Macrolide Use as Prophylaxis for Ventilator Associated Pneumonia

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Introduction

Pneumonia has accounted for approximately 15% of all hospital-associated infections and 27% of all infections acquired in the medical intensive-care unit (ICU), primary risk factor for this being mechanical ventilation (with its requisite endotracheal intubation). As it stands in the CDC recommendations, there are no real preventive measures to insure the incidence reduction of Ventilator Associated Pneumonia (VAP) aside from the general contamination precautions (2).

The use of macrolides has recently received much attention, demonstrating they also possess immunological modifying properties (4, 5, 6). Their use has shown to improve not only the mortality, but also the morbidity in severe pneumonias (7, 8). Recently, their use has been implemented into the treatment and prophylaxis of Cystic Fibrosis pulmonary infection, improving overall pulmonary function and reducing severity and number of exacerbations (9), even when cultured organisms showed resistance to the macrolides (10). Macrolides are now even been researched in the treatment of sepsis with encouraging preliminary results (11), one study showing reduction in mortality and morbidity, reduction in the time needed for extubation and delayed death in those that died from sepsis (12).

Our purpose was to evaluate if events of VAP could be prevented and/or modified in its severity, morbidity and prognosis by the use of prophylaxis with the administration of a macrolide course.

Study Design

The study was a prospective, double-blind, randomized, placebo-controlled, single-center clinical trial that was approved by the ethics committees of the hospital and by the IRB. During the period from August 2011 until March 2012, twenty patients were screened and 20 patients were enrolled. The study was concluded when the last patient of the 20 completed the scheduled treatment and observation span. Inclusion criteria were as follows: (1) written informed consent provided by first- or second-degree relatives, (2) patient on mechanical ventilation for less than 48 h before enrollment, (3) age above 21 years, (4) no clinical and radiographic evidence of pneumonic process, and (5) admission to the Intensive Care Unit.

Exclusion criteria were as follows: (1) underage at time of enrollment; (2) evidence of pneumonia either by clinical or radiologic data; (3) patient with leukemia or receiving chemo/radiotherapy; (4) pregnancy at time of enrollment; (5) Patient unable to give consent and no family present for consent; and (6) patients with underlyng cardiac arrhythmias. VAP was diagnosed in patients who presented with all of the following: (1) new or persistent consolidation on lung radiography, (2) purulent tracheobronchial secretions (TBSs), and (3) a clinical pulmonary infection score (CPIS) (16). The CPIS was determined as assessed by Pugin et al.

Treatment Administration

Patients were randomly assigned to receive placebo, azithromycin or clarithromycin treatment. The study drugs were administered during 14 consecutive days. Dosing consisted as follows: clarithromycin was 250mg PO every 12 hrs, azithromycin was 500mg IV daily and placebo was 250ml of normal saline solution once daily. All enrolled patients received concomitant antimicrobials only if infection at any site was identified at or after inclusion in study by primary care team.

Evaluation of Patients

Patients were observed for 28 days. All coadministered medications were recorded. Daily visits were performed at the same time of day as administration of the first dose of the study drug. Quantitative Tracheo-bronchial secretion (TBS) cultures were performed at baseline and on the fifth and tenth days of follow-up. A serious adverse event (SAE) was considered to be any unexpected event that (1) led to death, (2) put the patient's life in danger, (3) prolonged hospitalization, (4) was accompanied by permanent or considerable disability, or (5) was accompanied by any grade IV laboratory abnormality. Organ failure and death related to sepsis were not assessed as SAEs. Times to extubation or death were recorded.

Statistical Analysis

Unblinding for the study drug was performed when follow-up of all patients was completed. Primary end points were the number of days on therapy, number of days receiving mechanical ventilation, mortality and development of any pneumonic process . All end points were right censored on the 28th day. Comparisons of categorical variables by protocol type were performed using Fisher's exact test. Continuous variables were analyzed by Anova or Kruskal-Wallis if variables were not normally distributed. Statistical analyses were performed with STATA 11.0

Results

In the placebo group, VAP developed in 5 (83.33%) of cases within a median time of 5 days. In both the clarithromycin and the azithromycin group, VAP did not develop in any of the patients regardless of intubation time ($p < 0.004$). There were patients in all groups started on antibiotics for other infection other than pneumonia, the differences not being statistically significant, the most common being urinary tract infection (UTI). All patient in the treatment groups did not have clinically significant secretion, in contrast to control group were most patient begun to develop tracheal secretions 4-7 days after inclusion in study. Analysis showed no statistical difference between all groups for all-cause mortality. Specific cause mortality analysis is still pending. However initial overview shows that in placebo group most deaths were sepsis related vs. intracerebral bleeding complication in treatment groups. Whether this difference is statistically significant is yet to be determined. No study-drug–related SAE (0%) were observed among patients in either the treatment or placebo groups.

