Way of the future? Daptomycin use in bacteraemia and infective endocarditis. A review of the literature.

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Mike Webb is currently a trainee intern at the University of Auckland. Prior to undertaking his medical degree, he graduated from the University of British Columbia with a bachelor's degree in Human Kinetics and from Memorial University of Newfoundland with a master's degree in clinical epidemiology. Mike has published in the field of clinical epidemiology, specifically genetic epidemiology, with his paper "Autosomal recessive Bardet-Biedl syndrome: first-degree relatives have no predisposition to metabolic and renal disorders" appearing as an original research article in the April 2009 edition of Kidney International. This work was also presented in 2008 to the American Society of Nephrology. Mike's research interests include pharmaceutical RCT's, genetic epidemiology, and airway/anaesthesia.

ABSTRACT

Daptomycin ("Cubicin": Cubist Pharmaceuticals) is a naturally occurring lipoprotein antibiotic that has been indicated in the treatment of bacteraemia and infective endocarditis (IE) caused by *Staphylococcus aureus*. Here a review of literature is performed to assess the efficacy, safety, cost, and clinical utility of daptomycin versus standard therapy in bacteraemia and IE, and to assess the potential usage of daptomycin for this indication in practice.

INTRODUCTION

S. Aureus bacteraemia and infective endocarditis

Bacteraemia and IE are life-threatening diseases with considerable morbidity and mortality.[1-3] A large portion of bacteraemia and IE are caused by *S. aureus*.[1] *S. aureus* bacteraemia is correlated with poor patient outcomes and complications.[1] Standard therapy is often vancomycin with or without gentamicin, but other effective therapies may exist. Daptomycin, a naturally occurring cyclical lipoprotein and bactericidal agent against Gram-positive bacteria (including methycillin resistant *S. aureus*), is one such antibiotic that has shown promise as an alternative in the face of decreasing support of standard therapy and increasing minimum inhibitor concentrations required for eradication of the aetiological organism.[3,4]

DISCUSSION

Comparative efficacy of daptomycin versus standard therapy

Fowler et al. undertook a large-scale trial assessing the efficacy of daptomycin versus standard therapy (in this case vancomycin with or without gentamicin) in the treatment of *S. aureus* bacteraemia and IE in 2002-2005.[1] This was a randomized, open label, non-inferiority trial that assessed clinical and microbiological outcomes in patients with bacteraemia and right-sided IE. The investigators collected data from patients and adjudicated outcomes as such: successes were clinical cures and negative blood culture 42 days after treatment. Failures were persistent *S. aureus* cultures, clinical failure (assessed by clinician), and death for any reason. Daptomycin was shown to be not inferior to standard therapy for efficacy in this large-scale trial.[1] Further review of this trial is below.

Efficacy in methicillin resistant *Staphylococcus aureus* (MRSA)

Bacteraemia and IE due to infection with MRSA rates are increasing, and patient outcomes in this milieu of infection are poorer than those with methicillin sensitive *Staphylococcus aureus* (MSSA) infection.[2] To judge the efficacy of daptomycin against vancomycin and short course of gentamicin in treatment of MRSA bacteraemia and IE, a subset of the data from *Fowler et al.*[1] was assessed. The non-inferiority trial endpoints were similar to the original research with the exception of being MRSA specific. In this setting, there were no significant differences in efficacy between daptomycin and standard therapy.[2] This is in contrast to a more recent retrospective case control undertaken by *Moore et al.* that analyses the differences in outcomes between 118 patients treated with vancomycin alone and 59 patients treated with daptomycin for MRSA bloodstream infections for which the strain of *S. aureus* cultured required a MIC of > 1g/mL.[4] This cut off (MIC >1g/mL) is described in the literature as vancomycin resistance. This study showed a non-significant difference in clinical failure (defined as mortality, microbiological failure, or recurrence of infection), but a statistically significant trend towards lower mortality in the daptomycin group (20% vs 9% p=0.046). Sixty day mortality was also significantly lower in the daptomycin group (p=0.022).[4] The researchers noted that post hoc analysis factors associated with clinical failures were presence of acute renal failure and treatment with vancomycin.[4]

Comparative safety of daptomycin

Safety analyses were performed as a part of secondary outcomes in the studies of *Fowler & Rhem*.[1,2] Daptomycin was associated with skeletal muscle damage and myositis. *Rhem and Fowler*[1,2] noted that creatine kinase levels were significantly higher in the daptomycin group, as were concomitant musculoskeletal (MSK) adverse events. Standard therapy was correlated with higher nephrotoxicity which is a serious adverse effect. There was greater proportion of nausea and anaemia (p= 0.03 and 0.05 respectively) in the standard therapy arm of the MRSA subset.[2] Rhem 2 also noted that 7% of patients on daptomycin had to discontinue the use due to adverse events, whilst 16% of standard therapy patients discontinued for such reason.[1,2] Serious credibility concerns must be mentioned here, as the study was open-labeled and reporting or clinical judgments made in response to adverse events could be biased based on the clinician's role in the study or the funding study sponsor.

