January 3rd 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: Linezolidpaper31.12.13).

Title: Clinical Results of Linezolid in Arthroplasty and Trauma Related Infections. A retrospective analysis of 22 patients followed up for 5 years.

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The manuscript has been improved according to the suggestions of reviewers:

Response to reviewers

Please note that the changes to the document have been highlighted with underlining.

Reviewer 1

Reviewer comment one

As the authors state in the limitation section due to the fact that in the present investigation was analyzed

exciting data, the patient group was highly heterogeneous and the numbers are relatively small. Moreover, the lack of randomization and a control group further limits definitive conclusions. Clearly, follow up studies including a control group are needed.

Response to reviewer

Many thanks for your comment and we agree with the limitation of our study and as you have highlighted we have mentioned these limitations in our discussion and agree with the fact a further study is needed with a control group. Despite this limitation, our study group remains one of the largest available in the literature.

Reviewer comment two

Abstract In the abstract authors should include the aim of their study.

Response to reviewer

We have now stated a clear aim and thank you for pointing out this discrepancy.

Author's action

Abstract;

Aim

The aim of this study was to analyse the management of patients treated with linezolid for orthopaedic infections.

Reviewers comment three

In the third line replace "say" with "stay".

Response to reviewer

Thank you for pointing out our mistake and we have corrected this.

Author's action

Introduction

Treatment of infection following orthopaedic related procedures remains problematic requiring the use of both antibiotic administration and concomitant surgical management. The prospect of an effective oral agent could potentially reduce hospital stay and negate the requirement for parenteral treatment.'

Reviewers comment four

In the results authors should be state clearer the results of their study.

Response to reviewer

Many thanks for this comment and we agree that our results need to be clearer in the results section of our paper.

Author's action

We can have made the following additions to the final paragraph of the results and first paragraph of the discussion.

'Results

Resolution of infection was diagnosed clinically by absence of local and systemic signs and symptoms of infection, alongside radiological and biochemical assessment. Resolution of infection occurred in 17 (77.27%) of all patients at 3-57 months, with a significant reduction in CRP in all cases. Mean initial CRP was 123 mg/L (range 21-301), with a mean of 13.2 mg/L at resolution of treatment (range 54 -<5). (Table 1) The patients were followed up for a mean of 5 years after infection occurred.

Discussion

Our study clearer demonstrates good results with the use of Linezolid to treat orthopaedic related infections, with the resolution of infection in 77% of all patients at 3-57 months. Additional studies in the literature support our finding, with resolution of infection in up to 90% of patients. [10,13]'

Reviewers comment five

Key words Almost all key words are present in the Title. Authors should replace them with words that are not appearing in the Title of the manuscript.

Response to reviewer

We have altered the key words as suggested.

Author's action

Keywords; Antibiotic resistance, Linezolid, orthopaedic infections, osteomyellitis, periprosthetic joint infection

Reviewers comment six

Introduction Authors should include in their literature review the study of Mason et al. Orthopedics. 2008 Nov;31(11):1140 and discuss it.

Response to reviewer

We agree that this is a very interesting article and it should be included in our study. However, we felt that it would be best placed in our discussion when we explain the potential side effects of linezolid, rather than in the introduction.

Author's action

Discussion

Furthermore, there are several documented case reports of serotonin toxicity when linezolid is used with selective serotonin reuptake inhibitors. [37] The symptoms of serotonin syndrome are alteration of mental state, autonomic dysfunction, and neuromuscular disorders. None of our patients developed such symptoms, however it is important that surgeons and physicians are aware of the nonspecific presentation of serotonin symptoms and the treatment when using linezolid.

Reviewers comment seven

In the last paragraph of the Introduction section authors should clearly mention that their investigation is not based on measurements performed by them.

Response to reviewer

Thank you for your comment. The last paragraph of the introduction is copied below. Our study group does not fully understand what the reviewer means by requesting us to mention that our investigation is not based on measurements by ourselves. Please can you elaborate on this.

