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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 are available about stability under practical conditions of preparation and use, and compatibility with other intravenous drugs commonly used in the routine hospital setting.

Methods: Vancomycin stability [defined as recovery ≥93% of the original content (validated HPLC assay)] was examined throughout the whole process of centralized preparation, storage and use in the ward by infusion for up to 48 h, with allowances for deviations from 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 1 h at 25°C, followed by visual inspection (professional viewer), detection of particulate matter (particle analyser) 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 β-lactams (temocillin, piperacillin/tazobactam, ceftazidime, imipenem, cefepime and flucloxacillin) and moxifloxacin, but not with ciprofloxacin, aminoglycosides and macrolides. Propofol, valproic acid, phenytoin, theophylline, methylprednisolone and furosemide were also incompatible, whereas ketamine, sufentanil, midazolam, morphine, piritramide, nicardipine, urapidil, dopamine, dobutamine and adrenaline were compatible. No effect or incompatibility with *N*-acetylcysteine or amino acid solutions was detected.

Conclusions: Centralized preparation of vancomycin and its use by continuous infusion in wards is safe concerning stability, but careful attention must be paid to incompatibilities. Several drugs (including all β-lactams) require distinct intravenous lines or appropriate procedures to avoid undue contact.

Keywords: European Pharmacopoeia, β-lactams, propofol, valproic acid, phenytoin, theophylline, methylprednisolone, furosemide

Introduction

Vancomycin is increasingly used by continuous infusion because of facilitated monitoring (sampling time is not critical after the first loading dose, making interpretation of blood levels and pharmacokinetic calculations easier), potential decreased toxicity, easier nursing and the possibility of centralized preparation of ready-to-use solutions.[1–4] To safely implement this mode of administration in a routine hospital setting it is, however, essential to ensure that vancomycin remains stable over the whole process and that incompatibilities with other medications co-administered by the intravenous route are avoided. Vancomycin has been repeatedly reported to be stable in various media for several days (see Nornoo and Elwell,[5] LaPlante *et al.*[6] and Dotson *et al.*[7]), but few studies have been performed in the actual conditions of its clinical use, including potentially accidental exposure to high temperatures. Concerning compatibility, vancomycin is notorious for being incompatible with several β-lactams,[8–10] but few studies have examined other antibiotics or other commonly used drugs that are administered by the intravenous route in routine clinical practice.

In preparation for the implementation of continuous infusion of vancomycin in all non-intensive care unit wards of a 400 bed hospital, we initiated a study in which: (i) the stability of the drug

under the actual conditions of its use in patients (from its preparation in the Central Pharmacy to the end of the infusion) and after exposure to high temperatures was measured; and (ii) its compatibility with other drugs was tested *in vitro* using conditions mimicking their use in patients.

Materials and methods

Stability studies

These studies reproduced exactly the projected conditions of use of vancomycin by continuous infusion in our hospital. Hence, vancomycin (Vancocin®; Lilly, Illkirch, France) solutions (10 g/L in 5% glucose) were prepared in 250 mL VIAFLO® polyolefin bags (coextruded layers of polyethylene, polyamide, polypropylene; Baxter s.a., Lessines, Belgium) and stored at 4°C (for a maximum of 58 days; tested previously for stability[11]) until transferred to the ward where they were maintained in a domestic refrigerator (~4°C) until about 15 min before use. Patients were infused at a rate of 11 mL/h if they had normal renal function (lower and higher rates were used in case of decreased or increased calculated CL_{CR}). The infusion was made with the bag exposed to uncontrolled room temperature and normal light for typically 24 h, but for up to 48 h for patients requiring low infusion rates. At the end of the infusion, the amount of fluid remaining in the bags was collected and assayed for vancomycin content. In parallel, samples of concentrated solution of vancomycin (up to 83 g/L) were incubated at increasing temperatures up to 50°C and for up to 72 h to mimic situations that might cause an accelerated degradation such as: (i) the administration of vancomycin from motor-operated syringes (commonly used in several clinical set-ups and requiring the use of concentrated solutions); or (ii) accidental exposure to high temperatures during storage, transport and use.