Cost comparison of daptomycin versus standard therapy

A cost analysis study was performed to assess the valuation of two therapies based on the findings of *Fowler et al.*[1] The authors assessed the cost of the medication, the relative cost of successes and failures in terms of hospital stay, additional medications, monitoring, adverse event management costs, and procedural costs. No significant differences were seen.[5] This held true even if the cost of standard therapy was nil. A second retrospective analysis of the *Fowler* data[1] indicated that daptomycin was not inferior to the standard care in community-based parenteral antimicrobial therapy (vancomycin and gentamicin), demonstrating its suitability as a less expensive and safe alternative in comparison to a complete inpatient treatment.[6,7]

Clinical utility in the face of resistance

Community and hospital acquired *S. aureus* strains now have varying degrees of resistance to vancomycin.[8-10] This may reduce the clinical usefulness of vancomycin in some settings because large doses of the medication may be required to treat the tolerant strains of *S. aureus* infection and may even need co-administration of gentamicin: these lead to increased risk of nephrotoxicity.[9] A Korean study quantified the risk of vancomycin resistance, assessing 13 patients with vancomycin MIC >1g/mL versus 124 patients with MIC <1g/mL demonstrating statistically significant decreased survival (54% vs 78% p= 0.026).[11] This corresponded to a MIC >1g/mL hazard ratio of 7.0 (95% CI 2.2-22.1, p=0.001).[11] The study authors advocated use of an antibiotic agent other than vancomycin in these rarer but dire cases.[11]

Laboratory *S. aureus* has also shown tolerance to daptomycin, however, this occurs infrequently.[12] Tolerant strains required a doubled mean inhibitory concentrations of daptomycin (or greater if multiple resistant mutations were present) however both were uncommon in this study and in the literature.[12]

SUMMARY

Evidence reviewed here has demonstrated that daptomycin is clinically and biologically not inferior to the current standard therapy. Indeed we have also seen that in MRSA infections with high vancomycin MIC requirements, this novel antibiotic may have a positive effect on short and intermediate term survival.[4] Equivalence has also been demonstrated in financial and outpatient models.[5,6] This evidence, coupled with the alarming specter of vancomycin resistant strains of *S. aureus*, suggests that a more careful review of vancomycin as a first line therapy may be warranted. Head to head, it has been shown that daptomycin is better tolerated in terms of adverse events, and that serious nephrotoxicity is a concern in long-term high doses of vancomycin required for the treatment of IE and bacteraemia, particularly in the cases of gentamicin co-administration. On this basis, clinical use of daptomycin for these indications may be justifiable.

However, it is notable that a significant portion of the evidence relies upon the framework research by *Fowler et al.*[1] This study is not a stable enough platform upon which to introduce drastic changes. Because a great deal of the literature hangs on the scaffold of this research, the validity of subsequent works may also be questioned. While this study population was difficult to control and properly assess therefore subsequent care had been taken to create a rigorous study, there still were flaws in the trial design. The heterogeneity of the population in the study was potentially confounding. The population was comprised of small numbers of patients with various infections and variable severity of infections with confusing clinical stratification of disease states and complications. This decreases the precision with which the investigators may be able to link a specific illness to an indication for daptomycin because of decreased power and/or inability to make definitive statements due to significant inter-patient variability. The unblinded basis on which safety assessments were made may also be unreliable. In these studies where there is little variability between the medications, safety withstanding, a judgment of implementing clinical use based on safety may be fraught with error. However, all laboratory assessments were performed blind and by an independent body.

In cases of vancomycin resistance, however, the case control study undertaken by *Moore et al.*, demonstrates efficacy.[4] This again needs to be interpreted cautiously as it is a retrospective study with heterogenous infections and populations.[4] However, efficacy of daptomycin in reducing overall mortality in the short and long term was seen. The effect of daptomycin on the composite end point was clinically if not statistically significant. This effect may well be underestimated as immunosuppression and renal failure, an independent risk factor for clinical failure, were statistically significantly over represented in the daptomycin arm of this study.[4] Given the findings of *Wi et al.*, serious adverse effects of vancomycin resistance warrant discussion and evaluation of novel agents for use in this clinical setting.

Daptomycin resistance may be underreported because of its limited clinical use and the paucity of literature on this topic. It has been noted that nearly all literature available on daptomycin is sponsored by Cubist Pharmaceutical (daptomycin producer/marketer) and/or has been authored by employees/stockholders of this company.[1-3,5,6,10] Potential conflicts of interest are numerous. Despite these concerns, the evidence in large, peer-reviewed journals suggests that daptomycin may be a hope for the future. For daptomycin to be considered an efficacious, safe and reliable alternative, more rigorous, unbiased, evidence-based demonstration of superiority in efficacy, investigation of its tolerance and research in both synthetic lipoprotein antibiotics and novel therapies are required.

