dead volume in IV infusions [4, 9-11], but their focus was on the dynamics of IV drug delivery and on the time lag between the start of the infusion and the moment when the drug reached the patient's bloodstream. Depending on the flow rate and the size of the dead volume, a delay of 20–30 minutes can occur before any drug enters the circulation.

The IV fluids listed in the USB formulary that are used as vehicles for the administration of drugs by short infusion were identified. Using ERP software (SAP), a 12-month statistical analysis (July 2007 to June 2008) was performed to determine the number of units delivered from the hospital pharmacy to the different wards at USB (see Table 1).

Information was obtained from the pharmaceutical manufacturer B. Braun stating that a residual volume of 3–5 mL would remain in Ecoflac plus bottles [12]. The filling volume of Ecoflac plus bottles varies between 54–60 mL in 50 mL bottles and between 108–120 mL in 100 mL bottles [12]. Therefore, it was necessary to determine the exact filling volume of each bottle used in the study.

The wards at USB that most frequently ordered short infusions from the hospital pharmacy in the 12-month period mentioned above were then identified. It was found that 25 wards ordered more than 2,000 units during the study period; six of the wards (two wards of internal medicine, one haematological ward, one intensive care unit, an interdisciplinary emergency unit and a surgical ward) were sent a questionnaire in December 2008 in order to get detailed information about the following:

- Drugs administered as short infusion
- Frequency of administration (often, seldom)
- Preferred volume of short infusion
- Administration mode (infusion pump, gravity infusion)
- Handling of short infusions, e.g. flushing of the IV administration system after application or filling degree of the drip chamber at the end of the infusion
- Estimation of dead volume

At the same time, the drugs listed in the hospital drug formulary, which are available as powder for infusion or concentrate and are to be diluted and administered as short infusion, were evaluated. A three-month statistical analysis (August to October 2008) using ERP software (SAP) was performed and the results compared with the responses to the questionnaire.

Determination of dead volumes under laboratory conditions

The measurement of the dead volume of short infusions took place from December 2008 to February 2009. The analyses were conducted under laboratory conditions corresponding to those of short infusions used on the wards.

In the laboratory, 50 mL and 100 mL short infusion solutions were analysed. The solutions contained normal saline from two manufacturers: NaCl 0.9% in Miniflac 50 mL (LOT 8401B15) and 100 mL (LOT 8405A231) containers, (both manufactured by B. Braun Medical AG, Switzerland), and NaCl 0.9% 100 mL (LOT 1680708, Bichsel AG, Switzerland). The IV administration set used was an Intrafix Primeline Comfort 180 cm (LOT 8H25018311, B. Braun Medical AG, Switzerland). Each of the three products was analysed fivefold. Furthermore, five tests were performed with NaCl 0.9% in Miniflac 100 mL, each after reconstitution of Augmentin 2.2 g (GlaxoSmithKline AG, Switzerland). The density of all fluids was analysed.

The total weight of each bottle was measured for an evaluation of the dead volume. For the reconstituted antibiotic, the weight of the bottle

Table 1: Intravenous fluids suitable for administration of drugs by short infusion (12-month period)

Product	Volume	Manufacturer	Number of units
Glucose 5% Stechampullen	50 mL	B. Braun Medical AG	16,040 vials
Glucose 5% Miniflac	100 mL	B. Braun Medical AG	11,437 bottles
NaCl 0.9% Miniflac	50 mL	B. Braun Medical AG	15,988 bottles
NaCl 0.9% Miniflac	100 mL	B. Braun Medical AG	135,985 bottles
NaCl 0.9% Ecobag	100 mL	B. Braun Medical AG	5,285 bags
NaCl 0.9%	100 mL	Bichsel AG	6,931 bottles

before and after reconstitution was determined. After connecting the bottle to the IV administration set the infusion was started and the fluid was collected in a tared beaker. The infusion was stopped when the mark in the middle of the drip chamber was reached. The collected fluid was weighed and the resulted mass converted into the volume by means of its density. The dead volume was then determined, using a three-way stopcock and a 60 mL syringe, by the following steps:

- Drip chamber filled to the mark (centre ring)
- Drip chamber half filled
- Drip chamber emptied
- IV administration set completely emptied

Finally, the fluid remaining in the bottle was drawn up with a 10 mL syringe and a cannula, and the volume determined. The weight of an empty bottle was measured and used as a control. The difference between the total weight and the weight of the empty bottle was recorded and converted into the volume by means of the density, and compared with the experimentally determined volume.

