EVALUATION OF NEEDS FOR PHARMACOKINETIC MONITORING OF AMINOGLYCOSIDES AND VANCOMYCIN IN TERTIARY HOSPITAL

MASTER WORK

Supervised by:
Doc. Dr. Romaldas Mačiulaitis
Performed by:
Omar Mneimneh

Kaunas 2007
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>3</td>
</tr>
<tr>
<td>1. Definition of rational use of medicines</td>
<td>4</td>
</tr>
<tr>
<td>1.1 The problem of irrational use</td>
<td>4</td>
</tr>
<tr>
<td>1.2 Common types of irrational medicine use according to WHO</td>
<td>4</td>
</tr>
<tr>
<td>1.3 Measuring the type and the degree of irrational use</td>
<td>5</td>
</tr>
<tr>
<td>2. Guidelines for antimicrobial Chemotherapy</td>
<td>5</td>
</tr>
<tr>
<td>3. Aminoglycosides</td>
<td>8</td>
</tr>
<tr>
<td>3.1 Clinical pharmacokinetics</td>
<td>8</td>
</tr>
<tr>
<td>3.2 Pharmacodynamics</td>
<td>12</td>
</tr>
<tr>
<td>4. Vancomycin</td>
<td>13</td>
</tr>
<tr>
<td>4.1 Clinical pharmacokinetics</td>
<td>13</td>
</tr>
<tr>
<td>4.2 Pharmacodynamics</td>
<td>15</td>
</tr>
<tr>
<td>5. Clinical Application of pharmacokinetic data and dosing considerations</td>
<td>15</td>
</tr>
<tr>
<td>6. Methodology of the study</td>
<td>17</td>
</tr>
<tr>
<td>7. Results</td>
<td>18</td>
</tr>
<tr>
<td>7.1 Defined daily dose per 100 Occupied Bed Days of aminoglycosides</td>
<td>18</td>
</tr>
<tr>
<td>and vancomycin</td>
<td></td>
</tr>
<tr>
<td>7.2 Aminoglycosides and vancomycin uses in 2006</td>
<td>20</td>
</tr>
<tr>
<td>7.3 Consumption tendencies of aminoglycosides and vancomycin across three years</td>
<td>23</td>
</tr>
<tr>
<td>7.4 Gentamicin and vancomycin monitoring assessment in 2006</td>
<td>28</td>
</tr>
<tr>
<td>7.5 Carbamazepine, valproic acid and digoxin serum concentrations measurements assessment in 2006</td>
<td>29</td>
</tr>
<tr>
<td>7.6 Pharmacokinetic monitoring of patients in KMUC over 7 months</td>
<td>32</td>
</tr>
<tr>
<td>8. Discussion</td>
<td>40</td>
</tr>
<tr>
<td>Conclusions</td>
<td>42</td>
</tr>
<tr>
<td>Recommendations</td>
<td>43</td>
</tr>
<tr>
<td>Abstract</td>
<td>44</td>
</tr>
<tr>
<td>Annex</td>
<td>47</td>
</tr>
<tr>
<td>Reference</td>
<td>48</td>
</tr>
</tbody>
</table>
INTRODUCTION

Increasing resistance to antibacterial is a major public health problem. Antibacterial use is considered to be the main selective pressure driving this resistance and the rate at which resistance develops has been shown to be associated with drug consumption [1-3]. It has been suggested that reductions in the development of resistance will only result from significant changes in antibacterial use [3]. There are many antibacterial used in clinical practice. Most toxic groups, such as aminoglycosides and vancomycin deserve the biggest attention since their monitoring is crucial for their rational use. Consumptions and their tendencies are objects to country and health care specificities. Speaking about consumption of a high toxic antibiotic, we should also take into consideration the monitoring assessment practices. The use of serum drug level is appropriate for such a group of drugs with a narrow therapeutic index and a well-defined target serum concentration range.

Several ways are used to assess antibacterial consumption; through counting the expenditure, the distributions and individual prescription data. Worldwide, the calculation using the Defined Daily Dose (DDD) is widely used. DDD for most drugs have been defined by the World Health Organization (WHO) [4]. The DDD is the assumed average maintenance dose per day for a drug when used for its main indication in adult with normal organ function. Inpatient usage is usually expressed per 100 occupied bed days (OBD) to take into account variation in workload.

Since consumptions of gentamicin, amikacin, tobramycin and vancomycin and the level of Rational Drug Use (RDU) are unknown in our hospital, **the aim of this study was to evaluate pharmacoepidemiology of aminoglycosides’ and vancomycins’ use and check the level of pharmacokinetic monitoring during several years in tertiary hospital.** Our tasks were:

1. To obtain DDDs data of aminoglycosides and vancomycin for three consecutive years in tertiary hospital;
2. To compare the data year-on-year basis;
3. To sort the consumption tendencies of highest consuming departments; and
4. To evaluate the serum concentrations monitoring of aminoglycosides and vancomycin and to compare them with other highly toxic drugs;
5. To follow cohort of consecutive patients for whom aminoglycosides and vancomycin serum concentrations were measured and consider aspects for rationalization;
6. To define possible interventions for rationalization of therapy with antibiotics.
I. Definition of rational use of medicines:

Patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community.” (WHO, 1985).