REFERENCES

1. Fowler VG, Jr., Boucher HW, Corey GR, et al.
Daptomycin versus standard therapy for bacteremia and endocarditis caused by Staphylococcus aureus.
N Engl J Med 2006;355(7):653-65.

2. Rehm SJ, Boucher H, Levine D, et al.
Daptomycin versus vancomycin plus gentamicin for treatment of bacteraemia and endocarditis due to Staphylococcus aureus: subset analysis of patients infected with methicillin-resistant isolates.
J Antimicrob Chemother 2008;62(6):1413-21.

3. Steenbergen JN, Alder J, Thorne GM, et al.
Daptomycin: a lipopeptide antibiotic for the treatment of serious Gram-positive infections.
J Antimicrob Chemother 2005;55(3):283-8.

4. Moore CL, Osaki-Kayin P, Haque NZ, et al.
Daptomycin Versus Vancomycin for Bloodstream Infections Due to Methicillin-Resistant Staphylococcus aureus With a High Vancomycin Minimum Inhibitory Concentration: A Case-Control Study.
Clin Infect Dis. (2012) 54 (1): 51-58.

5. Bhavnani SM, Prakhya A, Hammel JP, et al.
Cost-Effectiveness of daptomycin versus vancomycin and gentamicin for patients with methicillin-resistant Staphylococcus aureus bacteremia and/or endocarditis.
Clin Infect Dis 2009;49(5):691-8.

6. Rehm S, Campion M, Katz DE, et al.
Community-based outpatient parenteral antimicrobial therapy (CoPAT) for Staphylococcus aureus bacteraemia with or without infective endocarditis: analysis of the randomized trial comparing daptomycin with standard therapy.
J Antimicrob Chemother 2009;63(5):1034-42.

7. Graninger W, Presterl E, Wenisch C, et al.
Management of serious staphylococcal infections in the outpatient setting.
Drugs 1997;54 Suppl 6:21-8.

8. Wang G, Hindler JF, Ward KW, et al.
Increased vancomycin MICs for Staphylococcus aureus clinical isolates from a university hospital during a 5-year period.
J Clin Microbiol 2006;44(11):3883-6.

9. Kern WV.
Management of Staphylococcus aureus bacteremia and endocarditis: progresses and challenges.
Curr Opin Infect Dis;23(4):346-58.

10. Jones DB.
Emerging vancomycin resistance: what are we waiting for?
Arch Ophthalmol;128(6):789-91.

11. Wi YM, Kim JM, Joo EJ, et al.
High vancomycin minimum inhibitory concentration is a predictor of mortality in methicillin-resistant Staphylococcus aureus bacteraemia.
Int J Antimicrob Agents. 2012 Aug;40(2):108-13.

12. Baltz RH.
Daptomycin: mechanisms of action and resistance, and biosynthetic engineering.
Curr Opin Chem Biol 2009;13(2):144-51.

FEATURE : EVENT REPORT

Health Fusion Team Challenge – working together in a multi-disciplinary team

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Mariam is a first year House Officer working at Christchurch Hospital. She was the 2012 Editor-in-Chief of the New Zealand Medical Student Journal. In her spare time, she can be found sleeping or playing Words With Friends.

Mrs W is a 58 year old woman who was diagnosed with a high grade glioblastoma multiforme (GBM) two years ago. She and her husband have been referred from the GP as she now presents with increasing confusion, unsteadiness on her feet, and her husband is struggling to cope with her care. He is particularly worried as Mrs W has limited insight into the seriousness of her condition.

You are a community-based specialist team that provides comprehensive health services to patients with chronic deteriorating conditions. Your task as a team is to make a multi-disciplinary plan for the management of Mrs W.

This is a summary of the brief a group of us received at the start of August last year. We were participating in a competition called the Health Fusion Team Challenge, and had four weeks to develop a plan to present for judgement at a competition in Brisbane.

The Health Fusion Team Challenge is an extracurricular activity designed for final year health professional students. Teams consisting of four to six students from various health professions work together to develop a management plan for a patient scenario. The participants are studying in various courses including medicine, nursing, social work, physiotherapy, speech language therapy, pharmacy, occupational therapy and dietetics. They are given a case of a patient with a chronic health problem and must work together to produce a management plan that addresses fairly complex health issues. The Challenge culminates with a public event, where the teams of students present their plans to a panel of judges and face additional on-the-spot questions. The aim of the Challenge is for each student to improve their communication, teamwork and clinical skills, while working with students from other disciplines.