Determination of dead volumes of short infusions prepared on the ward

In addition, observational tests were performed on two internal medicine wards to determine whether the dead volume of short infusions under real-life conditions was comparable with the results of the laboratory findings. The study was performed with the predominantly used NaCl 0.9% Miniflac 50 mL (LOT 8401B15) and 100 mL (LOT 8405A231), both manufactured by B. Braun Medical AG, Switzerland. On one ward, 10 Miniflac 50 mL and seven Miniflac 100 mL infusions were examined, and on the other ward, which only administered 100 mL short infusions, nine Miniflac 100 mL infusions were examined. In all cases, antibiotic drugs were reconstituted in the appropriate vehicle. The antibiotics observed were: Tazobac 4.5 g (Wyeth Pharmaceuticals AG, Switzerland), Augmentin 1.2 g (GlaxoSmithKline AG, Switzerland), Garamycin 40 mg (Essex Chemie AG, Switzerland), Rocephin 2 g (Roche Pharma AG) and Meronem 1 g (AstraZeneca AG, Switzerland). A subgroup analysis of each antibiotic was not performed because of the small number of samples.

The nurses on the two wards were instructed by the researchers how to record the relevant information and were given consecutively numbered and labelled Miniflac bottles for the tests after the total weight of each bottle had been determined. Furthermore, the density of each possible combination of antibiotic and short infusion (50 mL and 100 mL) was determined in the laboratory beforehand, as well as the additional weight of the reconstituted antibiotic. The nurses were asked to use only the labelled bottles together with the standard IV administration set (Intrafix Primeline Comfort 180 cm, B. Braun Medical AG, Switzerland) and to collect the Miniflac bottles together with the connected IV administration set after the end of the short infusion at a designated place on the ward. The names of individual nurses responsible for the administration of the infusions to the patients were not recorded.

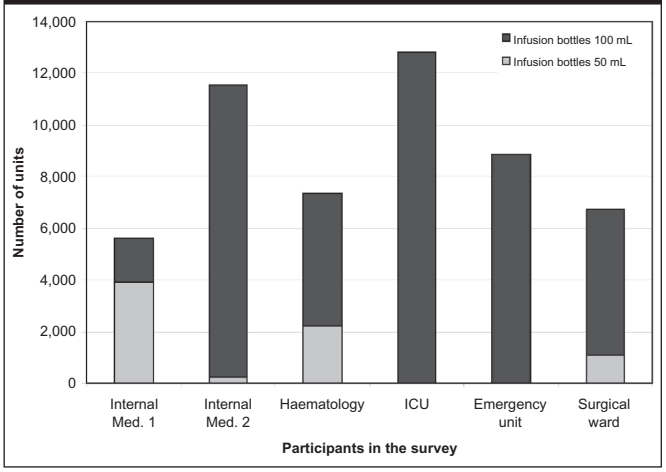
The determination of the dead volume was then calculated as described earlier. The infusion solution remaining in the IV administration line and the drip chamber was discharged using a three-way stopcock and a 60 mL syringe. The actual volume of liquid in the drip chamber was recorded as well as the antibiotic drug which was reconstituted in the vehicle by the nursing staff. The final steps involved emptying the fluid remaining in the bottle using a 10 mL syringe and a cannula, and determining the volume as well as the weight of the empty bottle. The additional weight of the antibiotic reconstituted in the short infusion was added to the weight of the labelled bottle in order to get the total mass. The difference between total weight and weight of the empty bottle was converted into the filling volume by means of the density.

Results

The responses to the questionnaire, which took place in December 2008, did not reveal a consistent handling of short infusions on the wards, and the dead volume was underestimated in part. No standards exist concerning the right moment for stopping short infusions, so it cannot be assumed that the drip chamber is usually empty at the end of administration of short infusions. The responses concerning the preferred volume of short infusions were largely consistent with the 12-month statistical analysis performed using ERP software (see Figure 1). A small discrepancy between the responses given in the questionnaire and the statistical analysis was found only on the surgical ward and concerned the use of 50 mL infusions. For the most part, 100 mL infusions were used, but on one internal medicine ward, 50 mL infusions were used almost exclusively.