'Although the efficacy of Linezolid has been well demonstrated in nosocomial pneumonia, bacteraemia, skin and soft tissue infections there is limited data supporting its use in complex orthopaedic infections. The aims of this study were to identify patients treated with linezolid for orthopaedic infection and evaluate its efficacy and tolerability. '

Reviewers comment eight

Methods; Second paragraph, line 10. Replace "where" with "were".

Response to reviewer

We have altered this spelling mistake in the methods

Author's action

Fifteen patients were initially started with parenteral vancomycin therapy prior to commencement of linezolid when patients were discharged from hospital.

Reviewer comment nine

Tables The tables in the manuscript are not presented in whole; authors should use the landscape presentation for these pages. Authors should change with each other the columns "Sex" and "Age". Authors should state the meaning of "N" and "Y" in the columns "Surgical intervention", "Concurrent antibiotics" as well as "Previous antibiotics".

Response to reviewer

Thank you for your comments regarding our table and its format. We have made all the changes suggested other than state the meaning of concurrent antibiotic. Concurrent antibiotic refers to the antibiotic that the patient was on as well as linezolid and we feel that this is already clear in the title.

Reviewer two

Reviewer comment 1

This is an interesting and important case series, but needs more detail. There are some typos

Response to reviewer

Many thanks for your comment. We have amend the typing mistake as requested.

Reviewer comment 2

At least some discussion of cost would be helpful, bed days saved, number of outpatient appointments required. Cost of drug vs vancomyocin and a picc line. Monitoring for myelosupression etc

Response to reviewer

We agree with the reviewer that the cost implications for the use of linezolid are great. However the main aim of this paper was analyse the management of patients treated with linezolid for orthopaedic infection within our unit and evaluate efficacy, tolerability and the resolution of infection. The points that you have highlighted are important and we have included them in our discussion but we have not performed a cost

broke down in our patients. This is mainly due to the fact we do not have a control group to compare them too.

Authors action

The following points have been added to our discussion

Linezolid has 100% oral bioavailability. [21] Oral administration avoids the morbidity associated with intra-venous access and line sepsis and the cost of insertion and monitoring of these devices. This may aid in shortening patient stay, as traditionally these patients have required lengthy admissions for parenteral antibiotics. This potentially has major cost implications for health care systems. However, this must be offset by the need to undertake more outpatient follow-up appointments and the fact regular blood tests need to be undertaken to monitor for myelosuppresion. Itani et al demonstrated statistically significant reduction in length of in-patient stay with MRSA soft tissue infection in patients treated with linezolid as opposed to vancomycin.[22] Further studies have also demonstrated reduction of length of hospital stay in patients with MRSA treated with linezolid. [9, 23]

Reviewer comment 3

I am surprised by the high incidence of monotherapy. This is unusual and raises concerns regarding resistance. Please discuss

Response to reviewer

We agree with the reviewer that there is the potential to develop resistance but resistance rates to linezolid are very low. Linezolid resistance occurred in <1% of *Staph. aureus*, coagulase-negative staphylococci , and enterococci isolates from the US between 2002 and 2009. (Ross JE, Farrell DJ, Mendes RE, Sader HS, Jones RN. Eight-year (2002–2009) summary of the linezolid (Zyvox® Annual Appraisal of Potency and Spectrum; ZAAPS) program in European countries. J Chemother. 2011;23(2):71–76).

Resistance usually develops after prolonged therapy with linezolid for serious infection, although nosocomial acquisition of both resistant enterococci and coagulase-negative staphylococci has been reported, including cases in patients with no prior treatment with linezolid. It has been proposed that combination with a second antibacterial agent, particularly rifampicin or fusidic acid, may delay the emergence of linezolid resistance in *S. aureus.* However, linezolid is most commonly still used as

monotherapy.