1.1 The problem of irrational use

Irrational or non-rational use is the use of medicines in a way that is not compliant with rational use as defined above. Worldwide more than 50% of all medicines are prescribed, dispensed, or sold inappropriately, while 50% of patients fail to take them correctly. Moreover, about one-third of the world’s population lacks access to essential medicines.

Inappropriate doses result in serious morbidity and mortality, particularly for childhood infections and chronic diseases, such as hypertension, diabetes, epilepsy and mental disorders.

Furthermore, over-use of antimicrobials is leading to increased antimicrobial resistance and non-sterile injections to the transmission of hepatitis, HIV/AIDS and other blood-borne diseases. Finally, irrational over-use of medicines can stimulate inappropriate patient demand, and lead to reduced access and attendance rates due to medicine stock-outs and loss of patient confidence in the health system. (WHO, September 2002)

Increasing resistance to antibacterials is a major public health problem. Antibacterial use is considered to be the main selective pressure driving this resistance [1, 2], and the rate at which resistance develops has been shown to be associated with drug consumption. [3]

1.2 Common types of irrational medicine use according to WHO are:

• the use of too many medicines per patient (polypharmacy);
• inappropriate use of antimicrobials, often in inadequate dosage, for non-bacterial infections;
• over-use of injections when oral formulations would be more appropriate;
• failure to prescribe in accordance with clinical guidelines;
• inappropriate self-medication, often of prescription-only medicines.
1.3 Measuring the type and the degree of irrational use.

There are several well-established methods to measure the type and degree of irrational use. Aggregate medicine (drug) consumption data can be used to identify expensive medicines of lower efficacy or to compare actual consumption versus expected consumption (from morbidity data). Anatomical Therapeutic Classification (ATC)/Defined Daily Dose (DDD) methodology can be used to compare drug consumption among institutions, regions and countries.

2. Guidelines for antimicrobial Chemotherapy

The essential feature of effective chemotherapeutic agent is the ability to inhibit microorganisms at concentration tolerable by the host. The most successful antimicrobial agents are those that target anatomic structures or biosynthetic functions unique to microorganisms.

The appropriate choice of chemotherapy for an infection depends on five considerations:

- The infecting organism and its antimicrobial susceptibilities
- The type of infection (e.g., abscess, bacteremia, meningitis, urinary tract infection)
- Host factors (e.g., neutropenia, immune deficiencies, concurrent illnesses, age, drug allergies, renal function)
- The antimicrobial agents (e.g., dosage, route of administration, drug interactions, serum levels and tissue penetration, potential toxicities, cost)
- Public health considerations.

The widespread use of antibiotics selects highly resistant organisms that subsequently pose a risk for the patient and the community.

Identifying the infecting organism and its antimicrobial susceptibilities is usually performed through laboratory procedures such as immunodiagnostic tests and cultures. Most laboratories test antimicrobial susceptibility by the disk diffusion method. When necessary, organisms can be treated by tube dilution techniques to determine the minimum inhibitory concentration (MIC) and the minimal bactericidal concentration (MBC) of various antibiotics. Newer techniques include the gradient diffusion method and various nucleic acid-based tests that can detect genes conferring antibiotic resistance
in bacteria. [5]

The efficacy of antibiotic therapy depends on drug delivery to the site of infection. Transport across the blood-brain barrier varies considerably among antibiotics. [6]

Because of widespread exposure, many patients develop allergies to antimicrobial agents. [7] A careful history of hypersensitivity should thus be obtained.

Patients with immunosuppressive illnesses are vulnerable to opportunistic pathogens. These patients may require broader antimicrobial coverage as well as intense therapy for ordinary pathogens. The same is true for patients with renal insufficiency or liver disease who can be usually susceptible to direct drug toxicity. Penicillins, cephalosporins, aminoglycosides, vancomycin and fluoroquinolones are excreted primarily by the kidney. Doses should be adjusted carefully.

In the elderly, physiological changes occur with age that can alter the pharmacokinetics of antimicrobial agents. The decrease in glomerular filtration rate (GFR) that occur with age as we mentioned can lead to the accumulation of drug excreted by the kidney. In the case of aminoglycosides and vancomycin, decreased dosage schedules are often required; ideally, drug levels should be measured and renal function should be monitored when these agents are given.

Like with any medicament, adverse drug reactions (ADR) may be observed with antibiotics. There are three general types of ADR to antimicrobial agents: Hypersensitivity which are not dose related, direct drug toxicity which is dose related and manifest with single or several organs, and finally microbial superinfection. The potential for toxicity varies widely from drug to drug. The principle antibiotics that are directly toxic to the kidney are aminoglycosides, polymyxins, and amphotericin B; azotemia and renal tubular damage may be caused by any of these drugs. Patients with preexisting renal insufficiency are at increased risk for toxic reactions to various antibiotics, including nephrotoxicity, seizures, ototoxicities which can be either vestibular or auditory, neurotoxicities, coagulopathies and other hematologic toxicities. Superinfection occur due to reduction of susceptible organisms from the normal flora of the skin, oral and genitourinary mucosa, and GI tract and exerts selective pressures that favor survival of drug-resistant organisms which can be at the site of original infection or else.

Finally, emergence of antimicrobial resistance is a public health concern. Due to its extensive use in intensive care units and other health care facilities, strongly favors the selection of resistant microbial species, particularly bacterial strains harboring plasmids that confer transmissible resistance. [8, 9]
Scheme 1. Inadequate drug utilization lead to an increase in mortality.

