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ARTICLE

A survey of beta-lactam antibiotics and vancomycin dosing strategies in intensive care units and general wards in Belgian hospitals

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Abstract Extended and continuous infusions with beta-lactam antibiotics have been suggested as a means of pharmacokinetic and pharmacodynamic optimisation of antimicrobial therapy. Vancomycin is also frequently administered in continuous infusion, although more for practical reasons. A survey was undertaken to investigate the recommendations by the local antibiotic management teams (AMTs) in Belgian acute hospitals concerning the administration (intermittent, extended or continuous infusion) and therapeutic drug monitoring of four beta-lactam antibiotics (ceftazidime, cefepime, piperacillin–tazobactam, meropenem) and vancomycin for adult patients with a normal kidney function. A structured questionnaire survey comprising three domains was developed and approved by the members of the Belgian Antibiotic Policy Coordination Committee (BAPCOC). The questionnaire was sent by e-mail to the official AMT correspondents of 105 Belgian hospitals, followed by two reminders. The response rate was 32 %, with 94 %, 59 %, 100 %, 100 % and 100 % of the participating Belgian hospitals using ceftazidime, cefepime, piperacillin–tazobactam, meropenem and vancomycin, respectively. Comparing intensive care unit (ICU) with non-ICU wards showed a higher implementation of extended or continuous infusions for ceftazidime (81 % vs. 41 %), cefepime (35 % vs. 10 %), piperacillin–tazobactam (38 % vs. 12 %), meropenem (68 % vs. 35 %) and vancomycin (79 % vs. 44 %) on the ICU wards. A majority of the hospitals recommended a loading dose prior to the first dose. For vancomycin, the loading dose and the trough target concentration were too low based on the current literature. This survey shows that extended and continuous infusions with beta-lactams and vancomycin are widely implemented in Belgian hospitals.

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Introduction

Beta-lactam antibiotics and vancomycin are commonly used to treat severe infections. Beta-lactams exhibit time-dependent killing, with minimal or no persistent effects with the time during which their free concentration remains above the minimum inhibitory concentration (MIC) ($fT >$ MIC) being the main pharmacokinetic/pharmacodynamic (PK/PD) index of efficacy. Vancomycin also has time-dependent killing, but shows moderate to prolonged

persistent effects, which makes the area under the concentration–time curve (AUC)/MIC ratio its main PK/PD index for efficacy [1].

Time-dependent killing antibiotics would, theoretically, benefit from continuous administration, and animal as well as in vitro studies have shown improved efficacy when using extended or continuous infusions [1]. A systematic review concluded that the continuous administration of beta-lactam antibiotics is not associated with an improvement in clinical cure or in decreased mortality, but the authors pointed out that the wide confidence intervals observed in this analysis did not allow excluding true differences between both forms of administration [2]. A systematic review focusing on continuous versus intermittent infusion of vancomycin showed that continuous infusion is not associated with differences in mortality but with a significantly lesser risk of nephrotoxicity [3]. Wysocki et al. also found that target concentrations were reached faster with continuous infusion and that there was lesser variability in the AUC_{24h} values [4].

In this context, a survey was undertaken in Belgium to gain knowledge about which recommendations were made by the local Antibiotic Management Teams (AMTs)[1] regarding dosing strategy (intermittent, extended or continuous infusion) and therapeutic drug monitoring of four beta-lactam antibiotics (ceftazidime, cefepime, piperacillin–tazobactam, meropenem) and vancomycin in adult patients with a normal kidney function.

Methods

A structured questionnaire survey covering three domains was developed: (1) hospital and contact information; (2) a form for each antibiotic about the dosing regimen, indications, use of therapeutic drug monitoring (TDM), type of administration (roller clamp, volumetric pump, syringe pump) and volume of infusion; (3) literature references or other information on which these regimens were based. The respondents could enter the AMT's recommendations for each antibiotic's (intermittent, extended or continuous infusion) unit doses (for intermittent administration) and loading (if applicable) and maintenance doses (for extended and continuous infusion); type of patients involved (all patients, intensive care patients, patients with a specific pathogen); therapeutic drug monitoring and the corresponding target concentration(s).

