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This work was presented in part at the 20th ECCMID on 11 April 2010, Vienna, Austria:

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'Use of daptomycin in complicated cases of endocarditis: experience in a tertiary referral centre in the United Kingdom' (Abstract.1179)

Abstract

***Introduction*:** Infective endocarditis (IE) is a serious form of infection with a high mortality. Medical management can be a challenge because of organ dysfunction, lack of clinical response or allergy to the recommended antibiotics. Daptomycin is a lipopeptide antibiotic with a potent bactericidal activity against Gram-positive bacteria. There are limited data on the use of daptomycin in complicated cases of IE.

***Aim*:** Report our experience of daptomycin use in complicated cases of IE through a prospective observational study (from 1 October 2008 to 30 September 2009).

***Methods*:** Daptomycin was prescribed for cases that were either unresponsive, or allergic to the standard therapy. Clinical characteristics and outcomes were reviewed. Success was defined as clinical improvement accompanied with resolution of laboratory markers of sepsis and continuation of above findings at least 8 weeks after the end of therapy.

***Results*:** Eight cases were evaluable. Native and prosthetic valves were involved in equal proportions. The range of organisms was wide: *S. aureus* – 2, *S. epidermidis* – 2, streptococci – 2, *Enterococcus faecalis* - 2. The median duration of therapy was 42 days. All patients were successfully treated. Daptomycin was well tolerated.

***Conclusion*:** Daptomycin is useful in the management of complicated cases of IE.

Key words – left sided endocarditis, prosthetic valve endocarditis, allergic reaction, therapeutic failure

Introduction

Despite advances in the diagnosis, surgical and medical management of infective endocarditis (IE), it continues to be associated with a high rate of morbidity and mortality.[1] Management of IE can be a challenge because of therapeutic failure with

the recommended standard antibiotics [2] as well as the need for prolonged duration of therapy during which allergic reactions or toxicity to the antibiotic/s are often encountered. Moreover, combination therapy with aminoglycosides is often unsuitable due to the presence of resistance in the causative organism or impaired renal function in the patient. Vancomycin is mostly recommended as an alternative agent to ß- lactam group of agents in the treatment of IE. [2, 3, 4] However, there is increasing concern regarding the efficacy of vancomycin in the recent literature. [5], [6] Despite this, there is currently a lack of clear guidance on management of patients with therapeutic failure or allergy associated with vancomycin/glycopeptides. As the options on alternative antibiotics are limited there is a need for new agents in the treatment of IE.

Daptomycin is a novel lipopeptide antibiotic with a unique mechanism of action against Gram-positive bacteria that is rapidly bactericidal in vitro. [7] It has been shown to be effective in experimental models of endocarditis as well as in clinical studies .[7, 8, 9]

Objective

The aim was to report our experience on the use of daptomycin in complicated cases of IE through a prospective observational study.

Methods

An observational study was carried out in a 1200 bed tertiary care and referral centre for adult cardiology (including cardiac transplantation) located in the West Midlands, UK. Cases of IE were identified prospectively following a positive blood culture report and consultations by the Cardiac Unit over a one year period from 1 October 08 to 30 September 09. Blood cultures were processed by the automated blood culture system BacT/Alert 3D, Biomerieux SA, Marcy-I'Etoile, France. The isolates were identified by the standard method. Antimicrobial sensitivity was performed by the automated method using Vitek 2, (Biomerieux, Marcy-I'Etoile France). Minimum inhibitory concentration for penicillin and ampicillin was performed on all streptococcal and enterococcal isolates respectively by the 'E' test (AB Biodisk, Solna, Sw**ed**en). High level aminoglycoside sensitivity was performed by the disc sensitivity testing using the BSAC method **(**BSAC standardized disc susceptibility testing method, version 8**).** Daptomycin sensitivity was performed by the 'E' test according to the manufacturers (AB Biodisk, Solna, Sw**ed**en) recommendation. Cases were followed up through routine ward visits during their hospital stay.