Infections from resistant strains can spread rapidly, first within an institution, then throughout a community, and eventually even globally.[10] Although antibiotic resistance is a worldwide problem, control depends on local measures, beginning with the judicious prescription of antibiotics by individual practitioners[11] and with formulary restrictions that reinforce prudence.[12]

Factors that may increase antimicrobial resistance in hospitals[13]:
- Greater severity of illness of hospitalized patients
- More severely immunocompromised patients
- Newer devices and procedures in use
- Increased introduction of resistant organisms from the community
- Ineffective infection control and isolation practices and compliance
- Increased empirical polymicrobial antimicrobial therapy
- High antimicrobial usage for geographical area per unit time
Part 3 and 4 cover the antibacterial activity, pharmacokinetical parameters, toxicity, and methods to control serum concentration of aminoglycosides and vancomycin.

3. Aminoglycosides

Aminoglycosides antibiotics are derivatives of naturally occurring fungal organisms that have, in most cases, been modified to increase activity and reduce toxicity. This group includes amikacin, arbekacin, dibekacin, gentamicin, isepamicin, kanamycin, neomycin, netilmicin, paromomycin, sisomicin, streptomycin, and tobramycin. They are rapidly bactericidal inhibitors of protein synthesis and are used primarily to treat infections caused by aerobic Gram-negative bacteria. All the aminoglycosides are similar in physical, chemical and pharmacological properties. Gentamicin, tobramycin, amikacin and netilmicin are the most widely used aminoglycosides for severe infections. Although these important agents are used extensively, serious toxicity is a major limitation. Ototoxicity and nephrotoxicity are the most frequent troublesome side effects.

The pharmacokinetic properties of these agents are influenced by a variety of physiological changes, and these changes may have a substantial effect on the pharmacological response in patients, with some having a higher risk of treatment failure or toxicity.

Aminoglycosides resistance is of increasing concern and occurs because of alteration in target ribosomal proteins, the acquisition of plasmids that encode for metabolizing enzymes, or impaired transport of drug into the bacteria. [14, 15] Perhaps the greatest problem is that aminoglycosides minimum inhibitory concentrations (MICs) have been increasing slowly for the past 20 years, but the concerns about toxicity and the narrow therapeutic window have not fostered a concomitant increase in the blood level targets. The result is that these antibiotics have become progressively less active during the past 10 years, to the point that they can’t be used alone in any serious infection.

3.1 Clinical pharmacokinetics
3.1.1 Absorption and Administration

Aminoglycosides are highly polar cations and poorly absorbed by the
gastrointestinal (GI) tract. These agents can be administered via intravenous (IV) infusion or intramuscular (IM) injection.[16] They are rapidly absorbed after IM administration. Peak serum concentration are generally achieved within 30 to 120 minutes after IM injection.[16] In younger patients with normal renal function, peak concentrations are achieved more rapidly. While in patients with compromised renal function, peak serum concentrations may be achieved within 2 to 5 hours after IM administration, depending on the degree of renal impairment.

Continuous intravenous infusion, slow bolus injection and intermittent infusions may also be administered.[16, 17, 18]

Intermittent infusions of 30 to 60 minutes are thought to be safer by those who are concerned by high peak concentrations. Continuous infusions of aminoglycosides to a target steady-state concentration of 4.0 μg/mL have been suggested to improve its efficacy specially in neutropenic patients.[19, 20] Bolus injections of aminoglycosides have been suggested in the European literature and widely used when allowed by hospital protocols.[21] This method of administration allows the drug to be rapidly infused with lower drug administration costs. However, reviewers have suggested that an increase in ototoxicity may be associated with high transient concentrations that result from bolus injections. Most of the current literature would seem to indicate that ototoxicity is better correlated with area under the curve (AUC) or total dose, rather than any single blood level.[22, 23]

3.1.2 Distribution

Intracellular distribution of aminoglycosides is limited by their polar nature and thus their distribution space is usually limited to the extracellular fluid compartment. Except for the inner ear and renal proximal tubule, which have active transport system for aminoglycosides. As a consequence, high concentrations are found, in the renal cortex [24, 25] and in the endolymph and perilymph of the inner ear [26, 27], which may explain the nephrotoxicity and ototoxicity seen with this class of antibiotics.

The apparent volume of distribution (V_d) of the aminoglycosides is 25% of lean body weight and is approximately equal to extracellular fluid volume.[28] Because these antibiotics appear not to enter most cells, the penetration of aminoglycosides into lungs using homogenates of tissue and into bronchial secretion is poor.[29]

These agents cross the placenta and achieve fetal serum concentrations that are 21 to 37% of maternal serum concentration.[30, 31] Hearing loss has occurred in children born to women receiving aminoglycosides during pregnancy.
3.1.3 Distribution Volume ($V_d$)

Several investigators demonstrated that the $V_d$ of aminoglycosides is variable between different patients.[32] This interpatients variation appears to have a substantial effect on serum concentration and dosage requirements. It has also been noted to occur during the course of antibiotics therapy. It is true for patients who are markedly dehydrated or fluid overloaded in the initial phase of treatment.

Clinically, monitoring of serum concentrations in patients with rapid fluid changes is imperative to ensure therapeutic serum concentrations.