Compatibility studies

For this study, drugs recommended for administration by the intravenous route were selected for: (i) their common association with vancomycin in clinical practice (antibiotics and antifungals); (ii) their common use in a hospital setting; and/or (iii) their known potential for incompatibility gained from an analysis of current databases.[12,13] We used a protocol similar to that used by us for the study of the compatibility of β-lactam antibiotics with other drugs that mimic the conditions of their use when co-administered through the same line from two distinct containers via a Y connector.[14,15] In brief, a solution of vancomycin at a concentration corresponding to its nominal concentration used in continuous infusion (10 g/L) was mixed with an equal volume of each of the tested drugs prepared at a concentration corresponding to its most common clinical use (taking into account the recommended concentration and time of infusion, as per the corresponding drug label; see Table 1). The mixtures were then kept at 37°C for 1 h to mimic what could happen if the infusion flow was stopped for that period. The solutions, transferred to glass vials, were then examined with the naked eye for signs of physical incompatibility (e.g. precipitation, flocculation) or colour change using an Allen LV28 Liquid Viewer (PW Allen & Co. Ltd, Tewkesbury, UK) operated with two polarizing filters and compared with a pure solution of vancomycin and distilled water. Solutions were thereafter tested for the presence of non-visible particles by passing them through a particle analyser [Sub Micron Particle Analyser COULTER N 4 MD (Coulter Corp., Miami, FL, USA)] with a threshold set at twice the value of a pure solution of vancomycin. Chemical compatibility was assessed by determining the vancomycin content in comparison with an untreated sample.

Vancomycin assay and criteria for stability

We used a validated HPLC method with UV detection (diode array analysis for confirmation of the absorption spectrum) as described in detail in a previous publication[16] (but without the serum extraction procedure steps) and using pure, untreated vancomycin (vancomycin hydrochloride hydrate; Sigma-Aldrich, St Louis, MO, USA) as an external standard. Stability was defined as <7% disappearance of the signal in a treated sample compared with an untreated control, in compliance with the provisions of the seventh Edition of the European Pharmacopoeia (online version) concerning the acceptable limit of content of vancomycin preparations (93%).[17]

Ethical approval

The protocol of this study (with respect to drug administration to patients) was approved by the Ethics Committee of the hospital in which the study was performed (CHU Mont-Godinne; internal number EC Mont-Godinne: 48/2007; unique Belgian number: B03920072246).

Results

The concentration of vancomycin in the remaining fluid of the infusion sets after up to 48 h was 10.1 g/L ($n=20$; range: 9.6–10.3 g/L) compared with the initial nominal concentration of 10 g/L, thus complying with the provisions of the European Pharmacopoeia (>93%). Concentrated vancomycin solutions (up to 83 g/L) suffered <5% degradation when kept for 72 h at up to 37°C. Only samples exposed to 50°C showed >7% degradation.

Table 1 shows the results of the compatibility studies. For anti-infectives, four out of the five β-lactams with activity against Gram-negative bacteria tested (temocillin, piperacillin/tazobactam, ceftazidime, imipenem) were incompatible. Cefepime was physically and chemically compatible when mimicking its administration by continuous infusion (but its degradation was >10% after 24 h at 25°C and after 14 h at 30°C and <10 h at 37°C) and chemically incompatible when mimicking its thrice-daily administration. Flucloxacillin was also incompatible. Conversely, all three aminoglycosides tested (amikacin, tobramycin and gentamicin) were compatible. Among the fluoroquinolones, ciprofloxacin was compatible, but moxifloxacin was chemically incompatible. Macrolides (erythromycin and clarithromycin) and fluconazole were compatible.

For other drugs commonly used in hospitalized patients, sedatives (ketamine, sufentanil, midazolam, morphine and piritramide), antihypertensives (nicardipine and urapidil) and vasopressive drugs (dopamine, dobutamine and adrenaline) were all compatible. In contrast, propofol (mostly used as a hypnotic, but also for procedural sedation), valproic acid and phenytoin (anticonvulsants), theophylline (bronchodilator), methylprednisolone (glucocorticoid) and furosemide (diuretic) were all physically incompatible. In contrast to what had been observed with β-lactams,[14,15] *N*-acetyl-cysteine (used as an antioxidant in cases of paracetamol intoxication) did not cause alteration of vancomycin and nor did amino acid solutions (used for parenteral nutrition).

