UMC Utrecht

Motivation and Clinical Relevance

Metrology for Drug Delivery

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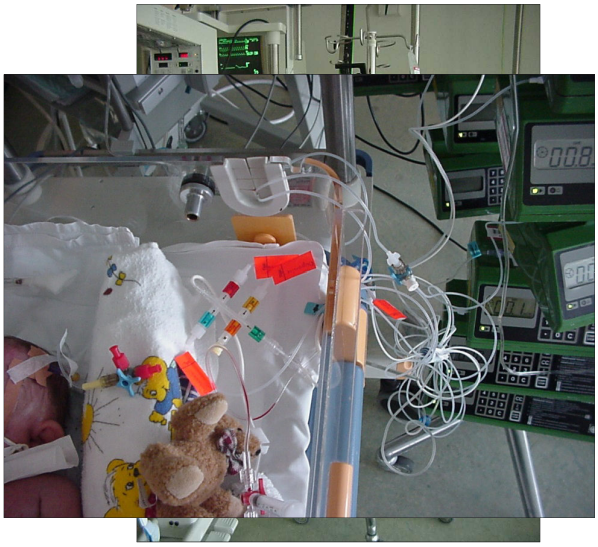
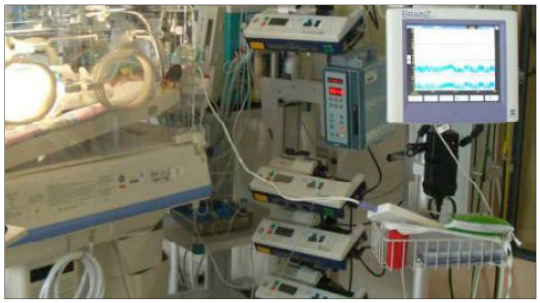
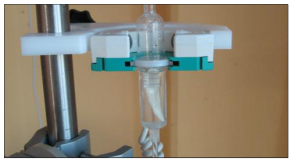
The Clinical Cause

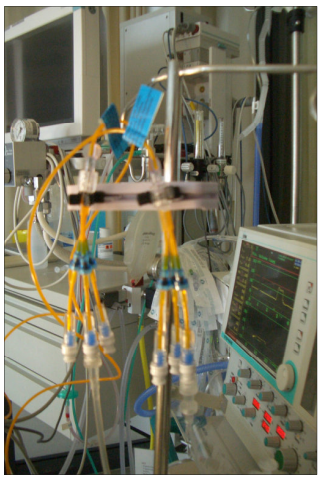


- Infant with acute blood pressure problem
- Dopamine infused to raise blood pressure
- No result
- Increasing dopamine flow rate
- No result
- Increasing dopamine again
- Overshoot
- No relation found with dopamine setpoint
- Decreasing dopamine flow rate
- No result
- Etc..