3.1.4 Excretion

Aminoglycosides are primarily eliminated unchanged by the kidney via glomerular filtration. They are actively reabsorbed by the proximal tubule, which is a major factor in their nephrotoxicity.[25] Active secretion may account for a small amount of drug eliminated by the kidney.

During the first 1 or 2 days of treatment with aminoglycosides, disappearance of drug from the plasma exceeds renal excretion by 10 to 20%.[33] After this initial phase, an amount steadily approaching 100% of the drug is recovered in urine with subsequent doses. This period represents saturation of aminoglycosides binding sites in peripheral tissue compartments.[34] The rate of elimination of aminoglycosides from these tissue sites is considerably slower than from plasma. The half-life for tissue-bound drug has been estimated to range from 30 to 700 hours.[33]

Aminoglycosides can be removed from the body by hemodialysis, continuous arteriovenous hemofiltration, or peritoneal dialysis. 5% of a given dose is removed in 4 hours of hemodialysis.[35] Dialysis can be used in aminoglycosides overdose.

Frequent monitoring of serum concentrations is required for patients receiving any form of dialysis, and it is also advisable to use data-fitting techniques to fully characterize the effects of dialysis on the aminoglycosides to design more precise dosing regimens.

3.1.5 Factors related to aminoglycoside disposition

Several factors have been reported to alter the disposition of aminoglycosides and influence serum concentrations and dosage requirements.
i) Renal function: Aminoglycosides elimination is estimated by renal function. When kidney’s function is altered, creatinine clearance too. Most of the early pharmacokinetic studies of aminoglycosides were conducted on volunteers with varying degree of renal function. Approximately 80 to 90% of the variance ($r^2$) in elimination of aminoglycosides was explained by changes of renal function. [36]

ii) Age: In healthy adults, cardiac output, renal blood flow, and glomerular filtration decrease with increasing age. Aminoglycosides which are eliminated by glomerular filtration are influenced by these physiological changes. The elimination and the clearance of this group of antibiotic decreases with increasing age.

iii) Neonates: Newborn infants, especially those born prematurely, experience dynamic changes in physiological parameters such as cardiac output, renal blood flow, renal function, and extra-cellular fluid. Consequently, the distribution volume, clearance and half-life of aminoglycosides very substantially from day to day, and therapeutic concentrations are extremely difficult to achieve and maintain. [37]

iv) Pediatric patients: These patients have a rapid elimination and a shortened half-life of aminoclycosides compared with values typical of older adults.[38]

v) Sex: An association between sex and the elimination rate of gentamicin was reported to be moderately significant. In a study of 1640 patients, women eliminated gentamicin more rapidly than men. [32]

vi) Body weight and ideal body weight: A research suggested that aminoglycosides are partially distributed into excess adipose tissue. It was also found that gentamicin distributes into 5 to 6% of excess weight, and with ideal body mass, the distribution volume was 19% of body weight. [28, 39]

vii) Obstetric patients: The total body weight, extracellular fluid compartment, total body water, cardiac output, renal blood flow, and glomerular filtration are all increased during the later phase of pregnancy. The elimination of gentamicin became extremely rapid.[40]

viii) Burn patients: Physiologically, burn patients are hypermetabolic, that’s what explain why these patients have an extremely rapid rate of aminoglycosides elimination. [40] In addition, these patients may also have high distribution volume and a prolonged drug half-life despite a calculated normal renal function.

ix) Concomitant diseases:
   a- Hepatic disease and Ascites: An expanded extracellular fluid volume attributed to the ascitic fluid explains the increase in distribution volume. Gentamicin appears to distribute rapidly into ascitic fluid, and larger doses are required to achieve the desired peak serum concentrations. [42]
b- Cystic fibrosis: These patients are usually hypermetabolic, and beside, with the younger age and prepuberty, they have high glomerular filtration, rapid elimination and finally fast creatinine clearance.

3.2 Pharmacodynamics

As we mentioned previously, aminoglycosides are rapidly bactericidal compounds that exhibit concentration-dependent bacterial killing. They are primarily indicated for the treatment of Gram-negative bacilli.

3.2.1 Adverse effects

Ototoxicity and nephrotoxicity are the most frequently occurring adverse effects. Both forms of toxicity are most likely related to elevated and prolonged serum concentrations and to cumulative AUC.[43] Ototoxicity may be reversible if recognized early, nephrotoxicity too after discontinuing treatment and careful monitoring and control of serum concentration. Risk factors for ototoxicity and nephrotoxicity are listed in table 1.

Table 1. Risk factors associated with ototoxicity and nephrotoxicity of aminoglycosides.

