Impact of infusion set-ups on drug delivery

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Outline

- Background
- Clinical Case
- Physics of the infusion system
- Basic technology and physics of infusion systems
- How physics can influence dose
- Take home and R&D outlook
- Infusion components
Background: How I was drawn to infusion

- Infant with acute blood pressure problem
- Dopamine infused to raise blood pressure
- No result
- Increasing dopamine flow rate
- No result
- Increasing dopamine again
- Overshoot
- No relation found with dopamine setpoint
- Decreasing dopamine flow rate
- No result
- Etc.
Background
The problem: Dosing errors during multi-infusion

Multi-infusion is administering more than one drug directly into the veins of a patient over one access point.

**Dosing errors** can lead to serious adverse events. Dosing errors can occur due to flow rate changes in any pump in a multi-infusion system. Adverse event severity depends on system component characteristics and flow rate change size and direction.
What are we talking about?

- Almost every patient receives medication therapy via infusion
- Many different applications
- Many users
- Many mistakes
- Of which some of high impact
2 basic mechanisms

- Gravity driven
- Motor driven displacement:
  - Volumetric pump
  - Syringe pump
Infusion schedule

Fluid containers:
• Bags
• Flasks
• Syringes

Driving forces:
• Gravity
• Positive displacement

Flow controllers:
• Drip chamber/ clamp: counting droplets
• Calibrated step motor
• Catheters and needles

Vascular access:
• Catheters and needles

Flow controllers:
• Drip chamber/ clamp: counting droplets
• Calibrated step motor
• Catheters and needles
Typical multi-infusion setup

- Syringe pump + syringe
- Check valves
- Catheter
- Filter
- Manifold

1. Syringe pump + syringe
2. Check valves
3. Manifold
4. Filter
5. Catheter
Physical parameters influencing flow

- System dead volume (combined volume)
  - Push out effect
  - Start up delay
- Compliance
- Resistance
- Pressure effects
- A case to explain
A clinical case

- Female patient, 62 years of age, no history of disease, had a subarachnoid hemorrhage yesterday
- She is operated for clipping of an aneurysm
- An arterial line and central venous pressure device are inserted
- Blood pressure has lowered too far after induction: Noradrenaline therapy (3ml/h) is started using a saline carrier flow (10 ml/h)

Onset of blood pressure increase only starts after approximately 15 minutes!

What causes this delay?
A clinical case

In our case:

Flow rate Noradrenaline: 3ml/h
Flow rate Saline carrier flow: 10 ml/h
Volume from three way stop cock to patient is 3 ml

Total flow = 13 ml/h
A clinical case

- The noradrenaline has to travel the 3 ml to reach the patient.
- With a flow rate of 13 ml/h: after 7 minutes the noradrenaline is halfway
A clinical case

In our case:
– After 14 minutes noradrenaline reaches the patient!
A clinical case

• This delay effect is called the dead volume.
  – The dead volume is the shared volume
    • In our case: 3 ml
  – The delay depends on:
    • The amount of volume
    • The flow rates

Besides delay in start of drug administration dead volume effects can also lead to other types of dosing errors
The dead volume effect can also lead to dosing errors when pumps are already running.
Dead volume effect: push out effect

Let's consider two syringe pumps:
- Both run at 1 ml/h
- One is filled with drug 1: red drug
- The other one is filled with drug 2: blue drug
- Up to the mixing point we have:
  - One line filled with only the red drug
  - One line filled with only the blue drug

Dead volume effect: push out effect
Dead volume effect: push out effect

- The flow rate in the dead volume is the combined flow rate of the two pumps.
- The dead volume contains both the red and blue drug:

Since the flow rate of red and blue are equal, the ratio is 50%/50%
Dead volume effect: push out effect

- Now we increase the flow rate of our red drug to 2 ml/h.
- The flow rate in the dead volume is now 3 ml/h.

The ratio of red and blue is still the same right after we changed the flow rate of the red pump!
After a while the dead volume is being filled with a new ratio of red and blue drug.