The study questionnaire was revised through pilot testing and was approved by the Belgian Antibiotic Policy Coordination Committee (BAPCOC) [5]. The questionnaire was sent by e-mail to the official AMT correspondent of each involved Belgian hospital (n=105) on March 25th 2011, with reminders on April 21st and May 9th 2011. The respondents could send back the questionnaire by e-mail or post.

Results

Thirty-four (32 %) responses were received, of which 27 (79 %) were from general and 7 (21 %) were from university hospitals. Ten (29 %) hospitals indicated to have less than 300 beds, 13 (38 %) had between 300 and 600, and 11 (32 %) had more than 600. The numbers of intensive care unit (ICU) beds ranged from 6 to 96. The questionnaires were completed by medical specialists in infectiology, pneumology or intensive care medicine (n=16), in clinical microbiology (n=10) or by clinical pharmacists (n=11) on behalf of the AMT.

The recommendations for the administration of beta-lactams and vancomycin are shown in Table 1. Ceftazidime, piperacillin–tazobactam, meropenem and vancomycin were used in almost all hospitals. Considering the non-ICU wards, the main recommendations were: (i) for ceftazidime: almost equal distribution between intermittent administration or continuous infusion (no hospital used extended infusion); (ii) for piperacillin–tazobactam and meropenem: mainly by intermittent infusion and, if not, by extended infusion only (meropenem was used by continuous infusion in one hospital only); (iii) for cefepime: mainly by intermittent infusion and, if not, by continuous infusion only; (iv) for vancomycin: about two-thirds by intermittent infusion and one-third by continuous infusion. Moving now to ICU wards, we see that: (i) continuous infusion was the predominant mode of administration for ceftazidime and vancomycin; (ii) extended infusion was most often recommended for meropenem (four hospitals mentioning that it was for infections with multidrug-resistant pathogens; one hospital recommended continuous infusion); (iii) intermittent administration remained predominant for cefepime and piperacillin–tazobactam, with extended infusion being the next most popular recommendation (continuous infusion was also recommended by several hospitals for cefepime, but by only one hospital for piperacillin–tazobactam).

The recommended dosing regimens for each mode of administration of each antibiotic are shown in Table 2. For the intermittent administration of beta-lactams, the most recommended daily doses were rather fixed for ceftazidime (6 g) and piperacillin–tazobactam (12–16 g), but variable for cefepime (3 to 6 g) and meropenem (2 to 6 g). For prolonged infusion (always limited to 3 h), similar daily doses as in the intermittent mode of administration were recommended for cefepime, piperacillin–tazobactam and meropenem, with a loading dose recommended only for the latter two antibiotics.

[1] The Belgian law provides that an AMT must be operating in each Belgian hospital where infectious diseases treatments are undertaken. AMTs have a mandatory role in the setting of hospital formularia and must intervene in the setting of local guidelines and analysis of local epidemiology.

Table 1 Recommendations for the administration of the four beta-lactam antibiotics and vancomycin: intensive care unit (ICU) versus non-ICU

	n	Non ICU				ICU			
		Intermittent infusions	Prolonged infusions		Combination	Intermittent infusions	Prolonged infusions		Combination
		II (%)	EC (%)	CI (%)	II/CI (%)	II (%)	EC (%)	CI (%)	II/CI (%)
Ceftazidime	32	19 (59)	0 (0)	13 (41)	0 (0)	6 (19)	0 (0)	26 (81)	0 (0)
Cefepime	20	18 (90)	1 (5)	1 (5)	0 (0)	13 (65)	5 (25)	2 (10)	0 (0)
Piperacillin–tazobactam	34	30 (88)	4 (12)	0 (0)	0 (0)	21 (62)	12 (35)	1 (3)	0 (0)
Meropenem	34	22 (65)	11 (32)	1 (3)	0 (0)	11 (32)	22 (65)	1 (3)	0 (0)
Vancomycin	34	19 (56)	0 (0)	12 (35)	3 (9)	7 (20)	0 (0)	24 (71)	3 (9)

For continuous infusion, a loading dose (usually corresponding to the normal unit dose of an intermittent administration) was recommended for ceftazidime, cefepime and meropenem, but not for piperacillin–tazobactam, while the maintenance dose corresponded, essentially, to the total daily dose of the intermittent administration mode. For vancomycin, the dose recommended was 15 to 20 mg/kg for its intermittent mode of administration and 30 mg/kg over 24 h preceded by a loading dose corresponding to what was recommended for intermittent administration for its continuous administration.