<table>
<thead>
<tr>
<th>Ototoxicity</th>
<th>Nephrotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Age</td>
</tr>
<tr>
<td>Impaired renal function</td>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Elevated trough concentrations</td>
</tr>
<tr>
<td>Elevated trough concentrations</td>
<td>Elevated peak concentrations</td>
</tr>
<tr>
<td>Elevated peak concentrations</td>
<td>Total daily dose</td>
</tr>
<tr>
<td>Total daily dose</td>
<td>Cumulative dose</td>
</tr>
<tr>
<td>Cumulative dose</td>
<td>Concurrent nephrotoxic drugs</td>
</tr>
<tr>
<td>Concurrent ototoxic drugs</td>
<td>Prior aminoglycoside exposure</td>
</tr>
<tr>
<td>Prior aminoglycoside exposure</td>
<td>Hypovolemia</td>
</tr>
<tr>
<td>Dialysis</td>
<td>Sex</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>Duration of treatment sepsis</td>
</tr>
</tbody>
</table>

Other side effects attributed to aminoglycosides include neuromuscular blockade, hypersensitivity reactions, and infrequent local GI, hematologic, and CNS toxicity.
3.2.2 Relationship of Serum concentration to Efficacy

Measurements of serum concentrations and adjustments in a patient’s dosing regimen to attain targeted concentrations have been proposed to improve patient’s response.[15, 44] Aminoglycosides have a narrow therapeutic index, and concentrations necessary for optimal efficacy approximate concentrations that are associated with a substantial risk of toxicity.

4. Vancomycin

Vancomycin is a bactericidic antibiotic which belong to the group of glycopeptide. It was introduced almost 50 years ago. In KMUC, it was introduced 23 years ago. This antibiotic is primarily used against Gram-positive infections caused by methicillin-resistant staphylococci and ampicillin-resistant enterococci. We shall note that vancomycin is used in combination with gentamicin for treatment of enterococcal infections.

4.1 Clinical pharmacokinetics
4.1.1 Absorption

Vancomycin is administered intravenously, intrathecaly, intraventricularly or orally. Intramuscular route is not used due to tissue necrosis and to sever pain at the site of injection. Most often, vancomycin is given IV to treat systemic infections. The oral administration does not usually result in measurable concentrations of the drugs in serum, even in the presence of severely impaired renal function.

However, patients with impaired renal function who were given oral vancomycin for the treatment of antibiotic-associated pseudomembranous colitis had serum levels that were therapeutic or potentially toxic.[45, 46] Inflammation of the gut wall appears to increase vancomycin bioavailability, and renal dysfunction decreases the drug clearance. It may be prudent to monitor vancomycin serum concentrations in patients with severely impaired renal function who are receiving oral vancomycin for the treatment of bacterial colitis.
4.1.2 Distribution

Compared with aminoglycosides, the variability in the volume of distribution ($V_d$) of vancomycin is extreme. It can be affected by factors such as age, sex, and body weight. However, fluid balance (underhydration or overhydration) is less of an issue with vancomycin; fluid balance does not affect the $V_d$ as much as with aminoglycosides. Also, the $V_d$ is not significantly correlated with creatinine clearance.[47]

4.1.3 Metabolism

Vancomycin is not metabolized to any great extent. Approximately 80 to 90% of the intravenously administered dose can be recovered unchanged in the urine in 24 hours.[48] The liver may also be involved to a small extent.

4.1.4 Excretion

As mentioned previously, 80 to 90% of a given IV dose of vancomycin can be recovered unchanged in the urine of adults with normal renal function. Because elimination is primarily by glomerular filtration,[49] dosage adjustment is necessary for alterations in renal function.

4.1.5 Effects of disease States and conditions

The elimination of vancomycin is affected by the renal function, which is affected by age, state and conditions for example burns. Terminal half-life is prolonged and the total body clearance is reduced in patients with impaired renal function. In patients with normal renal function, the usual serum half-life of vancomycin is 6 to 10 hours, whereas in patients with end-stage renal disease, the half-life may approach 7 days.[49, 50]

4.1.6 Effect of dialysis

In patients with renal failure undergoing dialysis and receiving vancomycin therapy, the elimination of the drug during the procedure must be considered when establishing a dosing regimen. Very little vancomycin is cleared by standard hemodialysis or peritoneal dialysis.[51, 52] That’s why some caution should be used in
evaluating vancomycin plasma concentrations in patients with renal failure who are being dialyzed.

4.2 Pharmacodynamics
4.2.1 Adverse effects

Ototoxicity and nephrotoxicity are the most important side effects associated with vancomycin therapy. The incidences of toxicities are quiet small; less than 2% for ototoxicity and approximately 5% for nephrotoxicity, and may be concentration related. [53]

Nonconcentration-related toxicities have also been reported. Rapid intravenous infusion of vancomycin, greater than 500 mg per 30 minutes in normal adults may result in a histaminelike reaction characterized by flushing, local pruritis, erythma of the neck and upper torso, tachycardia, or hypotension.[49, 54] This hypersensitivity reaction is often referred to as “red man syndrome”.

4.2.2 Clinical response

Studies appear to support the belief that vancomycin is a concentration-independent killer of Gram-positive organisms, yet there are some investigators who propose the need to achieve certain peak and trough concentrations for optimal activity.[55, 56] In other words, they came to a conclusion that the optimal dosing method for vancomycin may be one that achieves the lowest AUC while maintaining concentrations greater than the MBC.

5. Clinical Application of pharmacokinetic data and dosing considerations.

An understanding of the desired therapeutic range and pharmacokinetic parameters enables the clinician to select doses and dosing intervals that meet the specific needs of the patient.