The three-month statistical analysis of drugs that are commonly administered as short infusions is illustrated in Figure 2. On most wards, antibiotics and IV additives are given in this way. The latter were not mentioned by the nursing staff in the survey, probably because IV solution additives are usually added to long-term IV infusions with a volume of 500–1,000 mL rather than administered as a

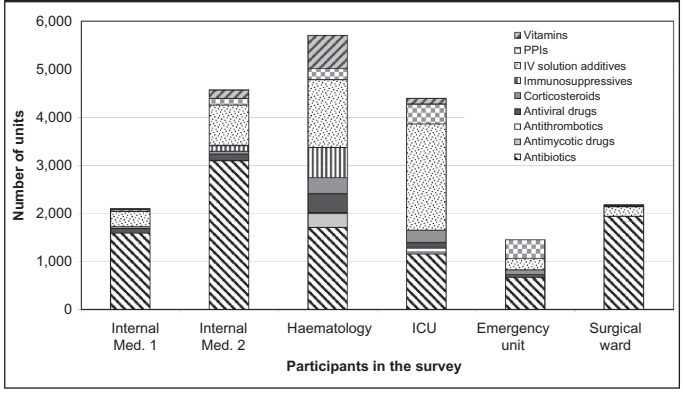
Figure 1: Infusion solutions delivered from the hospital pharmacy during a 12-month period



short infusion. Thus, the responses to the questionnaire were widely consistent with the three-month statistical analysis shown in Figure 2.

The results of the determination of dead volumes assessed in the laboratory tests (normal saline) are given in Table 2. Depending on the manufacturer of the infusion fluid, the dead volume varied between 24 mL and 27 mL when the drip chamber was filled to the mark and between 15 mL and 19 mL when the drip chamber was empty. When the IV administration set was completely empty, only the residue in the infusion bottle contributed to the dead volume. Depending on the manufacturer, this residue varied between 6.4 mL and 6.9 mL for Miniflac bottles, and 4.4 mL for bottles manufactured by Bichsel. Compared with the 100 mL Miniflac bottles, the percentage of the dead volume doubled using 50 mL Miniflac bottles.

Figure 2: Drugs for short infusion delivered from the hospital pharmacy during a 3-month period



The results for 100 mL Miniflac bottles were comparable with those after reconstitution of Augmentin 2.2 g.

The results of the observational tests on the two wards are summarised in Table 3. On one ward (internal medicine 2), 100 mL Miniflac bottles were used exclusively. In each case, the infusion had been stopped when the drip chamber was empty. Five out of the nine infusions had been performed with Tazobac 4.5 g, two with Augmentin 1.2 g, one with Rocephin 2 g and one with Meronem 1 g. The average of the dead volume amounted to 15% ± 0.72% standard deviation (SD).

On the other ward (internal medicine 1), 50 mL Miniflac bottles were used as well as 100 mL infusions. The infusions were either stopped when the drip chamber was empty, or the drip chamber was half-filled or filled to the mark, respectively. Depending on the actual volume of liquid in the drip chamber, the dead volume varied between 24% and 32% for 50 mL Miniflac bottles, and between 14% and 20% for 100 mL Miniflac bottles.

Discussion

It is well known that some drug solution remains in the IV administration set and the bottle at the end of infusion because of the dead volume of the IV administration set [3]; up to the present time and as far as is known, no systematic research has been carried out to quantify this phenomenon. It has been discussed, for example, controversially on web forums, whether the dead volume is of significant relevance and whether the IV administration set has to be flushed with the vehicle after the end of the short infusion as a consequence [5]. According to the findings of this study, the amount of short-infusion dead volume is mostly underestimated by the nursing staff. The study was able to demonstrate that parenteral drugs that are marketed in a lyophilised form are not generally overfilled by the manufacturer. Thus, it cannot be expected that a loss of the reconstituted drug because of vehicle residue at the end of the infusion would be routinely compensated.

A volume of 6.4 mL ± 0.55 mL SD remaining in Ecoflac plus bottles at the end of the infusion was determined; this exceeded the volume of 3–5 mL indicated by the manufacturer [12]. The results of the laboratory tests showed that, depending on the volume of infusion and the manufacturer, the total dead volume in the bottle and the IV administration set varied between 47% (50 mL) and 24% (100 mL) when the drip chamber is filled to the centre ring, and between 32% and 15% when the drip chamber is empty.