With respect to practical aspects of continuous infusion administration of cefepime and meropenem, one hospital prepared syringes with 2 g of cefepime to be administered over an 8-h period, but another hospital prepared syringes with 6 g cefepime for use over 24 h, whereas meropenem was usually prepared in a syringe containing 1 g of antibiotic to be administered over 6 h.

Concerning monitoring, all hospitals assayed vancomycin, recommending trough serum levels between 5 and 20 mg/L for intermittent administration and stable serum levels between 15 and 25 mg/L (two hospitals) and 20–30 mg/L (19 hospitals) for continuous infusion. One hospital was measuring the serum concentrations of meropenem.

Most of the participants did not provide data concerning the devices used for administration or infusion volumes. One hospital, however, mentioned a switch from an extended to an intermittent (loading dose of 1 g followed by 500 mg q6h) meropenem infusion after the observation of 40 % loss of the antibiotic dose due to line dead space [6, 7].

The hospitals based their recommendations on the scientific literature (65 %), an opinion leader (59 %), information from a university hospital (53 %), the "Sanford guide to antimicrobial therapy" (35 %) or summaries of product characteristics (SmPCs) (4 %) [8–10].

Discussion

To our knowledge, this survey represents the first attempt to describe the implementation of extended and continuous infusions in hospitals at a national level in Europe. The adoption of continuous and extended infusion regimens for beta-lactams was variable and largely depended on the

Table 2 Recommended dosing regimens for intermittent, prolonged and continuous infusions

	Intermittent	Prolonged	Continuous
Ceftazidime	2 g q8h/30 min		2 g/30 min loading dose+6 g q24h/24 h
Cefepime	1 g q8h/30 min	2 g q8h/3 h	2 g/30 min loading dose+2 g q8/8 h
	2 g q8h/30 min		2 g/30 min loading dose+6 g q24/24 h
Piperacillin–tazobactam	4/0.5 g q8h/30 min 4/0.5 g q6h/30 min	4/0.5 g q6h/3 h 4 g/0.5 g/30 min loading dose+4/0.5 g q6h/3 h	16 g/2 g q24h/24 h
Meropenem	0.5 q6h/30 min 1 g q8h/30 min	1 g q8h/3 h 1 g/30 min loading dose+1 g q8h/3 h	1 g/30 min loading dose+1 g q6h/6 h
	1 g/30 min loading dose+0.5 g q4h/30 min	2 g/30 min loading dose+1 g q8h/3 h 2 g q8h/3 h	
	2 g q8h/30 min	2 g/30 min loading dose+2 g q8h/3 h	
Vancomycin	15 mg/kg q12h/1 h		15 mg/kg/2 h loading dose+30 mg/kg q24h/24 h
	20 mg/kg q12h/1 h		20 mg/kg/2 h loading dose+30 mg/kg q24h/24 h

antibiotic, but it is remarkable that the implementation of these modes of administration was between 10 % and 44 % for the non-ICU wards and between 35 % and 81 % for the ICU wards. These modes of administration can, therefore, no longer be ignored. Actually, continuous infusion is included as an accepted mode of administration for both ceftazidime and vancomycin in the SmPCs of the corresponding branded products in Belgium (Glazidim® and Vancocin®), as well as in the Belgian edition of the "Sanford guide to antimicrobial therapy" [8–10]. The higher level of adoption in ICUs is consistent with the literature, suggesting that prolonged beta-lactam infusions are advantageous for infections with more resistant pathogens, in critically ill and immunocompromised patients, and in patients with unreliable pharmacokinetics [11].

A loading dose prior to the initiation of the extended or continuous infusion is essential to shorten the time needed for obtaining a steady-state concentration at the targeted level [12, 13]. This was not always recommended for beta-lactams, which is most unfortunate, because a simple but effective approach is simply to use the normal initial dose recommended for intermittent dosing. Studies have stressed the importance of using a sufficiently large loading dose of vancomycin when using continuous infusion to avoid insufficient drug concentrations in the early phase of therapy [14–16]. Even for the intermittent mode of administration, the Infectious Diseases Society of America (IDSA) consensus recommendations suggest a loading dose of 25–30 mg/kg in order to rapidly reach the desired target serum concentration [17]. Of note, this loading dose should be administered over at least 1 h (or even 2 h if the dose is 2 g) to avoid a "red man" syndrome. This was taken into account by all hospitals recommending continuous infusion, but not by those recommending intermittent administration.