The first step in calculating an appropriate dosing regimen for a patient is to estimate the patient’s pharmacokinetic parameters, including volume of distribution ($V_d$), antibiotic clearance ($CL_{antibiotic}$) based on estimated creatinine clearance ($CL_{Cr}$), elimination rate constant ($k_e$), and half-life ($T_{1/2}$)

The next step would be to calculate the antibiotic maintenance dose, dosing interval ($\tau$), and a loading dose (if desired).
For patients with stable renal function, peak ($C_{\text{max}}$) and trough ($C_{\text{min}}$) concentrations should be obtained at steady state. A useful clinical rule for obtaining serum concentrations at steady state is to measure serum concentrations after the third dose.

For patients with impaired renal function, a predose serum concentration and a series of postdose serum concentration should be obtained early in therapy.

Monitoring for adverse effects is very essential during aminoglycosides and/or vancomycin therapy. Serial monitoring of serum creatinine concentrations should be used to detect nephrotoxicity and ototoxicity. Ideally, a baseline serum creatinine concentration is obtained before antibiotic therapy is initiated, followed by serum creatinine measurements every 3 days for patients with stable renal function or daily if the patient is renally unstable.
6. Methodology of the study:

This was a retrospective observational study from Kaunas University of Medicine Clinic (KMUC) that is one of the largest hospitals in east Europe, with 34 clinical departments and 2600 beds.

Drug usage data of aminoglycosides and vancomycin and the beds occupied in the different units per year were obtained from the Hospital and Pharmacy computer system for the three financial years (2004-2006). We included data of packs issued to inpatients only. To convert pack usage into DDDs, we adapted an Excel spreadsheet which facilitated the calculation. It is based on the number of packs of all antibiotics used, the number of dose units in each pack and DDD values allocated by the WHO. Further DDD analysis was performed to express consumption per every 100 OBD for single unit in clinical departments. Average mean of DDD/100OBD was estimated for every year and mean values compared among all three years.

The 90% Drug utilization (DU90%) in 2006 was derived from database for gentamicin, amikacin, tobramycin and vancomycin; same hospital units in these DU90% highest consumers were presented as DDD/100OBD for descriptive purposes for all three years. Tobramycin use is compared between 2004 and 2005, sorted according to all hospital units.

All measurements of serum concentration of gentamicin and vancomycin were performed by routine laboratory tests and data received from the Medical Chemistry and Hematology laboratory database. Monitoring serum drug concentration started in November 2005. In 2006, 45 blood measurements were performed for gentamicin and vancomycin. No other aminoglycoside serum concentration was measured.

Data were processed with SPSS 16.0 using descriptive and comparative statistics for nonparametric values (Mann-Whitney test).

In may 2005, biomedical research ethical committee, see Annex 1, gave the legibility to assess the rationality of antimicrobial therapy through an observational study. Over 7 months, October 2006 - April 2007, patient’s disease histories and prescription charts in the 34 clinical departments were analyzed.
7. Results:
7.1 Defined daily dose per 100 Occupied Bed Days of aminoglycosides and vancomycin.

Results are summarized in Table 1. Mean (±SE) DDD/100OBD values of gentamicin (240mg) were 3.67±0.69 (median 1.31; CI95% 2.29-5.06) in 2004; 4.53±1.87 (median 0.86; CI 95% 0.79-8.27) in 2005, and 4.24±0.82 (median 1.05; CI95%2.60-5.88) in 2006.

Mean (±SE) DDD/100OBD values of amikacin (1000mg) were 0.55±0.17 (median 1.22; CI95% 0.23-0.88) in 2004; 0.44±0.13 (median 1.03; CI 95% 0.18-0.69) in 2005, and 0.52±0.13 (median 1.08; CI95%0.27-0.78) in 2006.

Mean (±SE) DDD/100OBD values of tobramycin (240mg) were 0.03±0.02 (median 0.14; CI95% 0.00-0.07) in 2004, 0.006±0.003 (median 0.03; CI95% 0.00-0.01) in 2005.

Corresponding values of vancomycin (2000mg) were 0.55±0.17 (median 0.10; CI95% 0.21-0.89) in 2004, 0.50±0.14 (median 0.16; CI95% 0.22-0.79) in 2005, and 0.53±0.14 (median 0.11; CI 95% 0.26-0.80) in 2006.
Table 1: Defined Daily Dose (DDDs) per 100 occupied bed days (OBD) for aminoglycosides and vancomycin across three financial years.

<table>
<thead>
<tr>
<th></th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SE)</td>
<td>CI 95%</td>
<td>Mean (SE)</td>
</tr>
<tr>
<td>Gentamicin DDD/100 OBD</td>
<td>3.67 (0.69)</td>
<td>2.29; 5.06</td>
<td>4.53 (1.87)</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td></td>
<td>p value</td>
</tr>
<tr>
<td></td>
<td>0.19*</td>
<td></td>
<td>0.35**</td>
</tr>
<tr>
<td>Amikacin DDD/100 OBD</td>
<td>0.55 (0.17)</td>
<td>0.23; 0.88</td>
<td>0.44 (0.13)</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td></td>
<td>p value</td>
</tr>
<tr>
<td></td>
<td>0.93*</td>
<td></td>
<td>0.41**</td>
</tr>
<tr>
<td>Tobramycin DDD/100 OBD</td>
<td>0.03 (0.02)</td>
<td>0.00; 0.07</td>
<td>0.006 (0.003)</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td></td>
<td>p value</td>
</tr>
<tr>
<td></td>
<td>0.58*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin DDD/100 OBD</td>
<td>0.55 (0.17)</td>
<td>0.21; 0.89</td>
<td>0.50 (0.14)</td>
</tr>
<tr>
<td></td>
<td>p value</td>
<td></td>
<td>p value</td>
</tr>
<tr>
<td></td>
<td>0.88*</td>
<td></td>
<td>0.71**</td>
</tr>
</tbody>
</table>

