An orchestra in need of a conductor

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CHAPTER 8

Summary and discussion
Future perspectives

Summary and general discussion

Intravenous (IV) therapy is arguably the most common treatment modality of seriously ill hospitalized patients. Despite its widespread use it remains a procedure that carries important risks due to the potential of errors and complications in all stages of its execution. Particularly in the ICU, these risks increase with the number of IV drugs used. Improvements to this therapy may benefit many patients around the world. The goal of this thesis was to explore various challenges and opportunities posed by multi-infusion therapy. In this chapter we summarize and discuss our main findings.

Challenges

Phlebitis is one of the most common complications of IV therapy, however its detection in the ICU is challenging as the current practice of visual assessment is not suited for ICU practice. In **chapter 2** we investigated the feasibility of using infrared (IR) thermography to objectively detect phlebitis in a population of ICU patients. A higher temperature difference between the peripheral venous catheter (PVC) insertion site and a nearby reference point as measured by IR thermography was associated with early onset phlebitis. We also found that catheter dwell-time was a predictor for phlebitis. The length of stay in the ICU is generally relatively short and consequently so is the dwell-time, which may explain why mostly early stage phlebitis was observed in our study. The use of IR thermography for the detection of phlebitis must be further investigated in the general ward as it is likely that more severe cases of phlebitis will be encountered there.

In **chapter 3** we explored the challenges that multi-infusion poses for the hospital pharmacy. Accurate information on in vitro drug compatibility is essential for safe IV administration. In **chapter 3A** we document that the maintenance procedures for parenteral drug guide (PDG) monographs that contain essential drug-related data for clinical practice, are highly redundant in hospital pharmacies throughout the Netherlands. The result is that each Dutch hospital maintains a highly similar, but separate PDG. Y-site compatibility data are commonly found in PDG monographs. However, compatibility information in particular is difficult to maintain and a suitable data model to store compatibility relations between drugs is currently not in use. We found that compatibility data is often infrequently updated, and sometimes not at all, leading to large differences in compatibilities reported in different monographs of the same drug. We therefore recommend a joint nationwide PDG as it may improve maintenance efficiency as well as the quality of its content.

Compatibility studies provide essential input for PDGs. Nevertheless, a standard methodology for compatibility research is currently lacking.[1] In **chapter 3B** we developed an improved procedure to determine the Y-site compatibility of drugs specifically aimed at ICU conditions. According to our procedure a combination of drugs is considered to be compatible when it passes both a visual test and a subsequent quantitative analysis using High Performance Liquid Chromatography-Diode Array Detection (HPLC-DAD). Both analyses were performed at 20°C and 37°C to reflect both the ambient temperature and the temperature under the patient's blankets. Although we were able to determine the compatibilities of most drug combinations in our study, not all combinations were suitable for

quantitative analysis with HPLC-DAD. For these combinations a suitable alternative quantitative analysis must be sought.

The number of available lumens is an important constraint in multi-infusion. In order to optimize the use of a single lumen a separator fluid can be administered between two incompatible drug solutions. Remarkably, empirical evidence on the factors that determine the required separator fluid volume (SFV) is lacking for this common procedure. In **chapter 4** we found that as a rule of thumb, twice the tubing's priming volume should be flushed to separate two incompatible solutions. When longer tubing is used, the ratio of SFV to the tubing's priming volume decreases, which can be explained from the effects related to Poiseuille flow.[2] Some drugs such as insulin may adhere to the inner wall of the tubing and may be more difficult to flush out.[3] Flushing procedures for such drugs remain to be studied.

Opportunities

New opportunities in multi-infusion arise when we consider the infusion system as a whole instead of as a collection of individual pumps. In **chapter 5** we developed a central user-interface that allows ICU nurses to monitor and control multiple infusion pumps at the same time. The usability of this new central user-interface was subsequently compared to the control of a set of individual, conventional infusion pumps that the participating ICU nurses operated on a daily basis. Although the participating ICU nurses were experienced users of the conventional pumps, they overall performed equally fast with the new central user-interface after minimal training. Fewer errors were made using the central control user-interface, and most errors using the conventional pumps appeared to originate from single tasks that required a counterintuitive workflow.

