When the solution becomes the problem: particulate formation in piperacillin/tazobactam continuous infusion

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Background

Continuous infusion (CI) of piperacillin/tazobactam (TZP) 16/2 g over 24h is attractive for

1. **OPAT** using elastomeric pumps
2. **Hospitalised patients requiring optimised dosing**, such as critically ill/obese patients, or patients infected with microorganisms needing increased exposure

Observed problem following implementation:

1. *Incomplete infusions through elastomeric pumps with a relevant dose not administered*
2. *Occurrence of thrombophlebitis*

➢ ***Particulate formation was hypothesised and investigated***

Methods

Several batches and brands of TZP in different concentrations and at different storage conditions were checked after 24h for:

- **Particulate formation** by visual inspection
- **pH** by using pH meter
- **Stability** by using HPLC-UV
  - Initial concentration measured immediately after diluting TZP was taken as 100%; stability was expressed as a % of this initial concentration

Table 1. *Overview of particulate formation, pH and stability (after 24h) of TZP from several batches and brands in different concentrations and storage conditions*

Batch (brand)	Tested concentration piperacillin (diluted in NaCl 0,9%)	pH at 0h	After 24h			
			Storage condition	Visual test[1]	pH[2]	Content piperacillin[3] (%)
18U2775 (Fresenius Kabi)	**88.9 mg/mL** (equivalent to 16 g/ 180 mL[4])	5.7	4°C	Clear	5.6	99.6
			22°C	Clear	5.2	96.3
			33°C	Clear	5.1	95.1
18X0328 (Fresenius Kabi)	**88.9 mg/mL**	**5.3**	4°C	Clear	5.3	99.8
			22°C	Precipitation	5.2	95.9
			33°C	Precipitation	5.0	90.7
18X4227 (Fresenius Kabi)	**32 mg/mL**	**5.1**	33°C	Precipitation	4.7	94.6
	40 mg/mL	**5.1**	33°C	Precipitation	4.8	94.1
	64 mg/mL (equivalent to 16 g/ 250 ml[5])	**5.1**	22°C	Precipitation	5.1	*Not analysed*
			33°C	Precipitation	5.0	*Not analysed*
	80 mg/mL	**5.2**	33°C	Precipitation	5.1	86.7
	88.9 mg/mL	**5.2**	33°C	Precipitation	5.1	81.4
18X3055 (Fresenius Kabi)	**64 mg/mL**	5.7	22°C	Clear	5.2	*Not analysed*
			33°C	Clear	5.0	*Not analysed*
	88.9 mg/mL	5.7	33°C	Clear	5.0	95.4
2251534BE (Mylan)	**88.9 mg/mL**	5.8	33°C	Clear	5.0	94.2
2220570BE (Mylan)	**88.9 mg/mL**	5.6	33°C	Clear	5.0	93.6
2251587BE (EG)	**88.9 mg/mL**	6.1	33°C	Clear	4.9	95.0
MN8288 (Sandoz)	**88.9 mg/mL**	5.9	33°C	Clear	4.9	95.0
220834 (Bidiphar)	**88.9 mg/mL**	5.5	33°C	Clear	4.8	92.3

[1]Visual inspection according to European pharmacopoeia
[2]Using pH meter to measure pH of the solutions, according to European pharmacopoeia
[3]Expressed as % of initial concentration, measured immediately after dilution
[4]Dosing and concentration applied in OPAT with administration through elastomeric pump
[5]Dosing and concentration applied in hospitalised patients with administration through infusion bag

Results

Table 1:

- Immediately after dilution (0h): **different initial pH values** observed in different batches (range: 5.1 - 6.1)
- Solutions with an **initial pH < 5.5** led to precipitation after 24h at 22°C & 33°C
- In solutions obtained from batch 18X4227, piperacillin (80 and 89 mg/mL) **significantly degraded to 86.7% and 81.4%** after 24h at 33°C

➢ *This supports the hypothesis that particulate formation is related to the β-lactam ring opening, accelerated by acidic pH, and followed by piperacillin molecules dimerisation*

For batch 18X4227, analyses were repeated at different concentrations at 33°C with check of particulate formation, pH and stability **at different time points:**

- No particulate formation + stability maintained after 3h for piperacillin concentrations up to 80 mg/mL
- No particulate formation + stability maintained after 18h for piperacillin concentrations up to 40 mg/mL

Measures to be taken to avoid particulate formation

- Manufacturing: modification of pH requirements for piperacillin in European Pharmacopeia (pH > 5.5 – 7 instead of pH 5 – 7)
- Procurement: procurement of TZP brands and batches with pH > 5.5 at batch release
- Administration in OPAT / hospitalised patients
  - ➢ **CI of TZP 16 g/ 24h only with batches with pH > 5.5 at batch release**
    - ➢ Alternative: CI of TZP 8 g (in 250 ml NaCl 0,9%) over 12h q12h or 4 g (in 100 ml NaCl 0,9%) over 3h q6h
  - ➢ Awareness for and immediate reporting of particulate formation
  - ➢ Awareness for and immediate reporting of incomplete elastomeric infusion over 24h: follow-up of pump weight at 24h to calculate remnant dose
  - ➢ Awareness for and immediate reporting of thrombophlebitis