Indication for daptomycin use included all cases of IE where the medical therapy with the standard antibiotics [2] was considered to be ineffective or inappropriate as follows: lack of clinical response; failure of inflammatory markers of sepsis to fall; evidence of progression of IE (as revealed by echocardiography); existing history of allergy or development of allergic reaction/toxicity; detection of resistance to the standard

antibiotics in the blood culture isolate. All cases of IE receiving daptomycin were recorded. Microbiological and relevant non microbiological laboratory results were reviewed through the electronic Microbiology laboratory system (Telepath) and the Patients Information and Prescribing system (PICS). Details of antibiotic therapy were recorded from the PICS. Subsequent blood cultures following initiation of any type of antibiotic therapy (standard or daptomycin) were only collected when clinically indicated (lack of resolution or progression of clinical /laboratory markers of sepsis) according to routine practice. Follow up after discharge from the hospital was undertaken through discussion with the admitting team and review of follow up notes (including laboratory results) of clinic appointment at a minimum period of 8 week of discharge. Further review was undertaken at a minimum period of 3 month of discharge through telephone contact with the respective general practitioners.

Definitions: A diagnosis of IE was established according to the modified Dukes criteria.[10] Success was defined as resolution of clinical and laboratory features (inflammatory markers i.e. C reactive protein levels ,CRP) of sepsis and continuation of these findings for a minimum period of 8 week from end of therapy. Relapse was defined as the reappearance of signs of sepsis following a period of clinical improvement in the absence of any other apparent cause and progressive disease as supported by echocardiography with or without repeat isolation of a causative organism from blood cultures.

Results

Clinical, microbiological and echocardiographic data on all of the 8 patients receiving daptomycin are summarised in Table 1. All patients received daptomycin as 2nd or 3rd line therapy. The minimum inhibitory concentrations (MIC) of daptomycin for the available isolates are shown in Table 2.CRP values in relation to Daptomycin therapy are shown in Figure 1.

All isolates were obtained from the original blood cultures at the time of initial presentation. There was no repeat isolation of the causative organism from subsequent blood cultures obtained from patients with un resolving/ progressive clinical features of sepsis while continuing on the initial antibiotic therapy. One patient was excluded from the analysis as *Streptococcus mitis* isolated from the blood culture was noted to be resistant to daptomycin. Daptomycin therapy was therefore discontinued after 6 days.

Three patients (No: 3, 4 and 6) were seen at other hospitals initially and transferred to our hospital within one week of presentation for surgical assessment. The remaining four patients were admitted to our institution directly. The number of sets of positive blood cultures varied from 1- 4 sets. One patient had a single set of positive blood culture with a *Staphylococcus aureus* isolate (*S. aureus* was also detected in the explanted mitral valve by 16S r DNA PCR amplification and sequencing) and the rest

of the patients had ≥ 2 sets of positive blood cultures. Four each of native and prosthetic valves were affected.

Among the native valve endocarditis (NVE), 2 each of aortic and 2 mitral valves were affected. Two patients (No 1 and 3) developed a severe allergic reaction to penicillin in addition to persistent clinical features of sepsis. One patient (No. 4) with persisting poor renal function had an isolate of enterococcus possessing high level resistance to aminoglycosides (gentamicin and streptomycin). Mono therapy with amoxicillin was considered inappropriate in this case. Overall, daptomycin was administered either as combination therapy (6 patients) or mono therapy (2 patients).