* p value compared between 2004 and 2005
** p value compared between 2005 and 2006
*** p value compared between 2004 and 2006

The changes of aminoglycosides and vancomycin DDDs per 100 OBD during 3 years period statistically were not significantly different. (p>0.05; Mann-Whitney test)
7.2 Aminoglycosides and vancomycin uses in 2006

The drug use of the highly toxic antibiotics was variable in the different units. DU90% of gentamicin was consumed by 28 units of KMUC during 2006. In 2006, General Surgery, Pediatric Surgery, Hematology, Pulmonology-immunology, Gynaecology, Eye disorders II, Thoracic Surgery and Face/Jaw Surgery departments consumed 55.13% of total gentamicin use. In the rest 20 units, the consumption for each varied between 0.88% and 3.62% of total gentamicin consumption. Figure 1 depicts major 8 units together with rest 20 that comprise DU90%.

Figure 1: Gentamicin use (%DDD) in 2006 sorted according to DU90%.
DU90% of amikacin was consumed by 23 units in 2006. Head / Brain traumas, Central reanimation, Burns and plastic surgery, General Surgery, Cardiology reanimation and intensive therapy and Thoracic Surgery consumed 53.8% of total amikacin use. In the other 17 units, the consumption for each varied between 0.94% and 4.57% of total amikacin use. Figure 2 depicts major 6 units together with rest 17 that comprise DU90%.

Figure 2: Amikacin use (%DDD) in 2006 sorted according to DU90%.

In 2006, tobramycin was out of use.
DU90% of vancomycin was consumed by 24 units of KMUC during 2006. These units include Cardiosurgery, Head / Brain Surgery, Central reanimation, General Surgery, Heart chest and vessels clinic, Cardiology II and Orthopedic and Traumatology consumed 55.29% of total vancomycin use. The consumption varied between 1.07% and 4.02% in the other 17 units for each. Figure 3 depicts major 7 units together with rest 17 that comprise DU90%.

Figure 3: Vancomycin use (%DDD) in 2006 sorted according to DU90%.
7.3 Consumption tendencies of aminoglycosides and vancomycin across 3 years.

The consumption tendencies in same units of gentamicin, amikacin, tobramycin and vancomycin during the three years period are illustrated in table 2, 3, 4 and 5 and figure 4, 5, 6 and 7.

Hospital units are highlighted where changes in drug use have been observed; No essential variation in aminoglycosides and vancomycin general consumption from the period 2004-2006.

| Table 2: Gentamicin consumption in same units of DU90% during 2004-2006. | DDD/100OBD |
|---|---|---|
| | 2004 | 2005 | 2006 |
| **General Surgery** | 17,62 | 21,45 | 21,55 |
| **Pediatric Surgery** | 10,35 | 10,08 | 8,93 |
| **Gynaecology** | 7,31 | 4,31 | 5,64 |
| **Eye disorders II** | 6,75 | 5,27 | 4,73 |
| **Face / Jaw surgery** | 5,23 | 3,79 | 3,75 |
| **Thoracic Surgery** | 5,16 | 4,98 | 3,76 |
| **AngioSurgery** | 4,67 | 3,31 | 1,75 |
| **Pulmonology-immunology** | 4,23 | 3,84 | 2,88 |
| Obstetric | 4,02 | 3,79 | 3,58 |
| **Hematology** | 2,65 | 4,06 | 3,88 |
| Children's disorders I | 2,43 | 1,72 | 2,30 |
| Central reanimation (intensive therapy unit) | 2,24 | 2,03 | 1,77 |
| Head / Brain surgery | 1,79 | 2,74 | 1,15 |
| Head / Brain traumas | 1,57 | 2,49 | 1,54 |
| Children's disorders II | 0,90 | 1,44 | 0,88 |
| Gastroenterology | 1,35 | 1,27 | 1,14 |
| Burns and Plastic surgery | 1,23 | 1,68 | 1,38 |
| Neurosurgery reanimation & intensive therapy (intensive therapy unit) | 1,14 | 1,66 | 1,11 |
Figure 4: Gentamicin consumption in same units of DU90% during 2004-2006.
Table 3: Amikacin consumption in same units of DU90% during 2004-2006.

