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RESEARCH ON THE INCIDENCE OF SIDE AND ADVERSE EFFECTS OF LINEZOLID AND VANCOMYCIN IN ADULT PATIENTS

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Abstract. We have searched for the incidence of side effects of linezolid and vancomycin therapy in adult patients with sepsis, hospitalised during 2000 – 2007 in the Infectious Diseases Hospital Iaşi. In the study, we admitted patients treated with vancomycin (n=255, median dose 1g bid i.v., mean therapy duration 8.41±2.46 days) and linezolid (n=197, median dose 0.6g bid, 64.97% p.o. and 35.02% i.v., mean therapy duration 10.82±3.58 days. We have only considered patients with at least 4 days of treatment with studied antibiotics and cases with identified etiologic bacteria. Main adverse reactions noticed for vancomycin were: coetaneous rash (31 cases, 12.15%), abdominal pain (18 cases, 7.05%), vomiting (10 cases, 3.92%). Phlebitis was noticed in 84 cases (32.94%). Only 1 case manifested convulsions (0.39%). Serum billirubine levels increased in 29 cases (11.37%). Main adverse reactions noticed for linezolid were: diarrhoea (12 cases, 6.09%), vomiting (8 cases, 4.06%), coetaneous rash (5 cases, 2.53%). Also, psychomotor agitation was noticed in 7 cases (3.55%). 2 patients (1.01%) presented intense cough, and this symptom was associated with prescribed antibacterial therapy. None of the cases taken into study imposed replacement of the antibacterial drug due to adverse reactions. The incidence of adverse reactions was significantly lower in the case of linezolid vs. vancomycin, in the conditions of comparable efficacy.
Keywords: linezolid, vancomycin, side effects, benefit – risk ratio

Introduction

Multi-resistant Gram-positive infections and especially hospital *Staphylococcus aureus* infections and *Enterococcus spp.* represent real challenges from the physicians' point of view. Among these, we emphasise on the reduced therapeutic options, increased incidence of resistant bacterial strains and the relatively great number of side effects.

Among the antibacterial chemoterapics used in treating severe multi-drug resistant Gram-positive infections, glycopeptides (especially vancomycin) and oxazolidinone (linezolid being the main representative of this class used in practice) are the most important therapeutic options. Recently, linezolid started to be used for the treatment of multidrug-resistant tuberculosis (Condos R. et al., 2008[1]).

Besides bacterial resistance, other side effects to antibacterials are important causes for limiting the use of these drugs.

Aim

We have searched for the incidence of side and adverse effects of linezolid and vancomycin therapy in adult hospitalised patients.

Patients and Method

The study included patients with at least 4 days

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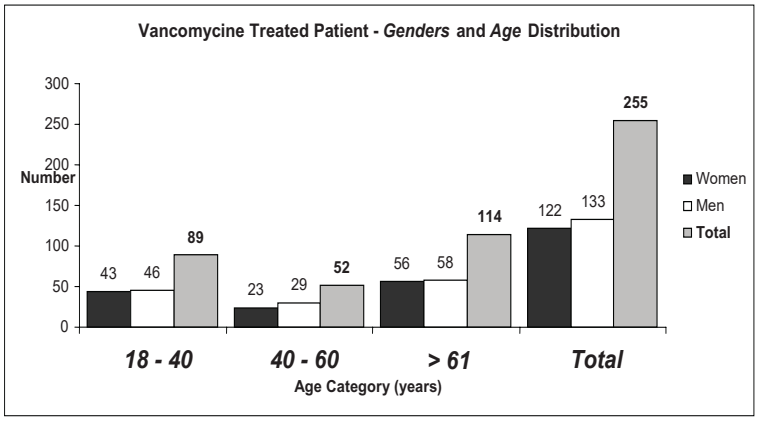

Figure 1 Vancomycin-treated patients – age and gender distribution

of treatment with vancomycin or linezolid and cases with identified bacteria (only mono-bacterial infections). Antibacterial therapy was performed according to the antibiogram.

Not included into the study were pregnant or breast-feeding women, patients in septic shock state, patients with neoplasm, patients with history of allergy or other adverse reactions to the studied anti-bacterial drugs.

The study was approved by the hospital's ethical committee.