Four patients had prosthetic valve endocarditis (PVE) of which 2 developed recurrences during the early postoperative period (having undergone valve replacement in our institution). One of the patients (no.5) had aortic valve endocarditis of his transplanted heart and had radiological evidence of embolisation to the spleen, liver and to the common ileac artery prior to valve replacement. He developed further complications associated with recurrence of endocarditis in the newly implanted valve with extensive aortic root abscess and development of heart block within 2 weeks of surgery, ongoing sepsis and renal failure. He was not suitable for re-operation. He received vancomycin and rifampicin initially for 6 weeks without clinical improvement. Antibiotic therapy was then changed to linezolid which was continued for 7 weeks. He improved temporarily but subsequently developed thrombocytopenia, lactic acidosis, rising inflammatory markers and clinical features of sepsis. Evidence of persistent IE was supported by echocardiography. Linezolid therapy was changed to daptomycin. He improved on daptomycin therapy and was discharged home 6 months after admission. He completed daptomycin therapy as an outpatient leading to a total of 8 months therapy. One other patient (no.7) in the above group developed IE in a prosthetic mitral valve accompanied with allergic reaction to vancomycin and possibly to rifampicin within 2 weeks of surgery. Another patient (no.4) received daptomycin in combination with amoxicillin as he failed to improve with combination therapy with aminoglycoside. Additionally, it was considered inappropriate to continue use of aminoglycoside in presence of persistent poor renal function. The remaining patient (no.8) in this group had a history of serious allergy to penicillin. She initially received clindamycin and rifampicin for surgical site infection and associated retrosternal collection due to *S. aureus* in the early post operative period. Antibiotic therapy was changed to daptomycin following a trans-oesophageal echocardiography which revealed vegetation on the recently implanted (at 2 weeks of surgery) aortic valve. Daptomycin therapy was continued as clinical progress associated with resolution of inflammatory markers of sepsis was evident (Figure 1).

A successful outcome was documented in all of the 8 patients, at a minimum follow up period of 8 weeks and at 3 month after the end of therapy. There was no report of relapse of endocarditis. No evidence of adverse events including elevation of creatine kinase was noted in any of the patients during daptomycin therapy.

Discussion

For several years, there have been no significant advances related to antimicrobial therapy for bacterial endocarditis. Daptomycin is a rapidly bactericidal antibiotic with activity against Gram-positive bacteria including both methicillin sensitive *S. aureus* and MRSA, Glycopeptide intermediate *S. aureus* (GISA) and heterogeneous GISA (in addition to vancomycin resistant *S. aureus*) strains. It demonstrates concentration dependent killing, in vitro synergy with a number of other antibiotics and in vitro penetration into bio film [11]. Recent reports on use of daptomycin in Gram-positive bacteraemia and endocarditis are encouraging [12.] A randomised trial by Fowler et al evaluating daptomycin compared with semi synthetic penicillin and Vancomycin for the treatment of endocarditis demonstrated no inferiority of Daptomycin [8]. The endocarditis patients were primarily of right-sided and native valve types. There were very few left-sided endocarditis cases in the above trial and using the definition applied in the study design, both daptomycin and the comparator fared poorly for left-sided endocarditis. Using the data from this study, cost-effectiveness of daptomycin was compared with that of vancomycin in combination with gentamicin in patients with MRSA bacteraemia with or without endocarditis. The results showed similarity of daptomycin with Vancomycin in combination with gentamicin [9]. Daptomycin is currently approved for the treatment of right sided endocarditis. Our study comprised of NVE as well as PVE, all of which were left sided. PVE is associated with significantly higher mortality than native valve endocarditis[1]. Additionally medical treatment of PVE is associated with a worse outcome [13]. Of the 4 cases of PVE in our series, 3 were successfully treated with daptomycin without undergoing surgery.

Increases in vancomycin MIC has been linked to increases in daptomycin MIC .[14] The clinical significance of such a finding is unknown but they suggest awareness of such problems in a patient who fails to improve on daptomycin therapy and has a history of prior vancomycin use. We did not observe lack of efficacy of daptomycin in either of the patients who received daptomycin subsequent to therapeutic failure with vancomycin. Limitations of our report include the small number of patients. It is interesting to note that we had one isolate (*St. mitis*) which revealed resistance in spite of absence of prior exposure to daptomycin. This highlights the risk of therapeutic failure even in the absence of prior exposure to daptomycin. There were 3 cases from whom the isolates were lost for daptomycin sensitivity (Table 2). We observed effectiveness of daptomycin in endocarditis cases, all of which were left sided, complicated and associated with a wide range of organisms.

Conclusion

Daptomycin is an effective and well tolerated agent in difficult to treat cases of left sided IE involving a wide a range of Gram- positive organisms. Further studies are

needed to confirm our observation of the efficacy of daptomycin in complicated and left sided IE.