Table 1. Demographic characteristics of study patients according by protocol type

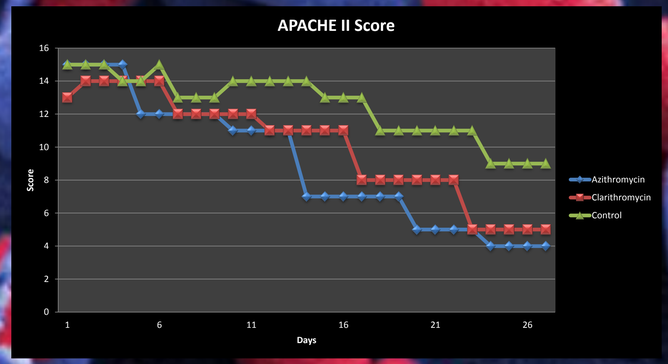
Variable	*Azithromycin (n=7) N(%)*	*Clarithromycin (n=6) N (%)*	*Control (n=7) N (%)*	*P-value**
Age (mean ± sd)	51.3 ± 22.1	54.7 ± 12.1	58.4 ± 14.2	0.7359
Age				0.635
< 55 yrs	5 (71.4)	3 (50.0)	3 (42.9)	
≥ 55 yrs	2 (28.6)	3 (50.0)	4 (57.1)	
Sex				0.602
Male	4 (57.1)	4 (66.7)	6 (85.7)	
Female	3 (42.9)	2 (33.3)	1 (14.3)	
Insurance type				0.175
Public	3 (42.9)	2 (33.3)	2 (28.6)	
Private	1 (14.3)	4 (66.7)	1 (14.3)	
None	3 (42.9)	0. 0.0)	4 (57.0)	

Table 2. Clinical characteristics of study patients per Study Group

Variable	*Azithromycin N(%)*	*Clarithromycin N (%)*	*Control N (%)*	*P-value**
Admission dx				0.999
Cerebrovascular accident	4 (57.1)	5 (83.3)	4 (57.1)	
Drug intoxication	1 (14.3)	0 (0.0)	1 (14.3)	
Diabetic ketoacidosis	1 (14.3)	0 (0.0)	0 (0.0)	
Asthma	1 (14.3)	0 (0.0)	1 (14.3)	
COPD	0 (0.0)	0 (0.0)	1 (14.3)	
CHF	0 (0.0)	1 (16.7)	0 (0.0)	
Clinical Parameters				
WBC	15.9 ± 7.4	19.8 ± 11.6	10.8 ± 4.6	0.1668
Temperature	36.4 ± 0.5	36.5 ± 0.3	33.8 ± 0.3	0.1014
Apache score at admission	14.4 ± 9.4	13.8 ± 4.7	15.0 ± 4.9	0.9570
Last apache score	4.2 ± 1.3	7.3 ± 0.10	11.5 ± 5.3	**0.0179**
GCS	8.4 ± 2.3	8.7 ± 2.9	7.9 ± 2.5	0.8415

Table 3. Morbidity and Mortality

Variable	*Azithromycin*	*Clarithromycin*	*Control*	*P-value**
Mean Intubation time (Days)	3.4	8.8	14.5	**0.0348**
Mean From admission to death (Days)	6	10	14	**0.7962**
Number of Deaths	2	2	3	**0.835**



Discussion

Analysis showed no statistical difference between all groups for all-cause mortality. Specific cause mortality analysis is still pending. However initial overview shows in placebo group most deaths were sepsis related vs. intracerebral bleeding complication in treatment groups. Whether this difference is statistically significant is yet to be determined. No study-drug–related SAE (0%) were observed among patients in either the treatment or placebo groups.

As noted in the study results, there was a statistically significant difference in the development of VAP and the duration of mechanical ventilation in patients receiving macrolides. It successfully prevented the development of VAP in all patients in treatment groups ($p<0.004$) and shortened the duration of use of mechanical ventilation by a mean of 8.4 days ($p=0.0348$).

Discussion (continued)

No positive cultures were obtained from sputum samples, making any analysis of pathogen-related response, morbidity and mortality impossible. Following the microbial susceptibility antibiogram from our institution, most isolates are multi-drug resistant (MDR) gram negative pathogens. This finding is in contrast to epidemiologic results from mainland United States, where gram-positive bacteria predominate in VAP. Our findings are more compatible with those from most of Europe, with species of *A baumannii* and *P aeruginosa* implicated in both early and late VAP.

The mechanism of action of macrolides in patients is still obscure. A conventional antibiotic effect is unlikely, noting the widespread resistant of the common pathogens of VAP. Beneficial effect has been noted in conditions such as cystic fibrosis, diffuse panbronchiolitis, and bronchiectasis. These types of patients are usually colonized and infected by gram-negative MDR's and publications have shown significant improvement in overall condition and decrease in pulmonary infections when begun on macrolides. It is also believed that macrolides may also act as inhibitors of quorum sensing among bacteria that colonize the airways.

The results of this study should be considered for the following reasons. Despite the small population, we were able to show that macrolide use appears to have effectively prevented VAP in 100% of cases. Patients on treatment groups had a mean intubation period which was significantly less than placebo group. These findings represent a decrease in morbidity for the patient and a reduction of costs when considering intubation duration, antibiotic administration, ICU stay, among other variables. Although all-cause mortality was not different among groups, we believe further analysis may still show a decrease in sepsis and/or pneumonia related mortality.

This study has several limitations. The most notable is its sample size. We believe this was due to the nature of our hospital, being a supratertiary care center and usually receiving some of the most complicated patients in our area. This translates to most patients being diagnosed with some type of pulmonary infection, excluding them from this study. To fully appreciate the full effects of macrolides in VAP and sepsis, other studies will have to be performed, with larger populations. The good tolerace seems to allow for this. It is the opinion of our research group that, despite the small sample size, this study shows a great efficacy in preventing VAP with good tolerance by patients.

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