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Research Paper

Long-term Conventionally Dosed Vancomycin Therapy In Patients With Orthopaedic Implant-related Infections Seems As Effective And Safe As Long-term Penicillin Or Clindamycin Therapy. A Retrospective Cohort Study Of 103 Patients

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Abstract

Objectives: Antimicrobial therapy is one of the cornerstones of orthopaedic implant-related infections (OIRI) treatment. Infections with Gram-positive bacteria are often treated with vancomycin, penicillin or clindamycin. A recent IDSA guideline suggests increasing the dose of vancomycin to increase the trough vancomycin target serum concentrations. This is deemed necessary because of an observed decrease in vancomycin susceptibility among Gram-positive bacteria. However, elevated vancomycin concentrations are correlated with the risk of nephrotoxicity, especially with prolonged therapy. Compared to most countries, rates of resistance against antibiotics among bacteria in the Netherlands are lower for currently available antibiotics, therefore lower target concentrations of vancomycin are probably efficacious for the treatment of infections.

In this study we evaluated the efficacy and safety of long-term conventionally dosed vancomycin therapy, as an initial therapy for OIRI, and compared this with long-term penicillin and clindamycin therapy, as initial therapy, in patients with Gram-positive orthopaedic implant-related infections.

Methods: A retrospective, observational study was conducted in 103 adult patients treated for OIRI, with vancomycin, penicillin or clindamycin for at least 10 days. The target trough serum concentration of vancomycin was 10-15 mg/l.

Results: 74% of our patients were treated successfully with vancomycin, as initial therapy, (no reinfection within 1 year) versus 55% of our patients treated with either an antibiotic of the penicillin class (mostly flucloxacillin) or clindamycin (p=0.08), as initial therapy. For patients treated with vancomycin we observed a serum creatinine increase of 6 µmol/l, for patients treated with either an antibiotic of the penicillin class or clindamycin the serum creatinine increase was 4 µmol/l (p=0.395).

Conclusions: In our population of patients with OIRI long-term treatment with conventionally dosed vancomycin, as initial therapy, was not significantly less effective and safe as long-term treatment with an antibiotic of the penicillin class or clindamycin, as initial therapy.

Key words: Orthopaedic implant-related infections, Gram-positive infections, Long term antimicrobial therapy, Vancomycin, Nephrotoxicity

Introduction

Vancomycin, a glycopeptide antibiotic, is often used in combination with surgical interventions, in the treatment of patients with orthopaedic implant-related infections (OIRI), caused by Gram-positive micro-organisms, which are not susceptible to either an antibiotic of the penicillin class (e.g amoxicillin, benzylpenicillin, flucloxacillin) or clindamycin. The susceptibility of bacteria for antimicrobials is usually determined with an antibiogram. The vancomycin starting dose in our hospital is 2000 mg per day, either as a continuous infusion over 24 hours or in 2 doses. [1] After 3-5 doses or at least 24 hours of continuous infusion (in order to reach steady state), the serum vancomycin level is routinely determined (therapeutic drug monitoring, TDM), and the maintenance dose regimen is calculated, based on this level, which is then followed by weekly TDM. The target levels are a trough concentration of 10-15 mg/l or, when administered continuously, a steady state concentration of 15-20 mg/l. These levels are based on the generally accepted target of vancomycin exposure in serum over 24 hours / MIC (minimal inhibitory concentration) microorganism > 400 and MIC values of vancomycin susceptible micro-organisms of ≤1 mg/l. [1, 2, 3]

In the most recent guideline of IDSA (Infectious Diseases Society of America), [3] a higher trough concentration of 15-20 mg/l has been suggested though, related to an expected reduced susceptibility of the micro-organisms for vancomycin (MIC > 1mg/l). This worldwide used guideline is mainly based on research in (methicillin resistant) *Staphylococcus aureus* infected patients, treated with vancomycin, from the United States where a decreased susceptibility to vancomycin has been observed among *Staphylococcus spp*. The guideline evoked major debate in The Netherlands, ultimately leading to only a small number of hospitals in the Netherlands having adopted this guideline. Elevated vancomycin levels are correlated with the risk of nephrotoxicity though, especially with prolonged therapy (>7-14 days), [4, 5] often the case in OIRI, where patients are typically treated ≥2 weeks. A recent meta-analysis showed an odds ratio of 2.7 for nephrotoxicity in patients treated with vancomycin doses leading to troughs > 15 mg/l compared to patients treated with doses leading to troughs ≤15 mg/l. [6] Therefore, implementing new guidelines aiming at higher vancomycin serum concentrations should be considered carefully.