Acknowledgments: We thank the Health Protection Agency (Reference laboratory) Colindale, UK for carrying out molecular identification on the explanted cardiac valve and tissues through 16S r DNA PCR (for patient no. 2)

***Funding*:** No funding was received for this work. This data was generated as part of the routine work.

***Conflict of interest*:** none

***Ethical standards*:** Ethical approval was not necessary as this was a part of a routine observational study.

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Case No.	Age In years	Type of intracardiac Infection	Echocardiogram	BC Isolate	Initial Antibiotic Therapy	Reason for change from initial Antibiotic Therapy to Daptomy
1	65yr	Native MV endocarditis	Severe MR with mitral valve prolapse [a]	*Strept. mutans*[b]	benzyl penicillin +gentamicin (14 days)	Persistent pyrexia after initial response , sweat and development of neutropenia
2	52yr	Native MV endocarditis	Severe MR with MV vegetation	*Staph. aureus* [c]	flucloxacillin + rifampicin (17 days)	Unresolving clinical and lab markers of s development of left cerebellar infarct an persisting renal failure while continuing initial therapy
3	25yr	Native AV endocarditis	Severe AR +Aortic root abscess	*Strept. Sanguinis*	benzyl penicillin + gentamicin +rifampicin (10 days)	Florid macular rash with pyrexia and ora mucosal inflammation and persistent pyr (probable penicillin allergy)
4	67yr	Native AV endocarditis	Moderate AR with AV vegetation	*Enterococcus faecalis*	amoxcillin (3 days)	HLgent –R, streptomycin-R and renal fai (mono therapy with amoxicillin was con inappropriate)
5	53yr	Prosthetic AV endocarditis in a previously transplanted heart	Native AV vegetation and Aortic root abscess of TxH. Subsequent aortic root abscess +mass on RCC of the recently replaced AV.	*Staph. epidermidis*	vancomycin + rifampicin 35 days followed by linezolid -47 days	Recurrence and progression of endocardi development of aortic root abscess (of th replaced AV and the aortic root), continu sepsis, lactic acidosis and thrombocytope
6	73yr	Prosthetic AV endocarditis	Prosthetic AV vegetation with aortic root abscess	*Enterococcus faecalis*	amoxicillin +gentamicin 17 days	Renal failure, persistently raised inflamm markers. Monotherapy with amoxicillin was considered inappropriate
7	76yr	Prosthetic AV endocarditis	Initial native MV vegetations + pacemaker lead vegetation.	*Staph. epidermidis*	vancomycin and rifampicin 21 days	Endocarditis of the recently replaced pros MV, pyrexia and macular rash (?relate rifampicin/vanc) in the early postoperativ

Case No.	Age In years	Type of intracardiac Infection	Echocardiogram	BC Isolate	Initial Antibiotic Therapy	Reason for change from initial Antibiotic Therapy to Daptomy
			Recurrence of vegetation of the prosthetic MV in the early postoperative period			
8	72Yrs	prosthetic AV endocarditis	vegetation on the prosthetic aortic valve with extension to aortic root in the early postoperative period	*Staph. aureus*	Clindamycin + rifampicin [d]	History of anaphylaxis to penicillin

Foot notes for Table 1:

BC :blood culture, MV: mitral valve, AV: aortic valve, MR :mitral regurgitation, AR: aortic regurgitation, RCC: right coronary cusp, TXH: transplanted heart, AVR: aortic valve replacement

DAP: Daptomycin, HLgent : high level gentamicin

a : Ruptured chordae tendineae was noted at operation, b: MV tissue was positive for *St. mutans* by PCR

c: MV tissue was positive for *S.aureus* by PCR

d: Initial antibiotics comprised of clindamycin and rifampicin (7days), aimed at treatment of a post-operative retrosternal collection. Patient was subsequently noted to have endocarditis when the above therapy was changed to daptomycin and rifampicin

