An orchestra in need of a conductor

Doesburg, Frank

DOI:
10.33612/diss.165632361

CHAPTER 1

General introduction

General introduction

The first intravenous (IV) injection is commonly attributed to Sir Christopher Wren, who in the year 1656 administered wine into the bloodstream of a dog using an IV infusion device created out of pig's bladder and a writing quill.[1] In a letter to a former Oxford colleague, William Petty, Wren states "I Have Injected Wine and Ale in a liveing (sic) Dog into the Mass of Blood by a Veine, in good Quantities, till I have made him extremely drunk, but soon after he Pisseth it out",[2] Wren continued his experiments with many different fluids, however the use of a quill was quite impractical as it was difficult to fixate in a vein and was not durable enough. Wren's colleague Richard Lower devised various new instruments to improve Wren's first IV infusion device and so laid the groundwork for IV therapy.[3]

Presently, IV therapy is one of the most common forms of treatments in hospitals worldwide. Although quills have been replaced by needles and plastic catheters, the basic principle of fluid administration into a vein is still the same. Using an infusion pump, IV fluids or drug solutions contained in a syringe or IV bag are administered through a series of tubes and connectors into the bloodstream of a patient at a predefined rate. Vascular access is provided by a catheter that is placed in a vein. Peripheral venous catheters (PVCs) are placed in a peripheral vein and usually contain a single lumen (Figure 1; left), thus allowing a single stream of IV fluids. A central venous catheter (CVC) is placed in a central vein and commonly contains two or three lumens that allow for separated streams of IV fluids (Figure 1; middle and right, respectively).

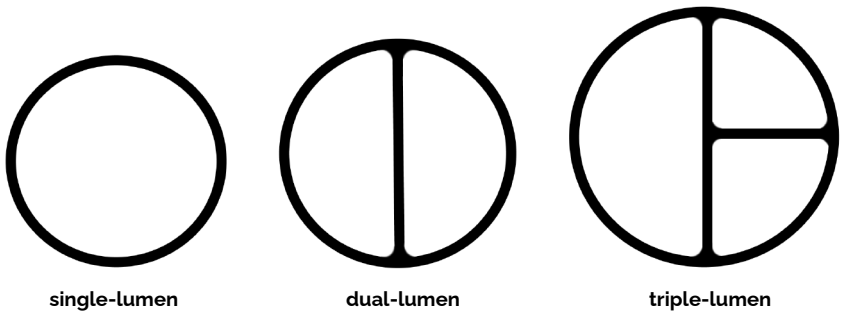

Figure 1. Schematic representation of cross-sections of a single, dual and a triple-lumen catheter

In the intensive care unit (ICU) in particular patients receive multiple IV fluids and drug solutions simultaneously.[4–6] In order to administer these fluids, a typical ICU patient is treated by using a combination of volumetric and syringe pumps. Volumetric pumps are generally used to deliver moderate to large flows (i.e. 5 to 999 ml/h) of infusion fluids (e.g. lactated Ringers solution, glucose 5%, or NaCl 0.9%). It is also a common scenario that a secondary IV bag with a drug is piggybacked with the primary infusion fluid.[7] Syringe pumps generally infuse drug solutions (e.g. noradrenalin) at lower rates (i.e. 0.1 to 100 ml/h) and are also used when more accurate or variable dosing is required.

A typical patient in our ICU may be treated using 2 volumetric pumps and 5 syringe pumps, which are connected to one triple-lumen CVC and two PVCs. As ICU patients commonly require more different IV fluids and drugs than there are lumens available, fluids originating from the different infusion pumps are often co-administered through a single lumen of a CVC or a PVC. This so-called multi-infusion introduces several challenges and opportunities, which will be explored in-depth in this thesis.

Thesis outline

One of the most common complications of IV therapy is phlebitis, which is an inflammation of a superficial vein that usually occurs at the insertion site of a PVC. As ICU patients commonly receive twice as many drugs as patients on a regular ward, phlebitis is more likely to occur in the ICU.[8] However, existing tools for the identification of phlebitis are not suitable for use in the ICU as they rely on subjective symptoms such as pain, and ICU patients are often sedated or receive analgesics. Nevertheless, an increased temperature around the insertion site is considered to be a cardinal sign of phlebitis that can be measured objectively.[9] Therefore, in **chapter 2** we assessed the feasibility of using infrared thermography to detect phlebitis by measuring the temperature difference between the PVC insertion site and a nearby reference point.

Reliable information on the preparation, storage, and administration of IV drugs is critical for clinical practice. Medical professionals in Dutch hospitals rely on parenteral drug guides (PGDs) that contain drug monographs to provide this information for each individual drug. Although all PDGs once originated from a single, countrywide PDG, hospital pharmacists and pharmacy technicians in each Dutch hospital organization now independently and manually maintain their own PDG. The degree of overlap in Dutch PDGs is currently unknown and it is unclear which data sources are consulted to update drug monographs. In **chapter 3A** we therefore assessed the similarities and dissimilarities in the management and content of PDGs in the Netherlands.