Table 2: Dead volume in 50 mL and 100 mL normal saline from laboratory tests

Type of infusion (manufacturer)	[n]	Drip chamber	Total volume (mL) ± SD	Dead volume (mL) ± SD	Dead volume (%) ± SD
NaCl 0.9% Miniflac 50 mL (B. Braun)	5	a	58.0 ± 0.61	27.3 ± 0.39	47.0 ± 0.55
		b	58.0 ± 0.61	22.9 ± 0.41	39.5 ± 0.61
		c	58.0 ± 0.61	18.6 ± 0.30	32.0 ± 0.34
		d	58.0 ± 0.61	6.9 ± 0.31	11.9 ± 0.55
NaCl 0.9% Miniflac 100 mL (B. Braun)	5	a	111.3 ± 0.42	27.4 ± 0.55	24.6 ± 0.54
		b	111.3 ± 0.42	23.7 ± 0.45	21.3 ± 0.39
		c	111.3 ± 0.42	19.4 ± 0.55	17.4 ± 0.53
		d	111.3 ± 0.42	6.4 ± 0.55	5.8 ± 0.50
NaCl 0.9% Miniflac 100 mL (B. Braun) Admixture with Augmentin 2.2 g	5	a	111.2 ± 0.59	26.8 ± 0.57	24.1 ± 0.55
		b	111.2 ± 0.59	22.7 ± 0.76	20.4 ± 0.70
		c	111.2 ± 0.59	18.9 ± 0.55	17.0 ± 0.49
		d	111.2 ± 0.59	5.9 ± 0.55	5.3 ± 0.49
NaCl 0.9% 100 mL (Bichsel)	5	a	103.6 ± 0.42	24.4 ± 0.37	23.6 ± 0.40
		b	103.6 ± 0.42	19.9 ± 0.42	19.2 ± 0.44
		c	103.6 ± 0.42	15.5 ± 0.36	14.9 ± 0.36
		d	103.6 ± 0.42	4.4 ± 1.28	4.2 ± 1.22

SD: standard deviation; a: drip chamber filled to the mark (centre ring); b: drip chamber half filled; c: drip chamber empty; d: IV administration set completely empty (only residue in the bottle contributes to the dead volume)

In order to compare the results of the laboratory tests and real-life conditions, observational tests were performed on two wards, one of them using 50 mL infusion solutions. The preliminary tests were conducted on two internal medicine wards. It was decided not to include further wards and waived the registration of nurses administering the short infusions. The number of samples on each ward was limited (internal medicine 1: ten tests with 50 mL and seven tests with 100 mL infusion solutions; internal medicine 2: nine tests with 100 mL infusion solutions). Because of the lack of internal guidelines, the infusions were stopped at different time points with the consequence of varying residual volumes in the drip chamber, depending on the type of ward and the nurse performing the administration. Therefore, the groups of tests had to be divided into subgroups according to the actual volume of liquid in the drip chamber at the end of the infusion. The findings of the 15 tests performed on the two wards with 100 mL Miniflac bottles with an empty drip chamber were comparable with those of the laboratory tests (14–15% vs 17%), but there were differences for the 50 mL Miniflac bottles (24.4% vs 32%, drip chamber empty and 32% vs 39.5%, drip chamber half-filled, respectively). The tests carried out on the internal medicine 1 ward resulted in more heterogeneous data with a wider SD compared with the internal medicine 2 ward. Therefore, it is possible that the observed differences between the tests on this ward and the laboratory tests with 50 mL Miniflac bottles resulted from a less accurate handling by the nursing staff, but this aspect was not explored.

As mentioned above, the filling volume of Ecoflac plus bottles can range from 54–60 mL for 50 mL bottles and from 108–120 mL for 100 mL bottles. Therefore, the percentage of the dead volume depends on the effective volume in the bottle. The total volume of the 100 mL Ecoflac plus bottles used in the study was nearer the lower value (see Table 2). Assuming the maximal total volume of 120 mL, the percentage of the total volume would slightly decrease from 21.3–19.8% (drip chamber half-filled) and from 5.8–5.3% (IV administration set completely empty). Therefore, the effective volume in the infusion bottle has only a little influence on the percentage of the dead volume and on the loss of drug.

As stated previously, both the residue in the IV administration set and the residue in the infusion bottle contribute to the dead volume at the end of infusion and to the loss of vehicle and drug. The residual volume in the bottle depends on the manufacturer of the vehicle. The differences between the products of the two manufacturers tested were small (B. Braun: 6.9 ± 0.31 mL or 6.4 ± 0.55 mL respectively versus Bichsel: 4.4 ± 1.28 mL). Therefore, the preferred use of products from a specific manufacturer would not help. Moreover, the percentage of residue in the bottle has only minimal influence on the total dead volume. In contrast, the residual volume in the infusion line is twice as large as the residue in the bottle when the drip chamber is empty, and three times the volume when the drip chamber is half filled. From this observation, a change of the infusion set could have a major effect on the dead volume. In any case, only the Intrafix Primeline