Applying the above inclusion and exclusion criteria, the studied groups were:

- for vancomycin: 255 patients (132 men and 123 women) (Fig. 1), hospitalised during 2000 – 2007. Median dose was 1g bid (intravenously) and mean therapy duration was 8.41±2.46 days (median: 11 days). The most frequently isolated bacteria were *Staphylococcus aureus* (123 cases), *Streptococcus pneumoniae* (47 cases), *Enterococcus spp.* (26 cases) and *Clostridium difficile* (24 cases).
- for linezolid: 197 patients (112 men and 85 women) (Fig. 2), hospitalised during 2004 – 2007. Median dose was 0.6g bid (64.97% per os and 35.02% intravenously) and mean therapy duration was 10.82±3.58 days. The isolated bacteria were *Staphylococcus aureus* (103 cases), *Streptococcus pneumoniae* (55 cases), *Enterococcus spp.* (26 cases) and *Clostridium difficile* (24 cases).

For each patient we performed physical examination, electrocardiogram, thoracic X-ray examination and main laboratory analysis (biochemistry, complete blood count etc) at admittance and during the hospitalising period.

No death cases have been reported during the hospitalising period in studied patients.

Results

For vancomycin, adverse reactions were reported in 102 patients (40% of total). Main adverse reactions noticed for vancomycin were: skin rash (31 cases, 12.15%), abdominal pain (18 cases, 7.05%), vomiting (10 cases, 3.92%). Phlebitis was noticed in 84 cases (32.94%). Only 1 case manifested convulsions (0.39%) and anticonvulsive therapy was used. Serum billirubine levels increased in 29 cases (11.37%).

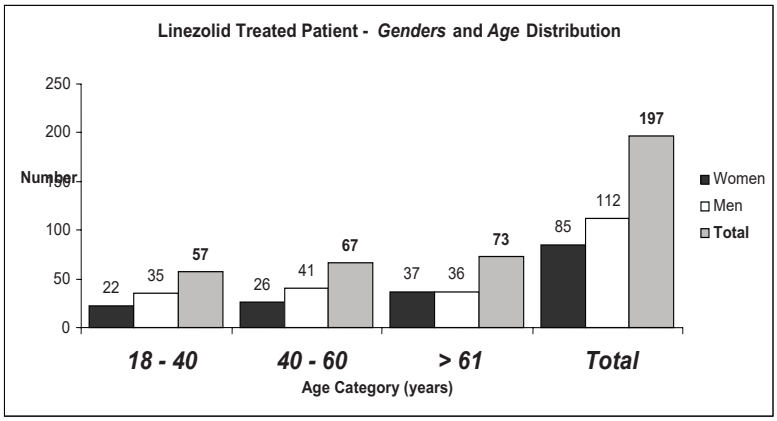

Figure 2 Linezolid-treated patients – age and gender distribution

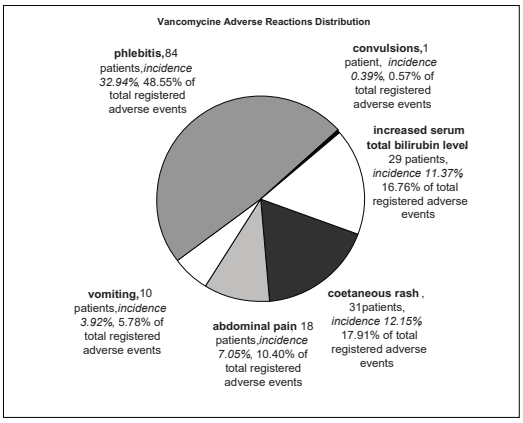

Figure 3 Vancomycine adverse effects

Allergic reactions were more common in women than in men (14.63% in women vs. 9,84% in men, $p<0.05$ – χ^2 test), but our study failed to determine a reasonable explanation for this fact.

For linezolid, adverse reactions were reported in 29 patients (11.37% of total). Main adverse reactions noticed for linezolid were: diarrhoea (12 cases, 6.09%), vomiting (8 cases, 4.06%), coetaneous rash (5 cases, 2.53%). Also, psychomotor agitation was noticed in 7 cases (3.55%). 2 patients (1.01%) presented intense cough, and this symptom was associated with prescribed antibacterial therapy.

In all cases, the intensity of side effects was considered mild to moderate.

Allergic side effects were treated with antihistaminic H_1 drugs in 80% of linezolid-treated cases and in 61.29% of vancomycin-treated cases. For treatment of vancomycin-induced convulsion (1 case, male) we used Phenobarbital.

None of the cases required interruption of antibacterial treatment due to adverse effects.

The incidence of adverse reactions was significantly lower for linezolid compared to vancomycin, in the conditions of comparable efficacy.