Author's action

We have included the following changes to our discussed;

Only 3 of the patients in our study group were treated with an additional antibiotic as well as Linezolid. In all cases this was oral Rifampicin. Resistance rates to linezolid have been reported to be low [28] Linezolid resistance occurred in <1% of *staphylococcus aureus*, coagulase-negative staphylococci , and enterococci isolates from the US between 2002 and 2009. [29] Resistance usually develops after prolonged therapy with linezolid for serious infection [30] although nosocomial acquisition of both resistant enterococci [31] has been reported, including cases in patients with no prior treatment with linezolid. [32] It has been proposed that combination with a second antibacterial agent, particularly rifampicin or fusidic acid, may delay the emergence of linezolid resistance in *staphylococcus aureus.* [33]

Reviewer comment 4

Discussion of the contraindications would be helpful.

Response to reviewers

We have added a discussion on this highlighted point.

Author's action

The following changes have been made to the discussion;

Other notable side effects include peripheral neuropathy. [36] A single patient within this study group developed a visual disturbance. Optic neuropathy secondary to linezolid has been described [14] and there are concerns that linezolid induced peripheral neuropathy may be an irreversible event. [34,36] Furthermore, there are several documented case reports of serotonin toxicity when linezolid is used with selective serotonin reuptake inhibitors. [37] The symptoms of serotonin syndrome are alteration of mental state, autonomic dysfunction, and neuromuscular disorders. None of our patients developed such symptoms, however it is important that surgeons and physicians are aware of the nonspecific presentation of serotonin

symptoms and the treatment when using linezolid. Additionally, contraindications to commencing linezolid include patients taking any medicine which inhibits monoamine oxidases A or B (e.g. phenelzine, isocarboxazid) or within two weeks of taking any such medicinal product. Unless patients are monitored for potential increases in blood pressure, linezolid should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis and/or patients taking any of the following types of medications: directly and indirectly acting sympathomimetic agents (e.g. pseudoephedrine), vasopressive agents (e.g. epinephrine, norepinephrine), dopaminergic agents (e.g. dopamine, dobutamine).

Reviewer comment 5

Can you account for the reasons behind the failures?

Response to reviewer

Three patients suffered adverse an adverse reaction to linezolid. One case complained of nausea and vomiting (patient 15), another of visual disturbances (patient 20) and in one instance linezolid treatment was stopped due to thrombocytopenia (patient 16). Two patients died (patient 14,16) as a sequalae of sepsis. Infection resolved in patient 20, but in patient 15, 19 and 21 treatment failed to clear the infection and patients were re-admitted. There infection subsequently resolved but this was after discontinuing linezolid. The reasoning behind these failures are not clear. This resulted in a readmission rate of 13% (3/22).

Author's action

The following has been added to the results section;

Three patients suffered adverse an adverse reaction to linezolid. One patient complained of nausea and vomiting (patient 15), another of visual disturbances (patient 20) and in one instance linezolid treatment was stopped due to thrombocytopenia (patient 16). Two patients died (patient 14,16) as a sequalae of sepsis. Infection resolved in patient 20, but in patient 15, 19 and 21 treatment failed to clear the infection and patients were re-admitted. There infection subsequently resolved but this was after discontinuing linezolid. The reason behind these failures are not clear. This resulted in a readmission rate of 13% (3/22).

Reviewer comment 6

Is there anything in your data to help guide who is suitable and who is not?

Response to reviewer

The limitation of our study is the small numbers and also the lack of control. Therefore it is difficult to draw any accurate conclusion with regards to suitability for treated. Our institute works closely with our microbiologists and as long as the patient does not have any contraindications for treatment we consider linezolid as a treatment option.

Reviewer comment 7

What was the readmission rate and reason for this.