Drug incompatibility is a common issue in the ICU as the co-administration of incompatible drugs or fluids can lead to precipitation, inactivation, occlusion, catheter failure or even embolism.[10] ICU patients typically have a triple-lumen CVC that facilitates the separated administration of incompatible drugs and fluids. It is the ICU nurse's responsibility to determine which drugs can be safely co-administered through each lumen using Y-site compatibility data derived from the PDG and compatibility charts. Unfortunately, these sources are often incomplete as many important combinations of drugs have not been studied or because contradictory results have been published. Existing compatibility studies often do not reflect the drug concentrations, contact time and temperatures as they occur in ICU practice. In **chapter 3B** we therefore developed a systematic Y-site compatibility testing procedure that better reflects ICU practice. This procedure was subsequently applied to drug pairs that were commonly administered simultaneously in the ICU.

When a sufficient number of IV lumens is not available, additional invasive PVCs or CVCs must be used which increases the risk of catheter-related complications such as bloodstream infections and phlebitis.[11–14] In order to reduce the number

of required lumens in the ICU, it is common practice to administer a separator fluid between two incompatible solutions. This volume must be sufficient to avoid mixing between the two solutions, but should also not be excessive due to the patient's fluid intake restrictions.[15,16] The factors affecting the volume of separator fluid required to safely separate two incompatible solutions are unknown. Therefore, in **chapter 4** we studied whether and how the administration rate, drug solvent, choice of separator fluid, its administration rate, and the tubing volume affects the volume of separator fluid required to safely separate incompatible drug solutions.

Most errors that occur in the ICU are related to IV therapy and the likelihood of adverse events increases by 3% with each additional IV drug.[17,18] A large proportion of these errors (40%) is directly related to the use of infusion pumps and often related to administration rates that are too high or too low. The usability of infusion pumps is commonly identified as an important contributor to the incidence of such medication errors.[19–24] The presence of a multitude of infusion pumps thus poses additional challenges for the ICU nurse, since the nurse is the primary operator of infusion pumps at the bedside. Combined with a sometimes hectic work environment in the ICU and a vulnerable patient population, the risk of errors and the severity of their consequences is considerable.[25] In **chapter 5** we developed a new user-interface for the centralized control and monitoring of multiple infusion pumps. We subsequently compared the usability of this user-interface with that of a conventional setup of multiple infusion pumps.

Another approach to reduce the number of required IV lumens involves a new procedure of drug administration called multiplex infusion. During multiplex infusion, incompatible solutions are sequentially administered through a single lumen, while being separated by a third solution that is compatible with the two flanking solutions. A centralized control system is required to choreograph the timed alternation of multiple infusion pumps that cannot be reliably performed manually. In **chapter 6** we developed and tested an algorithm that schedules alternating IV administrations of multiple incompatible infusion packets through a single lumen, taking compatibility-related, pharmacokinetic and pharmacodynamic constraints into account. The performance of this multiplex algorithm was compared to a conventional scheduling procedure as executed by ICU nurses.

Occlusions (blockages) of IV tubing can occur when stopcocks are not opened completely or when IV tubes are kinked. Occlusions can prevent vital and time-critical medication from being delivered into the bloodstream of patients. Using the conventional method of occlusion detection the pressure measured by an infusion pump is compared to a pre-set alarm limit, which it typically set between 300 and 800 mmHg.[26–29] However, using this conventional method it can take up to 2 hours before an occlusion is detected when a pump is set at a low rate (≤1 ml/h).[30] In order to improve the speed of occlusion detection we developed and evaluated the performance of three new occlusion detection algorithms in **chapter 7**.