Clinical relevance: widespread use of infusion

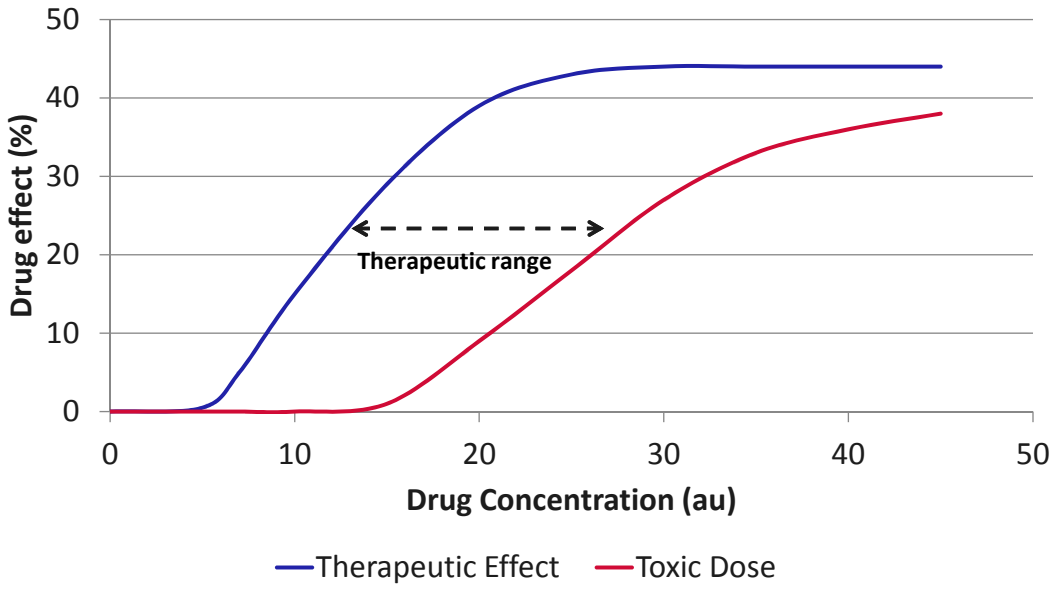






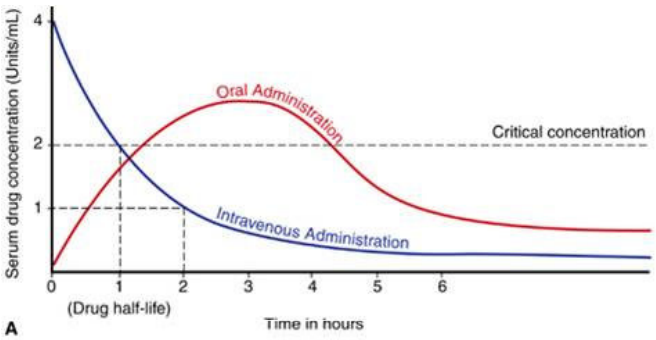
- Almost every patient receives IV Therapy
- Many different applications
- Many users
- Many errors/ adverse events
- Potentially high impact

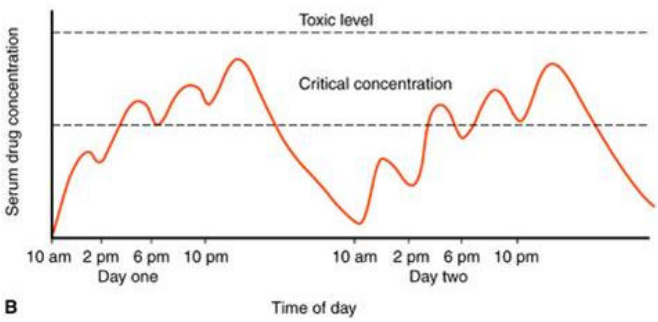
Therapeutic range



Small therapeutic range: Set point deviations are more relevant

Half life of drugs





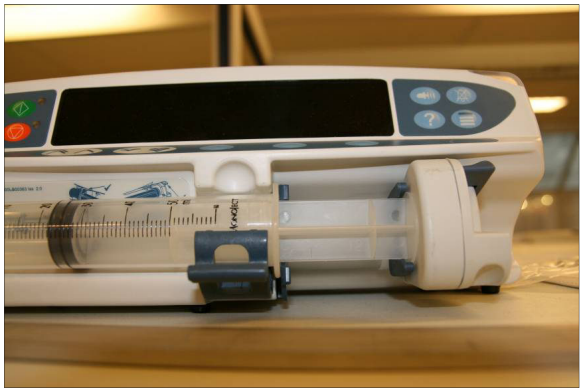
- Serum concentration is determined by
  - Administered dose
  - Half life of drug
- Short half life drugs
  - can be more easily controlled in theory
  - are more sensitive to dose/ flowrate changes

http://www.nursingbuddy.com/wp-content/uploads/2011/02/nursingbuddy.com-nursing-pharmacology-Half-life.jpg

Clinical relevance of flow rate accuracy

- Small therapeutic range
- Small drug half life
  - Vasopressors
  - Inotropics
  - Certain anesthetics
- Condition of the patient
  - Fluid intake restriction
- Drug concentration

Control mechanism infusion



Driving mechanism:

- Displacement of plunger by step motor

Control mechanism

- Change in step motor velocity

Setpoint parameter

- Flow rate

Non plunger displacement induced flowrate changes are not noticed by the system

→ poor measurability

→ poor controllability

Standards and regulations

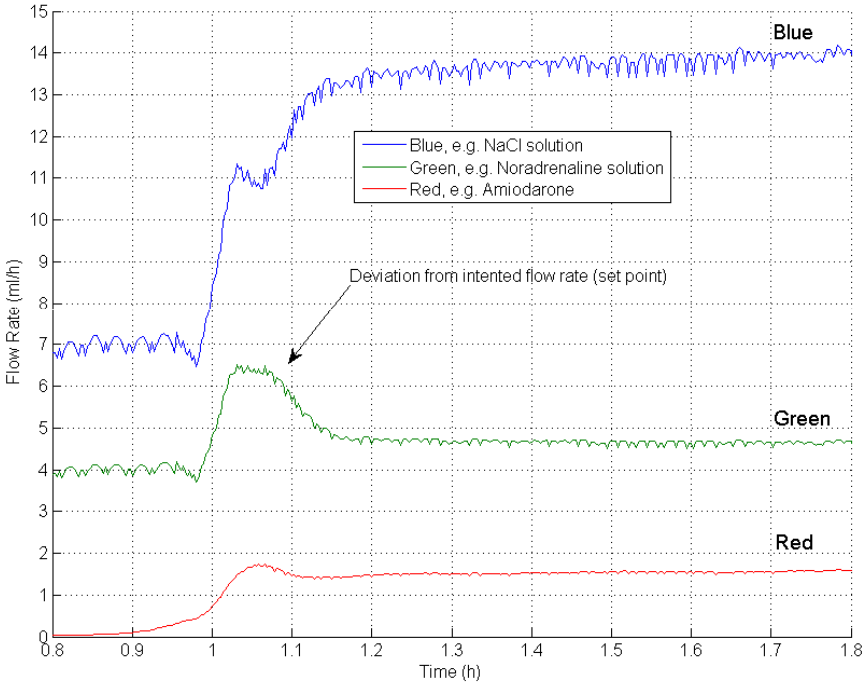
- Pumps: IEC/EN 60601-2-24
  - Describes “trumpet curve”
- Syringes: ISO 7886-2
  - Describes maximum compliance (compressibility)
  - Describes maximum “dead volume”

➡ No specific regulations for low flowrate/ specific applications

➡ No protocols describing maximum internal volume

➡ No output measurements of entire system (pump+syringe+infusion line and catheter)

In-vitro experiment : “push-out” effect

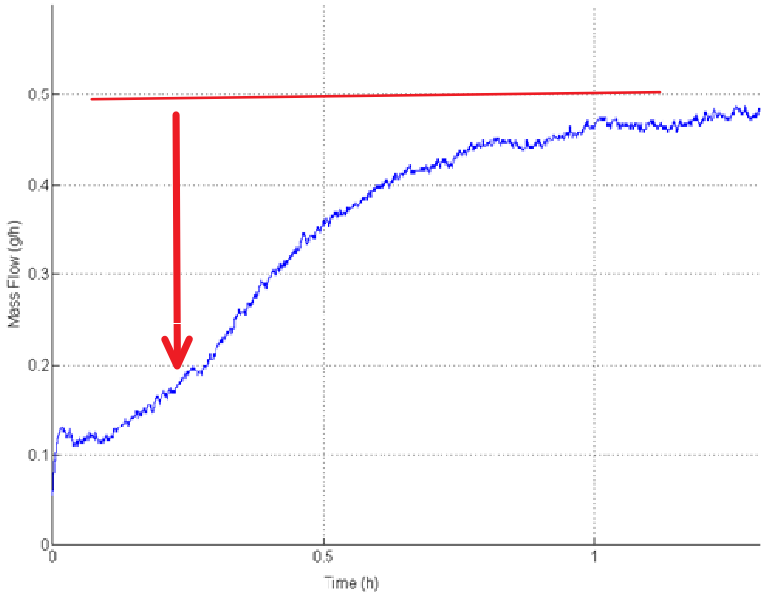


Blue : Set point increased

Green: “push-out effect”

Same direction

In-vitro experiment : “compliance” effect



Blue :
Set point
increased

Red :
Compliance
Effect
Opposite direction

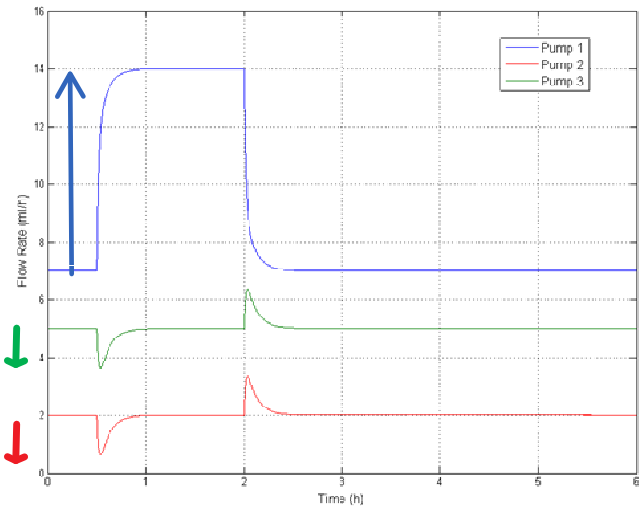
- Mass flow rate
- System compliance results in start up time