Response to reviewer

The readmission rate was 13% (3/22) and all of these patients required alteration to their antibiotic regimen and stopped linezolid treatment

Author's action

The following has been added to the results section;

Three patients suffered adverse an adverse reaction to linezolid. One patient complained of nausea and vomiting (patient 15), another of visual disturbances (patient 20) and in one instance linezolid treatment was stopped due to thrombocytopenia (patient 16). Two patients died (patient 14,16) as a sequalae of sepsis. Infection resolved in patient 20, but in patient 15, 19 and 21 treatment failed to clear the infection and patients were re-admitted. There infection subsequently resolved but this was after discontinuing linezolid. The reason for these failures are not clear. This resulted in a readmission rate of 13% (3/22).

Reviewer comment 8

What is the success rate for parenteral treatment?

Response to reviewer

None of our patients received parenteral treatment and therefore this was not discussed for this reason. We

do not have any experience of this and very few studies have reported results of this route of administration. Beringer et al demonstrated that linezolid oral suspension may be administered via the enteral route to hospitalized patients without compromise in its excellent bioavailability or rapid rate of absorption. (Beringer et al. Absolute Bioavailability and Pharmacokinetics of Linezolid in Hospitalized Patients Given Enteral Feedings. Antimicrob Agents Chemother. 2005 September; 49(9): 3676–3681

Reviewer 3

Reviewer comment 1

This is not a very well written manuscript. In abstract section, authors did not detailedly describe the aims and methods of the study.

Response to reviewer

Many thanks for your review. We agree that the abstract requires a clear aim and we have added this. However, we feel the methods are described in detail.

Author's action

Please see the changes to the abstract below;

Abstract

Introduction

Treatment of infection following orthopaedic related procedures remains problematic requiring the use of both antibiotic administration and concomitant surgical management. The prospect of an effective oral agent could potentially reduce hospital stay and negate the requirement for parenteral treatment.

Aim

The aim of this study was to analyse the management of patients treated with linezolid for orthopaedic infections.

Methods

Twenty-two patients with orthopaedic related infections receiving a course of linezolid were reviewed retrospectively. Patients were classified into either post trauma, post arthroplasty and non trauma related infections. A diagnosis of infection was based on clinical findings, positive microbiological specimens, and positive signs of infection on radiological imaging and raised inflammatory markers. Pathogens isolated, inflammatory markers both at presentation and at final follow up, length of linezolid treatment, adverse drug reactions, concomitant anti-microbial therapy, length of hospital stay and any surgical interventions were recorded.

Results

Infections were classified as post arthroplasty (n=10), post trauma surgery (n=8) or non-trauma related infections (n=4). Twenty patients (91%) underwent surgical intervention as part of their treatment. The number of required surgical procedures ranged from 1 to 6 (μ=2.56). Mean total length of stay per admission was 28.5 days (range 1-160 days). Furthermore, the mean duration of treatment with linezolid of patients who had resolution of symptoms was 31 days (range 10-84). All patients within this group were discharged on oral linezolid.

Pathogens isolated included methicillin resistant staphylococcus aureus, coagulase negative staphylococci, coliforms, enterococcus, staphylococcus epidermidis, streptococcus viridans, escherisia coli, group B streptococcus and pseudomonas.

An overall 77% of patient's demonstrated resolution of infections at follow-up with a mean C-reactive protein reducing from 123 mg/l to 13.2 mg/l.

Conclusion

This study demonstrates that the use of linezolid offers excellent efficacy in orthopaedic related infections when used alongside appropriate surgical management.

Reviewer comment 2

The conclusion was not reliable because this study was not a randomized and controlled study. In addition, the sample number was small with only 22 patients.

Author's response

Many thanks for your comment and we agree with the limitation of our study and as you have highlighted we have mentioned these limitations in our discussion and agree with the fact a further study is needed with a control group. Despite this limitation, our study group remains one of the largest available in the literature.

Reviewer comment 3

Orthopedic operation related infection is a severe complication, and often seen clinically. It usually first needs thorough debridement, then according to culture and susceptibility test to select suitable antibiotics.

Response to reviewer

We agree with this comment and is the same approach we took in the management of this cohort of patient.

Thank you again for publishing our manuscript in the *World Journal of Orthopaeidcs*.

Sincerely yours,

Mr S Graham

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