In our hospital MICs of bacteria are not routinely determined. However, an extensive European database with current MICs for most existing micro-organisms in Europe is available. [7] A significant number of micro-organisms in this database have MIC values > 1.0 mg/l for vancomycin. However, we expect that the reported MIC values are not valid for the Netherlands. This may be due to several measures that reduce antibiotic resistance such as restrictive prescribing of antibiotics and stringent infection control practices. [8] Therefore, bacteria in the Netherlands (and several other Northern European countries) show much lower MICs for the current antibiotics compared to many countries, including the USA, [9] most likely resulting in lower serum levels of vancomycin to be efficacious. Unfortunately we found no data comparing MIC values in the Netherland to MIC values in Europe and worldwide.

In this study we evaluated the efficacy and safety of long-term conventionally dosed vancomycin therapy, and compared these with long-term penicillin and clindamycin therapy, the antibiotic regimens that are regularly prescribed in patients with Gram-positive orthopaedic implant-related infections.

Methods

A retrospective, observational study was conducted. Data of all adult patients treated in the OLVG (Onze Lieve Vrouwe Gasthuis) hospital between January 2006 (availability of digital files) and July 2014 for an infection of orthopaedic implant material, initially with vancomycin, a penicillin (amoxicillin, benzylpenicillin, flucloxacillin) and/or clindamycin have been collected and analysed.

Inclusion criteria were: infected orthopaedic implant material (both arthroplasty and internal fixation implants), determined after January 2006 by means of a positive culture; first treatment with vancomycin (with dose adjustments based on weekly measured serum concentrations*), penicillin and/or clindamycin for a minimum of 10 days (considering the nephrotoxicity concerns with prolonged therapy). Patients undergoing a debridement or 1-stage revision of a prosthesis due to a *Staphylococcus spp* infection were co-treated with rifampicin according to the guidelines. [10]

Exclusion criteria were: patients on dialysis before start of treatment, concomitant use of antimicrobials for co-infection, missing data (vancomycin concentrations, follow-up data).

* Target: trough serum level 10-15 mg/l

The indication for a debridement was an early (maximum 3 months after index surgery) or acute haematogenous infection. The indication for a 1-stage revision was an adequate soft tissue condition, no major bone loss and good antibiotic susceptibility (preferably with rifampicin) of the infecting

microorganism. In patients not meeting these criteria a 2-stage revision was performed. Finally, in a few remaining patients, not suitable for other treatment, the arthroplasty of osteosynthesis hardware was only removed and no reimplantation was performed.

Outcome

The first endpoint of the study was the efficacy of long-term vancomycin as the initial therapy, compared to penicillin and/or clindamycin therapy as the initial therapy. Efficacy was defined as no reinfection of implant material or joint/bone in the first year after treatment. If during the treatment infection with a different microorganism occurred, the treatment of these microorganisms was included in the total treatment.

The second endpoint of the study was the absence or presence of nephrotoxicity of long-term vancomycin therapy, compared to the control group. Nephrotoxicity was defined as a prolonged increase of the serum creatinine of >45µmol/l or an increase of > 50% of baseline serum creatinine (as confirmed by at least two consecutive laboratory measurements during- and up to 2 weeks after the start of the vancomycin therapy). [5, 6]

Statistics

The statistical package SPSS (version 22, IBM) was used to analyse the data.

All categorical data are reported in number (%) and analysed with a Chi-square analysis. All continuous data are reported in mean ± SD and analysed with t-test or median (interquartile range 25%-75%) and analysed with Mann-Whitney test when appropriate.

The difference between the groups was analysed with the confidence interval (95%) of the proportion.

Ethics

This study was approved by the Institutional Review Board of the OLVG hospital. We received no outside funding.

Results

Our study found a non-significant (p=0.08) difference in efficacy in favour of vancomycin treatment (table 2).

The average serum creatinine level increased slightly in both groups during antimicrobial treatment. For patients treated with vancomycin we observed an increase of 6 µmol/l (median, 25-75% 0-12 µmol/l), for patients treated with either penicillin or clindamycin the increase was 4 µmol/l (median, 25-75% 1-12 µmol/l). The difference was not statistically significant (p=0.395). One patient treated with vancomycin and one treated with penicillin/clindamycin experienced nephrotoxicity during or straight after treatment. Both patients recovered within a few months.