- 2 ml/h: 100% Red
- 1 ml/h: 100% Blue
- 3 ml/h: 67% Red, 33% Blue

Dead volume effect: push out effect.
Dead volume effect: wrap up

• Because of the volume in the combined infusion line and catheter, a startup delay is experienced when starting a new medication
• If pumps are already running and a flow rate is changed, the dead volume causes a push out effect by pushing the existing volume out of the combined line

• Other effects: Compliance and resistance and pressure effects
Compliance effect

The infusion system has compliance (elasticity of the infusion system)

\[ C = \frac{\Delta V}{\Delta P} \]

At first one would think the syringe pump is only displacing the plunger (no pressure driven system) at a certain velocity

However, part of the pressure is expanding the infusion system, instead of driving the plunger
Compliance/Resistance: start-up phenomena

• Compliance and Resistance
  • Compliance expands components
  • Resistance ‘resists’ the flow
  • Highest component resistance: narrow tube such as vascular access devices.

[Volume per pressure]

[Pressure per ml/h]
Compliance effect

- Compliance: deformation of components at pressure changes
- When we increase the flow rate of a syringe pump, the pressure in the syringe increases
- As a result some parts will deform
  - The plunger of a syringe will be compressed
  - Infusion lines can expand

This is the largest effect. You can see this yourself by pressing against a syringe.
Compliance effect

- Compliance: deformation of components at pressure changes
- When we increase the flow rate of a syringe pump, the pressure in the syringe increases
- As a result some parts will deform
  - The plunger of a syringe will be compressed
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Extra volume is created and will be filled with fluid. This fluid was supposed to enter the patient!
Since some fluid does not reach the patient but is being used to fill the extra volume, our drug administration is delayed.

Besides delays, compliance can also lead other types of dosing errors.

Let's consider two syringes again:
- Blue drug pumping at 1 ml/h
- Red drug pumping at 1 ml/h which we will increase to 2 ml/h

Dosing errors occur when we make a change in the flow rates of one of the pumps.
Compliance effect

• Again we have two pumps:
  – Both are set at a flow rate of 1 ml/h
Compliance effect

- We increase the flow rate of the red pump to 2 ml/h
  - Some red fluid will be stored in the extra volume of the red syringe, because of the increased pressure
  - The flow rate change of the red drug is delayed

Pressure here will increase as well!
We increase the flow rate of the red pump to 2 ml/h
- The pressure in the blue syringe will increase as well
- The blue syringe will also be deformed
• We increase the flow rate of the red pump to 2 ml/h
  – The pressure in the blue syringe will increase as well
  – The blue syringe will also be deformed

Fluid is stored in the extra volume of the blue syringe. The flow rate decreases.
• We increase the flow rate of the red pump to 2 ml/h
  – After a while a new equilibrium is reached

Flow rates are now: 2 ml/h for red. 1 ml/h for blue
Compliance effect

- What happens if we decrease the flow rate of a syringe pump?
Compliance effect

- The syringes will go back to their original volume
  - The drug that was stored in this volume will be administered to the patient

- A delay in decrease for red drug
- An overdose for blue drug
Compliance effect

- Compliance effect is caused by pressure or volume change
  - The higher the resistance to flow, the greater the compliance effect

- Compliance effect causes:
  - Delays in changes in flow rate
  - Dosing error in the pumps where the flow rate is not changed

- Acts in opposite direction as the flow rate change
  - If we **increase** the flow rate of one pump
    - The drug of the other pumps will be administered at a rate that is **too low**
    - The drug of the pump where the flow rate is increased will be administered at a rate that is **too high**
Compliance effect and pressure changes

• Compliance effects are also visible
  – when changing the height of a syringe pump
  – when infusion lines are occluded

• Pumps are typically placed in different heights because users differ in height

• Lines are occluded when the flow is blocked
Conclusion

- Compliance and resistance
  - Delays flow rate change
  - Acts in opposite direction to flow rate change
  - Effects can be caused by pressure
  - If flow rate is low compared to stored volume, the dose effect is large
  - Clinically relevant dosing errors occur mostly at low flow rates and with fast acting drugs with a small therapeutic bandwidth