References

1. Bergman, N. A. Early Intravenous Anesthesia. *Anesthesiology* **72**, 185–186 (1990).
2. Bennett, J. A. A study of Parentalia, with two unpublished letters of Sir Christopher Wren. *Ann. Sci.* **30**, 129–147 (1973).
3. Rivera, A. M., Strauss, K. W., van Zundert, A. & Mortier, E. The history of peripheral intravenous catheters: how little plastic tubes revolutionized medicine. *Acta Anaesthesiol. Belg.* **56**, 271–82 (2005).
4. Fahimi, F., Forough, A. S., Taghikhani, S. & Saliminejad, L. The rate of physicochemical incompatibilities, administration errors. Factors correlating with nurses' errors. *Iran. J. Pharm. Res.* **14**, 87–93 (2015).
5. Knudsen, L., Eisend, S., Haake, N. & Kunze, T. Physicochemical compatibility of commonly used analgesics and sedatives in the intensive care medicine. *Eur. J. Hosp. Pharm.* **21**, 161–166 (2014).
6. Staven, V., Wang, S., Gronlie, I. & Tho, I. Development and evaluation of a test program for Y-site compatibility testing of total parenteral nutrition and intravenous drugs. *Nutr. J.* **15**, 29 (2016).
7. McLaughlin, K. *et al.* Safety of Intravenous Push Lacosamide Compared With Intravenous Piggyback at a Tertiary Academic Medical Center. *Ann. Pharmacother.* **55**, 181-186 (2020) doi:10.1177/1060028020943569.
8. Moyen, E., Camiré, E. & Stelfox, H. T. Clinical review: medication errors in critical care. *Crit. Care* **12**, 208 (2008).
9. Marsh, N. *et al.* Inter-rater agreement on PIVC-associated phlebitis signs, symptoms and scales. *J. Eval. Clin. Pract.* **21**, 893–9 (2015).
10. Maison, O. *et al.* Drug incompatibilities in intravenous therapy: evaluation and proposition of preventive tools in intensive care and hematology units. *Eur. J. Clin. Pharmacol.* **75**, 179–187 (2019).
11. Evans, R. S. *et al.* Reduction of peripherally inserted central catheter-associated DVT. *Chest* **143**, 627–633 (2013).
12. Hilton, E. *et al.* Central catheter infections: single- versus triple-lumen catheters. Influence of guide wires on infection rates when used for replacement of catheters. *Am. J. Med.* **84**, 667–72 (1988).
13. Maki, D. G., Kluger, D. M. & Crnich, C. J. The Risk of Bloodstream Infection in Adults With Different Intravascular Devices: A Systematic Review of 200 Published Prospective Studies. *Mayo Clin. Proc.* **81**, 1159–1171 (2006).
14. Hadaway, L. Short peripheral intravenous catheters and infections. *J. Infus. Nurs.* **35**, 230–240 (2012).
15. Silversides, J. A. *et al.* Conservative fluid management or deresuscitation for patients with sepsis or acute respiratory distress syndrome following the resuscitation phase of critical illness: a systematic review and meta-analysis. *Intensive Care Med.* **43**, 155–170 (2017).
16. Claure-Del Granado, R. & Mehta, R. L. Fluid overload in the ICU: evaluation and management. *BMC Nephrol.* **17**, 109 (2016).
17. Van Soest-Segers, B., Cheung, K. & Hunfeld, N. Op IC vooral doseerfout bij infuus. *Pharm. Weekbl.* **4**, 16–18 (2009).
18. Kane-Gill, S. L., Kirisci, L., Verrico, M. M. & Rothschild, J. M. Analysis of risk factors for adverse drug events in critically ill patients*. *Crit. Care Med.* **40**, 823–8 (2012).
19. Liljegren, E., Osvalder, a.-L. & Dahlman, S. Setting the Requirements for a User-Friendly Infusion Pump. *Proc. Hum. Factors Ergon. Soc. Annu. Meet.* **44**, 132–135 (2000).
20. Husch, M. *et al.* Insights from the sharp end of intravenous medication errors: implications for infusion pump technology. *Qual. Saf. Health Care* **14**, 80–6 (2005).
21. Gagnon, R. *et al.* A User-Centered Evaluation of three Intravenous Infusion Pumps. *Proc. Hum. Factors Ergon. Soc. Annu. Meet.* **48**, 1773–1777 (2004).
22. Ward, J. R. & Clarkson, P. J. An analysis of medical device-related errors: prevalence and possible solutions. *J. Med. Eng. Technol.* **28**, 2–21 (2004).
23. Graham, M. J. *et al.* Heuristic evaluation of infusion pumps: implications for patient safety in Intensive Care Units. *Int. J. Med. Inform.* **73**, 771–9 (2004).
24. Vijayakumar, A., Sharon, E. V, Teena, J., Nobil, S. & Nazeer, I. A clinical study on drug-related problems associated with intravenous drug administration. *J. Basic Clin. Pharm.* **5**,

49–53 (2014).
25. Kalisch, B. J. & Aebersold, M. Interruptions and multitasking in nursing care. *Jt. Comm. J. Qual. Patient Saf.* **36**, 126–32 (2010).
26. Joe, H. B., Moon, B.-K., Lee, Y.-J. & Min, S.-K. Arrangements of the intravenous parallel infusions with anti-reflux valves decreasing occlusion alarm delay. *Korean J. Anesthesiol.* **66**, 300–5 (2014).
27. Managing Occlusions of the Delivery System. in *The Biomedical Engineering Handbook* (ed. Bronzino, J. D.) (CRC Press, 1999).
28. Deckert, D. *et al.* The Effects of Multiple Infusion Line Extensions on Occlusion Alarm Function of an Infusion Pump. *Anesth. Analg.* **108**, 518–520 (2009).
29. Chua, J. & Ratnavadivel, A. Comparison of flow pressures in different 3-way infusion devices: an in-vitro study. *Patient Saf. Surg.* **12**, 19 (2018).
30. Donmez, A., Araz, C. & Kayhan, Z. Syringe pumps take too long to give occlusion alarm. *Pediatr. Anesth.* **15**, 293–296 (2005).