Table 3: Dead volume in 50 mL and 100 mL normal saline from clinical practice test

Type of infusion antibiotic	[n]	Drip chamber	Total volume (mL) ± SD	Dead volume (mL) ± SD	Dead volume (%) ± SD
Internal medicine ward 1 NaCl 0.9% Miniflac 50 mL Augmentin, Rocephin, Tazobac	3	b	58.4 ± 1.42	18.8 ± 1.26	32.2 ± 1.86
NaCl 0.9% Miniflac 50 mL Augmentin, Garamycin, Tazobac	7	c	59.1 ± 0.91	14.4 ± 1.13	24.4 ± 1.86
NaCl 0.9% Miniflac 100 mL Rocephin	1	a	111.6	22.0	19.7
NaCl 0.9% Miniflac 100 mL Augmentin, Garamycin, Rocephin, Tazobac	6	c	113.0 ± 1.18	15.8 ± 2.25	13.9 ± 1.93
Internal medicine ward 2 NaCl 0.9% Miniflac 100 mL Augmentin, Meronem, Rocephin, Tazobac	9	c	111.3 ± 1.08	16.7 ± 0.66	15.0 ± 0.72

SD: standard deviation; a: drip chamber filled to the mark (centre ring); b: drip chamber half filled; c: drip chamber empty.

Comfort 180 cm administration set was used in the study, because it is the standard IV administration set at USB and used almost exclusively. A change of infusion set should be considered in future.

Generally, at USB the IV administration set is neither disconnected nor flushed at the end of infusion, which is in accordance with the hygiene guidelines in the hospital and with the guideline for prevention of catheter-associated infections published by the German Robert Koch Institute [13]. In this regard, the use of the Soluset administration set could be a further solution to address the problem of dead volume. Administration of IV medicines via Soluset enables flushing of the administration set at the end of a short infusion without disconnecting the administration set and the bottle. Thus, a loss of drug solution at the end of the infusion could be avoided. Compared with the Intrafix Primeline system, the Soluset system is much more expensive and is therefore only used on the haematological ward and intensive care units.

The study demonstrated that a significant amount of infusion volume and thus of the active compound is lost at the end of infusion because of dead volume, particularly for 50 mL short infusions. Primarily, this is a problem of missing guidelines at USB and about a lack of awareness of dead volume. As a consequence, there is no standardisation in terms of quantity of the infusion volume and the handling at the end of the infusion, and both 50 mL infusion solutions and 100 mL infusions are used on various wards. This could cause a problem regarding patient safety, especially for those drugs whose dosage is adjusted to body weight, e.g. aminoglycoside antibiotics or antiepileptic drugs. For example, in the case of a 70 kg patient prescribed gentamicin therapy and a once-daily dose of 5 mg/kg body weight, 350 mg of gentamicin is to be administered. A loss of around 30% would result in the administration of only 245 mg of gentamicin to the patient. However, it was not the aim of this study to deal with clinical consequences; further investigations would be necessary to quantify the clinical relevance of such potential under-dosing.

Therefore, it seems to be important to address the problem of dead volume by internal guidelines and nurse training. Particularly in the paediatric setting, the problem arising from dead volume has been acknowledged and a standard operating procedure for the administration of IV medicines to paediatric patients has been implemented [14]. For this reason, the results of the investigations undertaken in this study were discussed with the nursing staff and the committee responsible for internal nursing guidelines. As a first consequence, the guideline concerning the handling of IV infusion was supplemented with a chapter referring to IV short infusions. Where possible, the volume of short infusions is now recommended to be 100 mL as a minimum, and the infusion should be stopped only when the drip chamber is empty. Furthermore, the nursing staff and the physicians were informed about this recommendation through an article in the quarterly bulletin of the hospital pharmacy.

Conclusion

Medicinal products marketed as powders for injection or infusion are not generally overfilled by the manufacturer and thus do not compensate a possible loss of drug because of dead volume in a short infusion. A considerable amount of the infusion volume and therefore of the active compound is lost because of dead volume in the administration set and the bottle. This bears a potential risk regarding medication safety.

We recommend that the volume of short infusions should be 100 mL as a minimum and that the infusion should be stopped only when the drip chamber is empty. For the future, there should be discussion whether or not special IV administration sets such as Soluset should be used for potentially critical drugs in order to flush the system at the end of short infusion. In this context, it will be necessary to define the drugs that are potentially critical and the maximal percentage rates of loss that can be accepted.

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Conflict of interests

The authors declare no conflicts of interest.

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