Discussions and conclusion

In the current study, the incidence of hepatic adverse effects of vancomycin (increased bilirubine serum level) was higher than that reported by other authors (Springer B.D. et al., 2004[10]), while the incidence of vancomycin-induced allergic reactions is similar to that reported by other authors (Shimada K., 2003[9]). No "red-man" syndrome (which is specific to glycopeptides and especially to vancomycin) has been noticed. Other very rare adverse effects to vancomycin administration mentioned by medical literature, but not detected by us, include: bullous dermatitis, priapism, anaemia, thrombocytopenia, pancytopenia, severe arterial hypotension. Also, the current study couldn't evaluate the ototoxicity of vancomycin (this adverse effect being evaluated by other authors at a 5% incidence).

Our data are in agreement with that of Falagas and Vardakos (2008)[2] studies, reporting linezolid as being more efficient than glycopeptides against multidrug resistant Gram-positive bacteria and vancomycin-resistant enterococci. Also, linezolid determined less frequent and less severe side effects compared to vancomycin. Falagas and Vardakos

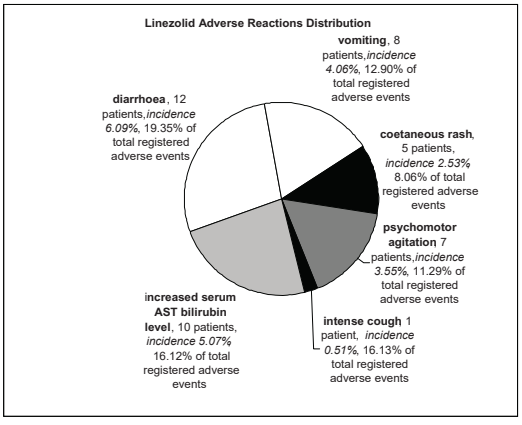

Figure 4 Linezolid adverse effects

(2008)[2] consider that linezolid is associated with a greater incidence of adverse events such as nausea, vomiting, diarrhoea and headaches, while thrombocytopenia and fungal infections are very rare. Myalgia / arthralgia was the most important of the noticed adverse effects to linezolid in the study performed by Linden P.K,, 2002[5]. Linezolid, administered in doses ranging from 200 mg every 12 hours (low) to 600 mg every 12 hours (high), administered both orally and injectable, also determined a lot of side reactions, but these were less severe than those induced by vancomycin. In our study, the incidence of vomiting was 4.06% and the incidence of diarrhoea was 6.09%. We have not noticed cases with fungal infections clearly related to linezolid administration (Norrby R., 2001[7]). Regarding thrombocytopenia, arterial hypertension and serotonin-like syndrome, we have reported no cases. Peripheral or optic neuropathy or linezolid associated with lactic acidosis, reported by other authors (Martini B.C., 2008[6]; Scotton P. et al, 2008[8]), did not appear in our patients. In about 10% of our patients we have reported insomnia, but this could not be linked to linezolid treatment.

Generally, the adverse reactions to linezolid therapy noticed by our team were less severe than those reported by other authors.

We consider that the benefit/risk ratio is very favourable for this particular drug.

One should specifically consider the progressive increase of bacterial resistance to antibacterial drugs, as it substantially reduces the therapeutic possibilities of using different drugs. Also, the other side effects should not be neglected or under-reported. The incidence of infections with multi-drug resistant Gram-positive bacteria has progressively increased during the last decades. Especially infections with MRSA (multidrug resistant *Staphylococcus aureus* strains) and enterococci determine more frequent and severe problems.

In case of vancomycin resistant strains, such as *S. aureus* and *E. faecalis* vancomycin use is limited.

The most frequently used in such cases are linezolid 600 mg bid and tigecycline 100 mg every 24 h (LaPlante K.L. et al., 2006[3]). In this context, vancomycin and linezolid side effects are particularly important for clinical practice.

In infections with vancomycin-resistant enterococci (VRE), quinapristin / dalfopristine and linezolid are the antibacterial drugs of election (Linden P.K., 2007[4]). Quinapristin / dalfopristine is a streptogramin. This antibiotic impairs bacterial protein synthesis and late peptide chain extrusion steps. Though bacteriostatic, it has a lot of important side effects. Quinapristin / dalfopristin (now applied as a phase III clinical trial therapy) can be considered a valuable perspective in Gram-positive infections treatment. Also, tigercycline (GAR-336, an analogue of minoycline), oretavacin (LY333328, a glycopeptide) and ramoplanin (a new glycolipodepsipeptide antibacterial drug) are possible therapy alternatives.

The septic state may significantly modify the incidence of side effects to antibacterials and this is more evident in case of allergic effects.

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