- Dead volume effect:
  - At flow rate change volume after mixing point, having old concentration ratio
  - acts in same direction as the flow rate change
  - Clinically relevant dosing errors occur mostly at high carrier flow rates and with fast acting drugs with a small therapeutic bandwidth

- For each flow rate change: combination of Dead Volume and Compliance effects
  - Delay in intended administration change
  - Dosing errors contrary to expectations of user
  - Dosing errors in the other pumps as well

Impact of infusion systems

Physical characteristics have an influence on actual flow rate

Dead volume

• effects can cause very serious and even fatal effects, especially in high flow rate critical applications
• Should be taken into account for establishing infusion system performance

System mechanical compliance and resistance

• should be measured, especially for low flow rate applications and for applications using fast acting drugs with a narrow therapeutic bandwidth
• adaptation of standards for critical application should be seriously considered

We still are in desperate need for innovations in infusion devices, mitigating these effects

Problem mitigation

- Decreasing dead volume
- Decreasing compliance
- Use of prediction models
- Education of users

- New infusion lines: InnOfuse

- Adapt materials standards (SIP MeDD project)
- E-learning in cooperation with ESICM

https://academy.esicm.org/course/view.php?id=210
Previous research: Metrology for drug delivery project & support for uptake (MeDD I June 2012-May 2015; SIP MeDD May 2016-April 2019)

Within the MeDD project and always in cooperation with clinicians, we have conducted both quantitative/technical and qualitative research in order to establish the causes of dosing errors in multi-infusion. We found that

• Multi infusion applications, especially of potent, short acting drugs, can cause clinically relevant variations in drug delivery

• Standards on how infusion devices should be used and maintained can contribute to improved stability and accuracy of medication dosage in multi-infusions

• Besides technical innovations we find that education to clinicians about the ambiguous effects can prevent or mitigate the dosing errors.

• We aim to provide this education by developing an E-learning with ESICM as its primary supporter. [https://academy.esicm.org/course/view.php?id=210](https://academy.esicm.org/course/view.php?id=210) Workshop is offered.
Research outlook

- Improve measurement and calibration of multi-infusion setups: MeDD II proposal:
- **SRT-h18**: [Metrology for drug delivery](#)
- Exploring new possibilities for solving system dead volume and compliance
- Providing E-learning workshops for multi infusion users (specialised nurses and doctors)
Take home
Impact of infusion setups on drug delivery

• Dead volume effects can lead to dosing errors that are potentially very dangerous
• Compliance effects cause clinically relevant dosing deviations that are counter intuitive
• There still is a need for technical solutions to mitigate these effects
• Using simulations based on analytical methods can help predict what is actually happening in multi-infusion
• Changing standards for infusion component compliance and creating awareness amongst users via E-learning workshops can help us create safer infusion
Researchers involved in infusion

Prof. Dr. A.C.G. Egberts (Toine), Head of Pharmacy, medication management
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Dr. P. Lemmers (Petra) MD PhD, Associate professor in Neonatology, perinatal neurology

Dr. Ir. A.M.D.E. Timmerman (Annemoon), Medical Physicist, Infusion medical physics
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Dr. Ir. J.E.N. Jaspers (Joris), Associate professor labour saving devices,
Head of Innovation, MTKF Dpt

Dr. M.K. Konings (Maurits), Senior Research Physicist, inventor of medical devices MTKF Dpt

Ir. B. Riphagen (Brechtje), Entrepreneur, owner of Innofuse

Dr. Ir. R.A. Snijder (Roland), Biomedical Engineer, PhD

Ir. P.P.A. Klaver (Paul), Clinical Physicist, clinical research
• Yes it can. This is called back flow

- The drugs from the red syringe will flow into the blue syringe

- The blue syringe is deformed

It is hard to calculate the flow rate to the patient

It is hard to calculate the flow rate of the back flow