- This time is long enough to cause thrombosis

Computer simulation (method)

- Schematic representing a multi-infusion set-up with N pumps. Network Q1, Q2 .. Qn are sources (pumps). qn is the flow rate output of pumpn- (before the mixing point)
- Electric analogue for multi-infusion setup to simulate the outflow
- Standard analytical methods (Laplace domain)
- System of 3 pumps was calculated

Results of computer simulation (compliance effect)



- initial situation : steady state values
- At t=0.5, pump #1 is set to 14
- the flow rates of the parallel pumps #2 and #3 react to the pressure difference caused by the flow rate changes of pump #1, in the form of altered storage of fluid in the compliance (capacitor effect) of the (plunger of the) syringe

↓ ↓ **Equal lengths**

Combining the results

In-vitro experiment :
"push-out" effect

↑ Blue : Set point increased

↑ "push-out effect" ***Same direction***

In-vitro experiment :
compliance effect

↑ Blue : Set point increased

↓ compliance effect ***Opposite direction***

Computer simulation :
compliance effect

↑ Blue : Set point increased

↓ compliance effect ***Opposite direction***

↓ **Equal lengths**

Implications of results 1

↑ "push-out effect"
Same direction

↓ compliance effect
Opposite direction

Mathematical fact :

IF :

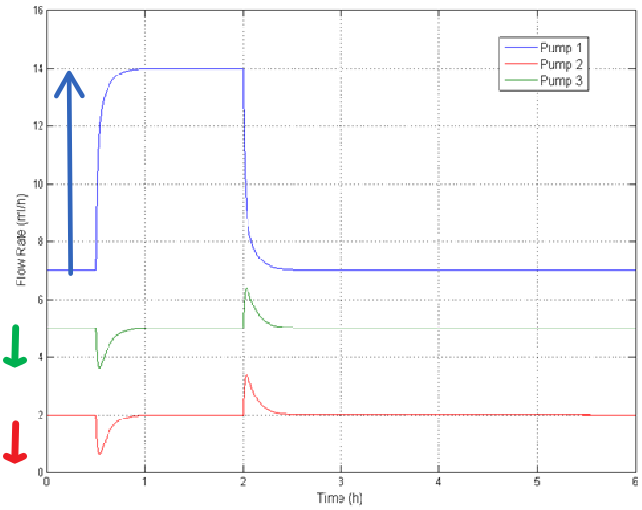
- Two opposite effects that play a role
- Effects may be of same order of magnitude
- Strength of effects depends on many factors

⇒ **THEN**

Direction and strength of total net result may be hard to predict and counter-intuitive

Implications of results 2

Results of computer simulation (compliance effect)



↓ ↓ **Equal lengths (absolute : ml/h)**

⇓ **implies**

Impact on "red" medication *relatively* high as a *percentage* of the red set point value

Discussion

- The in-vitro experiments, as well as the computer simulation, of a 3-pump multi-infusion set-up, show:
- Internal volume effect produces a deviation in *the same direction* as the direction of the change in flow rate set point (of another pump, e.g. the "blue" pump),
- Syringe compliance effect produces a deviation in *the opposite direction* with respect to the direction of the flow rate set point change
- Syringe compliance effects are particularly important at low flow rates
- At low flow rates, deviations have a higher clinical relevance

Conclusions

- In-vitro experiments as well as computer simulations show that the direction as well as the strength of the net compound deviations in multi-infusion are highly unpredictable and often counter-intuitive.
- Accurate measurement of the mechanical compliances in the multi-infusion set-up adds to controllability and thus to safety
- Increased focus and effort should be directed to the metrology of mechanical compliances at low flow rates.
- Regulation concerning mechanical compliances should be updated and more strictly specified, especially for low flow rates

Disclaimer

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