Discussion

This study is the first, to our knowledge, to systematically assess the stability and compatibility of vancomycin in conditions directly pertinent to its use by continuous infusion in hospitalized patients, with solutions kept at room temperature without replacement for up to 48 h and with attention paid to other drugs that could be co-administered through the same infusion

Table 1. Compatibility of vancomycin with other drugs under conditions mimicking their co-administration through the same infusion line; items shown in bold correspond to conditions of incompatibility[a]

Drug	Dose (mg)[b]	Volume per administration (mL)	Time of infusion (h)	Drug:vancomycin weight ratio[c]	Results[d]
Anti-infectives					
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[e]
	2000	**10**	**0.33**		**i (chem)**
flucloxacillin	**1000**	**4**	**0.33**	**6.31**	**i (phys)**
amikacin[f]	1500	100	0.25	25.25	c
tobramycin[f]	600	100	0.25	10.1	c
gentamicin[f]	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
Sedatives/anticonvulsants/analgesics					
ketamine	480	48	24		c
sufentanil	0.12	24	24	2.1×10^{-5}	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)**[g]
valproic acid	**1200**	**12**	**24**	**0.21**	**i (phys)**
phenytoin	**750**	**15**	**0.25**	**12**	**i (phys)**
Bronchodilators					
theophylline	**200**	**10**	**0.33**	**2.39**	**i (phys)**
Antihypertensives, vasodilators and drugs acting on the sympathetic nervous system					
nicardipine	120	120	24	0.02	c
urapidil	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
Hormones					
insulin	60 IU	0.6	3	0.08 IU/mg	c
methylprednisolone	**500**	**10**	**0.5**	**4.0**	**i (phys)**
Miscellaneous					
N-acetyl-cysteine	10000	100	24	1.74	c
amino acid solution[h]	18000	1000	24	3.16	c

[a]See Servais and Tulkens[14] for a general description of the methods.
[b]Calculated (when appropriate) for a 70 kg male subject.
[c]In final infusate.
[d]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 analyser); chem, chemically incompatible—less than 93% recovery (>7% loss of antibiotic compared with nominal content).
[e]Physically and chemically compatible, but degradation of cefepime limits its stability to 24 h at 25°C, 14 h at 30°C and <10 h at 37°C (see Baririan *et al.*[15]).
[f]Assuming a once-daily schedule (30 min infusion of the total daily dose).
[g]Trapping in emulsion.
[h]VAMIN® (standard amino acid solution for parenteral nutrition; 18 g of amino acid nitrogen/L).

line. The experimental set-up included conditions that could be accidentally encountered, such as exposure to high temperatures and prolonged contact of drugs in the infusion set in cases of flow arrest. While this may lead to overestimation of risk, it also heralds conditions that clinicians may need to carefully assess when dealing with specific situations and a patient's therapeutic needs. This is particularly important for incompatibilities with the anti-Gram-negative β-lactams (all classes). These antibiotics are indeed commonly associated with vancomycin in empirical therapies of severe infections. Incompatibility of vancomycin with ceftazidime,[18] cefpirome,[19] cefotaxime[9] and ceftriaxone[8] has already been described, but not studied in the context of continuous infusion of vancomycin. Although incompatibilities with β-lactams are often described as concentration dependent (as seen for cefepime here and reported for aztreonam[20]), only very diluted solutions (down to 1 g/L) appear safe in this context, making these drugs quite difficult to use in practice. Thus, β-lactams should be considered as incompatible with vancomycin for all practical purposes, and their administration, if therapeutically needed, must imply specific measures such as the use of independent lines or multiple-way catheters, or the temporary suspension of the vancomycin infusion. Alternative anti-Gram-negative antibiotics such as aminoglycosides or ciprofloxacin may also offer a viable solution.

Globally speaking, the other incompatibilities detected are scattered among pharmacological classes without evidence of a specific relation to structure or biophysical properties. However, the number of drugs tested is limited. The main message is, therefore, that clinicians will need to request specific compatibility tests for all other drugs not mentioned here that they intend to use for specific patients. In this context, efforts coordinating various sources of information such as those appearing in monographs[13] or developed for online use (http://www.stabilis.org) represent a useful development. It will, nevertheless, remain essential for practitioners to determine whether the conditions of testing actually apply to their projected use of the drug and, if not, to undertake the appropriate studies.

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Transparency declarations

None to declare.

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