

# STABILITY AND COMPATIBILITY OF VANCOMYCIN FOR ADMINISTRATION BY CONTINUOUS INFUSION.



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## Background

- Vancomycin is increasingly used by continuous infusion but few specific data is available about stability under practical conditions of preparation and use and compatibility with other intravenous drugs commonly used in routine hospital setting.

## Methods

- Vancomycin stability (defined as recovery .93% of the original content [validated HPLC assay]) was examined for the whole process of centralized preparation, storage, and use in the ward by infusion for up to 48 h, with allowances for deviations of recommended practice (exposure to high temperature; use of concentrated solutions [up to 83 g/L]).
- Compatibility was assessed by mimicking co-administration in a single line via Y-shaped connectors with contact of 30 min at 25°C, followed by visual inspection in professional viewer, detection of particulate matter (particle analyzer), and HPLC assay of vancomycin.

## Results

- Vancomycin was stable during the whole process and also during 72 h exposure of concentrated solutions at temperatures up to 37°C.
- Major incompatibilities were seen with -lactams (temocillin, piperacillin/tazobactam, ceftazidime, imipenem, cefepime, flucloxacillin) and moxifloxacin but not with ciprofloxacin, aminoglycosides and macrolides.
- Propofol, valproic acid, phenytoin, theophyllin, methylprednisolone, and furosemide were also incompatible,
- Ketamine, sufentanil, midazolam, morphine, piritramide, nicardipine, uradipil, dopamine, dobutamine, and adrenaline were compatible.
- No effect of N-acetyl-cystein or aminoacid solutions was detected.

**Table 1:** Compatibility of vancomycin with other drugs under conditions mimicking their co-administration through the same infusion line\*

| Drug  | Dose (mg) <sup>a</sup> | Volume per administration (ml) | Time of infusion (h) | drug: vancomycin weight ratio <sup>c</sup> | Results <sup>d</sup>  |
|---|------------------------|--------------------------------|----------------------|--|-----------------------|
| <b>Antibiotics</b>  |                        |                                |                      |  |                       |
| temocillin  | 2000                   | 20                             | 0.33                 | 12.63                                      | i (phys)              |
| piperacillin/tazobactam   | 4000                   | 20                             | 0.33                 |  | i (phys)              |
| ceftazidime   | 6000                   | 48                             | 24                   |  | i (phys)              |
| imipenem  | 1000                   | 40                             | 0.5                  |  | i (phys)              |
|   | 1000                   | 200                            | 0.5                  |  | i (phys)              |
| cefepime  | 4000                   | 48                             | 24                   |  | c <sup>e</sup>        |
|   | 2000                   | 10                             | 0.33                 |  | i (chem)              |
| flucloxacillin  | 1000                   | 4                              | 0.33                 | 6.31                                       | i (phys)              |
| amikacin <sup>g</sup>   | 1500                   | 100                            | 0.25                 | 25.25                                      | c                     |
| tobramycin <sup>g</sup>   | 600                    | 100                            | 0.25                 | 10.1                                       | c                     |
| gentamicin <sup>g</sup>   | 600                    | 100                            | 0.25                 | 10.1                                       | c                     |
| ciprofloxacin   | 400                    | 200                            | 1                    |  | c                     |
| moxifloxacin  | 400                    | 250                            | 1                    |  | i (chem)              |
| erythromycin  | 100                    | 20                             | 0.33                 |  | c                     |
| clarithromycin  | 500                    | 10                             | 0.33                 | 6.31                                       | c                     |
| fluconazole   | 200                    | 100                            | 0.5                  |  | c                     |
| <b>Sedatives / Anticonvulsants / Analgesics</b>   |                        |                                |                      |  |                       |
| ketamine  | 480                    | 48                             | 24                   |  | c                     |
| sufentanil  | 0.12                   | 24                             | 24                   | 2.1 × 10 <sup>-5</sup>                     | c                     |
| midazolam   | 600                    | 120                            | 24                   | 0.11                                       | c                     |
| morphine  | 5                      | 5                              | 1                    | 0.02                                       | c                     |
| piritramide   | 10                     | 5                              | 1                    | 0.04                                       | c                     |
| propofol  | 300                    | 300                            | 24                   |  | i (phys) <sup>g</sup> |
| valproic acid   | 1200                   | 12                             | 24                   | 0.21                                       | i (phys)              |
| phenytoin   | 750                    | 15                             | 0.25                 | 12   | i (phys)              |
| <b>Bronchodilators</b>  |                        |                                |                      |  |                       |
| theophylline  | 200                    | 10                             | 0.33                 | 2.39                                       | i (phys)              |
| <b>Antihypertensives, vasodilators and drugs acting on the sympathetic nervous system</b> |                        |                                |                      |  |                       |
| nicardipine   | 120                    | 120                            | 24                   | 0.02                                       | c                     |
| uradipil  | 2400                   | 480                            | 24                   | 0.42                                       | c                     |
| isosorbide dinitrate  | 6                      | 30                             | 1                    | 0.02                                       | c                     |
| furosemide  | 960                    | 96                             | 24                   | 0.17                                       | i (phys)              |
| dopamine  | 0.4                    | 1                              | 0.016                | 0.1  | c                     |
| dobutamine  | 0.84                   | 0.84                           | 0.016                | 0.21                                       | c                     |
| adrenaline  | 0.5                    | 10                             | 0.33                 | 0.0063                                     | c                     |
| <b>Hormones</b>   |                        |                                |                      |  |                       |
| insulin   | 60 UI                  | 0.6                            | 3                    | 0.08 UI/mg                                 | c                     |
| methylprednisolone  | 500                    | 10                             | 0.5                  | 4.0  | i (phys)              |
| <b>Miscellaneous</b>  |                        |                                |                      |  |                       |
| N-acetylcystein   | 10000                  | 100                            | 24                   | 1.74                                       | c                     |
| amino acid solution <sup>h</sup>  | 18000                  | 1000                           | 24                   | 3.16                                       | c                     |

\* see ref. 14 for a general description of the methods

<sup>a</sup> calculated (when appropriate) for a 70 kg male subject

<sup>b</sup> in final infusion

<sup>c</sup> Key: c, chemically and physically compatible; i, incompatible; phys, physically incompatible (precipitate, flocculation and/or presence of particles as evidenced by passing solutions through a particle analyzer); chem, chemically incompatible less than 90% recovery (> 10% loss of antibiotic compared to nominal content).

<sup>d</sup> assuming a once-a-day schedule (30 min infusion)

<sup>e</sup> physically and chemically compatible, but degradation of cefepime limits its stability to 24h at 25°C, 14h at 30°C, and <1h at 37°C (see reference 15)

<sup>f</sup> trapping in emulsion

<sup>g</sup> VAMIN® (standard amino acid solution for parenteral nutrition, 16 g aminoacid nitrogen/L)

## Conclusion

- Centralized preparation of vancomycin and its use by continuous infusion in wards is safe concerning stability,
- Careful attention must be paid for incompatibilities with several drugs (including all -lactams), requiring distinct intravenous lines or appropriate procedures to avoid undue contact.



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