In both groups 3 patients passed away in the first year after treatment and could not be included for efficacy, their deaths did not appear to be related to the antibiotic therapy nor the infection.

Discussion

The results of this study demonstrate that the efficacy of vancomycin as an initial treatment for patients with infected orthopaedic implant material is comparable to the treatment with penicillin or clindamycin. Although the numbers are small and therefore statistical significance cannot be calculated for the different treatment groups, this appears to apply to all groups.

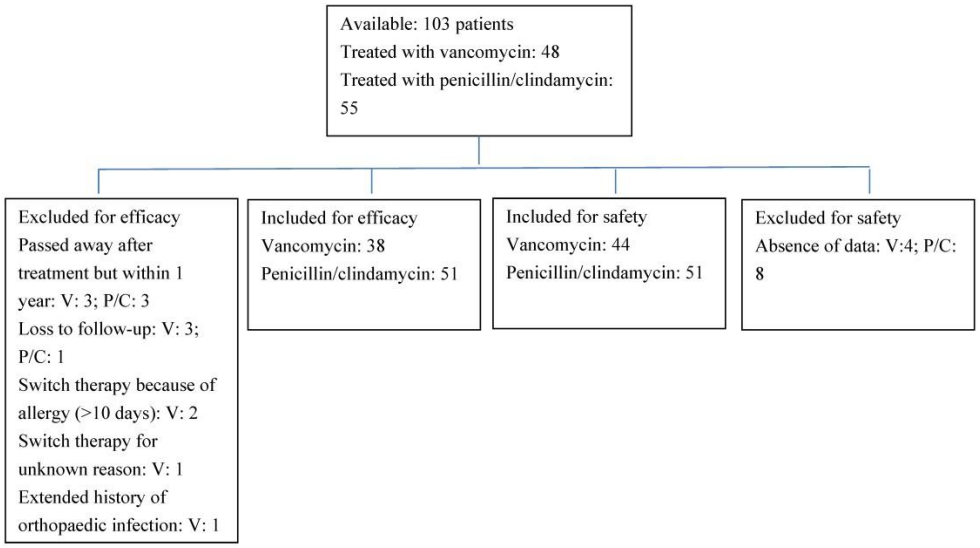

Fig 1. Inclusion. V = vancomycin; P/C = penicillin/clindamycin

The loss of renal function during and after treatment with vancomycin was not clinically relevant and not significantly different compared to the treatment with penicillin/clindamycin.

The baseline table (table 1) shows that patients with an infected hip arthroplasty are more often treated with vancomycin than with penicillin/clindamycin. This correlates with the type of infecting microorganism: in 68% of hip arthroplasty the source of infection is a coagulase-negative *Staphylococcus* species (CNS), which is often resistant to both penicillin and clindamycin. Knee arthroplasties appeared to be infected more frequently with a *Staphylococcus aureus* (SA) species that is predominantly more susceptible to penicillin (mainly flucloxacillin) and clindamycin and therefore not treated with vancomycin.

Exclusion

Several more patients in our vancomycin group were excluded from analysis regarding the endpoint cure rate compared to the penicillin/clindamycin group, partially because of allergy to vancomycin and loss to follow-up. Regarding the endpoint safety, more patients in the control group were excluded for analysis due to absence of data regarding renal function, most likely because determination of renal function is more standard during the treatment with vancomycin, than it is with penicillin/clindamycin.

Previous literature

In 2013 Kuiper et al. published a retrospective cohort study evaluating the treatment of prosthetic joint infection by antibiotic treatment combined with debridement, irrigation and retention in 3 Dutch hospitals. [11] They found a cure rate of 66%. A 2005 review by Sia et al. shows how the percentage of successful 2-stage revisions (mainly in the USA) is rather diverse but with an average of 87 (range 57-100%). [12] For 1-stage revisions this number is 78% (75-100%) and for debridement, irrigation and retention 48% (14-89%). A recent French study reports a reinfection rate of 27% (n=26) in patients undergoing a 2-stage revision combined with a high dose vancomycin (trough >15 mg/l) treatment after infection with SA and CNS. [13] These numbers are similar to those we found in our patients treated with conventionally dosed vancomycin.