Centralized control of multiple pumps creates new opportunities for clever cooperation between infusion pumps. When we combine the concept of central pump control from chapter 5 with the flushing strategy from chapter 4, it is possible to alternate the administrations of many incompatible drug solutions through a single lumen with a separator fluid between them. During this so-called multiplex infusion, we take advantage of the fact that the administration of many IV drugs can be interrupted without compromising treatment effectiveness. Until now such an advanced infusion strategy was not possible due to the limited programming capabilities of infusion pumps. In **chapter 6** we developed and evaluated a multiplex algorithm that takes drug-specific constraints (e.g. compatibilities, maximal interruption time and rate) into account in order to create an administration schedule for multiplex infusion. We evaluated the performance of this algorithm using a large database of real ICU drug administrations to assess the number of lumens required for IV treatment. In nearly all cases one triple-lumen central venous catheter would have been sufficient if the drugs were multiplexed. This is an important result as it will avoid the need for additional PVCs in many cases, thus preventing complications that occur in 20-40% of all PVCs.[4–6]

In **chapter 7** we combined pressure signals from multiple infusion pumps to allow the detection of co-occluding infusion pumps. We developed two novel single-pump occlusion detection algorithms that were both able to detect some occlusions much faster than conventional pressure threshold algorithms. A third

occlusion detection algorithm was coupled to the single-pump algorithms to detect co-occlusions with other pumps by correlating pressure signals after a single-pump occlusion was detected. When the pressures of two pumps coincidentally rise, it is likely that the occlusion is localized in a segment of the tubing shared by the two pumps. Such information may be used as an occlusion localization feature that helps nurses to pinpoint and resolve occlusions faster.

Future perspectives

The basic principles of IV therapy today are still the same as those in 1656 when Christopher Wren performed the first infusion of wine into the vein of a dog.[7] Since then, many advances have been made that have markedly improved the capabilities and safety of IV therapy. The invention of the electronic infusion pump has boosted the number of solutions that can be administered simultaneously, as well the precision with which critical drug solutions can be administered.

However, an increasing number of infusion pumps together with many other medical devices at the bedside stretches the cognitive demands on ICU nurses further than ever before. Centralized control and monitoring of multiple infusion pumps in the ICU is therefore a sensible, and perhaps necessary step to make multi-infusion safer and easier to manage. The opportunities that arise from central control will certainly not be limited to multiplex infusion and multi-pump occlusion detection that we discussed in this thesis. Significant progress has been made in (semi) closed-loop systems that convert blood glucose measurements into new pump settings to maintain a stable glucose level.[8,9] Automatic relay systems that switch to a new pump when a syringe is empty have already found their way into clinical practice.[10] Clinical advisory tools exist that assist nurses with the safe co-administration of drugs, and smart pumps provide a warning when an unintended harmful dose of a drug is about to be administered.[11,12] In the near future such smart tools may become embedded into a centralized pump control system.

In the neonatal ICU the challenge of vascular access may be even more significant than in the adult ICU.[13] Future development of multiplex infusion should also take the constraints for neonatal patients into account, which includes a more limited fluid intake regimen compared to the adult ICU patients. In order to reduce the fluid intake, drug solutions that are compatible with multiple other drugs may be used as a separator fluid instead of an infusion fluid. The small-volume IV tubing used in the neonatal ICU will require a smaller separator fluid volume compared to the tubing used in adults. A method to determine the minimally required separator fluid volume is presented in this thesis.

A clinical trial to assess the safety of multiplex infusion is required before its introduction into clinical practice. For this purpose, blood concentrations of selected IV drugs could be compared between conventional and multiplexed drug administration, where a maximal deviation of ±10% from the conventional concentration would be considered to be acceptable. A careful selection of drugs must ensure that all relevant pharmacokinetic models are represented in the study. A multi-pump platform with centralized pump control must be supplied by an industrial partner to facilitate multiplexed drug administration. The clinical performance of our new occlusion detection algorithms may be evaluated by processing real-time infusion pump pressure readings in parallel with conventional detection performed by the same pump.

For the determination of drug compatibilities testing procedures should reflect the clinical situation as much as possible. However, the current standard of compatibility testing focuses on drug pairs, while in ICU practice combinations of three or more drug solutions are often employed. Likewise, drug solutions are

rarely administered in a 1:1 volume ratio. Determining the compatibility of three or more solutions in different ratios requires an immense effort. Nevertheless, using multiple remotely controlled infusion pumps coupled with a suitable on-line detection system such as a Diode Array Detector such a task may be automated.

As a final take on the future of multi-infusion we may consider the bedside pumps as an orchestra. Currently, each orchestra member is oblivious to his peers and is only able to play a single tune (albeit in various tempi). In this thesis we introduced a new conductor (i.e. centralized pump control), tuned the instruments and started rehearsals. Ultimately, the success of each composition depends on the acceptance of the audience (i.e. the patients and nurses). At this time we are testing whether the concepts of centralized pump control and multiplex infusion are suitable for use in clinical practice by ICU nurses. A good usability combined with training will be critical for user acceptance and introduces exciting new challenges for the future.

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