Case No.	Isolates	Daptomycin MIC mg/l (E test)
Case 1	*Streptococcus. mutans*	NK
Case 2	*Staphylococcus. aureus*	NK
Case 3	*Streptococcus Sanguinis*	0.75
Case 4	*Enterococcus faecalis*	0.5
Case 5	*Staphylococcus. epidermidis*	0.5
Case 6	*Enterococcus faecalis*	2
Case 7	*Staphylococcus. epidermidis*	0.25
Case 8	*Staphylococcus aureus*	NK
Case 9	*Streptococcus. mitis*	2(Resistant)[e]

Foot notes for table 2:

NK – not known as the isolate failed to be saved in the laboratory

e- Patient received daptomycin for 6 days only when daptomycin resistance was confirmed.

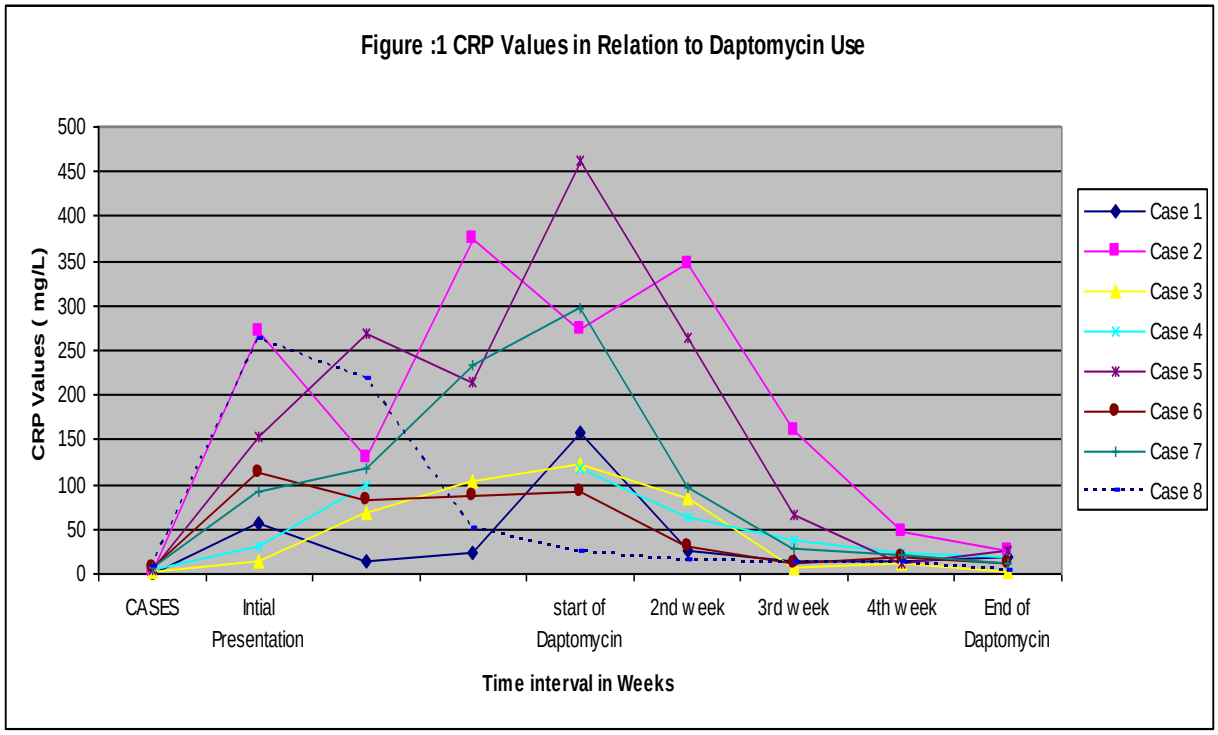
Figure :1 CRP Values in Relation to Daptomycin Use
CRP Values (mg/L)
500
450
400
350
300
250
200
150
100
50
0
CASES
Intial Presentation
start of Daptomycin
2nd week
3rd week
4th week
End of Daptomycin
Time interval in Weeks
Case 1
Case 2
Case 3
Case 4
Case 5
Case 6
Case 7
Case 8

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