We found that treatment regimens based on either conventionally dosed vancomycin or penicillin/clindamycin were not associated with a decrease of renal function. This is in accordance with the reviews by Ye et al. and Elyasi et al., [14, 15] who found that conventionally dosed vancomycin therapy monitored by TDM did not lead to an increased risk of nephrotoxicity.

Table 1. Patient Characteristics

		Vancomycin No (%) N=48	Penicillin/clindamycin No (%) N=55	p-value
Age in years (SD)		68 (+/- 14)	64 (+/- 11)	0,094
Gender, male		24 (50)	26 (47)	0,782
Implant material	Total hip	31 (65)	26 (47)	0,091
	Total knee	9 (19)	21 (38)	
	Other	8 (17)	8 (15)	
Type of surgery	1-stage revision	13 (27)	4 (7)	
	2-stage revision	9 (19)	19 (35)	
	Debridement	24 (50)	25 (45)	
	Other	2 (4)	7 (13)	
Potentially nephrotoxic co-medication	None	8 (17)	10 (18)	
	NSAID/COX2 inh	25 (52)	31 (56)	
	NSAID/COX2 inh + ACE-inh/ARB	3 (6)	9 (16)	
	Other	12 (25)	5 (9)	
Gentamicine local	none or in cement prosthesis*	22 (46)	23 (42)	
	gentamicine collagen sponge	1 (2)	7 (13)	
	gentamicine beads	25 (52)	25 (46)	
Antibiotic treatment in days; median (25-75 %)	vancomycin/penicillin or clindamycin	38 (15-44)	35 (16-42)	0,669
	total antibiotic treatment**	90 (53-195)	90 (42-180)	0,770
Serum creatinine before treatment in µmol/l; median (25-75%)		61,5 (55,25-78,75)	63 (52-73)	0,790
Type of micro-organism	SA	3 (6)	16 (29)	< 0,01
	CNS	43 (90)	13 (24)	
	> 1 microorganism cultured	12 (25)	9 (16,4)	
	> 1 microorganism cultured including CNS	12 (25)	2 (4)	
	Other	2 (4)	19 (35)	

*Systemic gentamicin exposure from cement is very low. [16]
**Lifelong treatment is cut off at 1 year
SA= *Staphylococcus aureus*
CNS=*coagulase negative Staphylococcus*

Table 2. Number of patients with successful treatment (no reinfection within 1 year)

		Vancomycin No (%) N=38	Penicillin/ clindamycin No (%) N=51	p-value
Total		28 (74%)	28 (55%)	0,08
Type of treatment	1-stage revision	7(70)	2(50)	
	2-stage revision	5(83)	12(67)	
	Debridement	14(70)	10(45)	
	Other	2(100)	4(57)	
Implant material	Total hip	15(65)	13(59)	
	Total knee	6 (75)	14(67)	
	Other	7 (100)	1(13)	
Type micro-org anisme	SA	2(100)	9(56)	
	CNS	18(75)	3(27)	
	Other	2(100)	12(67)	
	> 1 micro organism	10(63)	4(67)	

SA= *Staphylococcus aureus*
CNS=*coagulase negative Staphylococcus*

Strengths and limitations

Considering the low incidence of infection in orthopaedic implant material, our retrospective research approach is a suitable method to evaluate the possible differences in safety and efficacy of different therapeutic regimens. However, one of the disadvantages is the possible absence of required data, leading to exclusion of several patients. Another disadvantage of this cohort study is that comparing both groups is rather difficult considering the differences between the microorganisms such as pathogenicity and persistency, also the difference in susceptibility of the microorganism for the applied antibiotics and thereby the differences in efficacy and mechanism of action between the antibiotics. A major disadvantage is the small number of evaluable patients, making it difficult to demonstrate a clinical significance of differences between the groups.

Implications for future research

We recommend a prospective randomized controlled trial (multicentre since large numbers will be needed) to be conducted, with an adequately calculated sample size, comparing the safety and efficacy of the treatment of infected orthopaedic implant material with vancomycin doses leading to a trough level of 10-15 mg/l compared with vancomycin doses leading to a trough level of 15-20 mg/l.

Conclusion

In this retrospective study of patients with infected orthopaedic implant material, long-term conventionally dosed vancomycin as the initial treatment seems as effective and safe as long-term penicillin and/or clindamycin therapy. Because of the small number of patients and the retrospective nature of the study no definite conclusions can be drawn. Further studies, preferably prospective and randomised, are needed.

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Competing Interests

The authors have declared that no competing interest exists.

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