Serum concentrations for beta-lactam antibiotics were not measured (except in one hospital). A recent study shows that standard dosing regimens for piperacillin–tazobactam, ceftazidime and cefepime may lead to serum concentrations insufficient to cover less susceptible pathogens in the early phase of severe sepsis and septic shock [18]. But optimal targets for beta-lactam therapy remain controversial [19]. Low trough drug concentrations in critically ill patients seem to be associated with increased renal clearance, suggesting that TDM could be useful for this type of patient [20]. For vancomycin, the trough serum levels (5–20 mg/L) recommended by the participating hospitals are too low to achieve an AUC/MIC ratio of ≥400 in most patients if the MIC of vancomycin for the target organism is≥1 mg/L [17]. For continuous infusion, optimal serum levels are less clearly defined, with targets of 15–20, 20–25 and 25–30 mg/L mentioned in the literature [4, 17, 21, 22]. These should cover organisms with a vancomycin MIC up to 1 and 2 mg/L for the lowest and largest targets, respectively. Should organisms with a vancomycin MIC>2 mg/L become frequent [these organisms should be reported as resistant according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) interpretative criteria], we may face a severe limitation in our therapeutic approach with this antibiotic, because stable concentrations>28 mg/L (needed to obtain a satisfactory AUC/MIC ratio) have been associated with a significant increase in renal toxicity [23]. Nevertheless, a meta-analysis shows that continuous vancomycin infusion is associated with a significantly lower risk of drug-related nephrotoxicity compared with intermittent infusions with the same daily dose [3]. As there is a tendency to use higher vancomycin dosages, it is important to determine their impact on drug-related toxicity [24, 25].

Antibiotic stability and incompatibility with other drugs are important considerations in the implementation of prolonged infusions. Piperacillin–tazobactam, ceftazidime and vancomycin are stable for at least 24 h at 25 °C, but concentrated solutions of cefepime quickly change in colour [26] and meropenem is unstable [27, 28]. Several drugs incompatibilities have been described [9]. Vancomycin is incompatible with all beta-lactams, and both beta-lactams and vancomycin are incompatible with propofol [9]. In ICU wards, the problem is easily be avoided, as most patients have multiple-lumen catheters, but this may not be the case in non-ICU wards, where most patients have single-lumen catheters.

A first limitation of the study is the low response rate (32 %), which questions the generalisability of our conclusions. However, all type of hospitals, based on the number of beds and academic profile, were represented. A second limitation is that no valid information was obtained on the mode of administration or infusion volume. Implementing prolonged infusions can have important practical implications, such as the availability of syringe pumps, multi-lumen catheters (to avoid direct drug interferences) and appropriate control of the amount of antibiotic effectively delivered.

It is clear that the Belgian AMTs are in favour of prolonged infusions. However, there is much variation in the recommended dosing regimens, especially for meropenem, which reflects the variability in the literature data (Table 2). It is important to emphasise that AMTs have the responsibilities to support their recommendations for continuous and/or extended infusions of antibiotics with clear guidelines for appropriate administration (doses, schedules, stability, incompatibility) to allow their safe and easy implementation by physicians, nurses and clinical pharmacists.

Conclusion

This survey showed that extended and continuous infusion of ceftazidime, cefepime, piperacillin–tazobactam, meropenem

and vancomycin are widely implemented in Belgian hospitals. For intensive care unit (ICU) wards, a majority of the hospitals recommended ceftazidime and vancomycin in continuous and meropenem in prolonged infusions. For non-ICU wards, ceftazidime, meropenem and vancomycin were frequently used in continuous and/or prolonged infusions, despite the lack of evidence of clinical advantage for non-critical patients. Conversely, cefepime and piperacillin–tazobactam are mostly used as intermittent administration. A majority of the hospitals recommended a loading dose prior to the first dose. For vancomycin, the recommended loading dose and trough target serum concentrations were too low if considering the current literature data.

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