<table>
<thead>
<tr>
<th></th>
<th>DDD/100OBD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2004</td>
</tr>
<tr>
<td>Thoracic surgery</td>
<td>20,16</td>
</tr>
<tr>
<td>Head / Brain traumas</td>
<td>13,65</td>
</tr>
<tr>
<td>Burns and Plastic surgery</td>
<td>10,38</td>
</tr>
<tr>
<td><strong>General Surgery</strong></td>
<td><strong>10,43</strong></td>
</tr>
<tr>
<td>Central reanimation (intensive therapy unit)</td>
<td><strong>8,06</strong></td>
</tr>
<tr>
<td>Neurosurgery rean &amp; int therapy (int therapy unit)</td>
<td>3,71</td>
</tr>
<tr>
<td>Urology</td>
<td>3,55</td>
</tr>
<tr>
<td><strong>Pulmonology-immunology</strong></td>
<td><strong>5,10</strong></td>
</tr>
<tr>
<td><strong>Cardiology and intensive therapy</strong></td>
<td><strong>4,36</strong></td>
</tr>
<tr>
<td>Head / Brain surgery</td>
<td>1,99</td>
</tr>
<tr>
<td>Nephrology</td>
<td>1,16</td>
</tr>
</tbody>
</table>

Figure 5: Amikacin consumption in same units of DU90% during 2004-2006.
Table 4: Tobramycin consumption in all units during 2004-2005

<table>
<thead>
<tr>
<th></th>
<th>DDD/100OBD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2004</td>
</tr>
<tr>
<td><strong>Children's disorders I</strong></td>
<td>61,54</td>
</tr>
<tr>
<td>Hematology</td>
<td>19,23</td>
</tr>
<tr>
<td><strong>Neurosurgery reanimation &amp; intensive therapy</strong></td>
<td>15,38</td>
</tr>
<tr>
<td>Pulmonology-immunology</td>
<td>3,85</td>
</tr>
<tr>
<td><strong>UROLOGY</strong></td>
<td>0,00</td>
</tr>
</tbody>
</table>

Figure 6: Tobramycin consumption in all units during 2004-2005.
Table 5: Vancomycin consumption in same units of DU90% during 2004-2006.

<table>
<thead>
<tr>
<th>Service</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiosurgery</td>
<td>27,76</td>
<td>28,80</td>
<td>20,46</td>
</tr>
<tr>
<td>Burns and Plastic surgery</td>
<td>8,10</td>
<td>9,77</td>
<td>4,02</td>
</tr>
<tr>
<td>Cardiology II</td>
<td>6,84</td>
<td>2,28</td>
<td>4,31</td>
</tr>
<tr>
<td>General Surgery</td>
<td>6,42</td>
<td>4,72</td>
<td>5,63</td>
</tr>
<tr>
<td>Cardiosurgery reanimation and intensive therapy</td>
<td>4,80</td>
<td>3,23</td>
<td>1,15</td>
</tr>
<tr>
<td>Neurosurgery reanimation &amp; intensive therapy unit (neurology clinic)</td>
<td>3,92</td>
<td>1,64</td>
<td>2,30</td>
</tr>
<tr>
<td>Spinal, cord and peripheral nerves surgery</td>
<td>3,05</td>
<td>8,29</td>
<td>1,92</td>
</tr>
<tr>
<td>Head / Brain traumas</td>
<td>2,07</td>
<td>1,68</td>
<td>3,36</td>
</tr>
<tr>
<td>HEAD / BRAIN SURGERY</td>
<td>1,23</td>
<td>10,65</td>
<td>11,03</td>
</tr>
<tr>
<td>Endocrinology</td>
<td>1,87</td>
<td>2,01</td>
<td>1,71</td>
</tr>
<tr>
<td>Children’s reanimation and intensive therapy unit</td>
<td>1,85</td>
<td>2,12</td>
<td>1,07</td>
</tr>
</tbody>
</table>

Figure 7: Vancomycin consumption in same units of DU90% during 2004-2006.
7.4 Gentamicin and vancomycin monitoring assessment in 2006.

In total 28 vancomycin measurements and 17 gentamicin measurements were performed in 2006. No other measurements were performed for amikacin and tobramycin. From 28 vancomycin measurements, 3 were low, 10 - normal and 15 high. The intensity of Serum concentration measurements for vancomycin in 2006 was 1/84 DDDs. While for gentamicin, from 17 measurements, 5 low, 5 normal and 7 high. The intensity of Serum concentration measurements were 1/1516 DDDs for gentamicin which is also considered to be very low. The Figures 8 and 9 depicts proportional expression of findings for gentamicin and vancomycin.

Figure 8: Vancomycin serum concentrations measurements in 2006.
7.5 Carbamazepine, valproic acid and digoxin serum concentrations measurements assessment in 2006.

In 2006, 178 serum concentrations for carbamazepine were performed. 57 were low, 96 - normal and 25 high. While 574 measurements of valproic acid were performed. 153 were low, 333 - normal and 88 high. For digoxin, 89 serum concentrations were measured. 27 were low, 40 - normal and 22 high. The Figures 10, 11 and 12 depicts proportional expression of findings for carbamazepine, valproic acid and digoxin.
Figure 10: Carbamazepine serum concentrations measurements in 2006.

Figure 11: Valproic acid serum concentrations measurements in 2006.
Figure 12: Digoxin serum concentrations measurements in 2006.

Figure 10, 11 and 12 shows that 42-55% of valproic acid, carbamazepine and digoxin dosing are in the inappropriate range.
7.6 Pharmacokinetic monitoring of patients in KMUC over 7 months.

From October 2006 to April 2007, 17 consecutive patients from 8 hospital units were monitored (9 male; 8 female). 5 were treated with gentamicin, 10 with vancomycin, 1 patient treated with gentamicin and vancomycin and 1 patient treated with amikacin and vancomycin. We mainly focused on the pharmacokinetic monitoring (numbering days starting at the beginning of antibiotic therapy) - safety and efficacy assessment.

**Patient number 1:** V.M., 61 years old man suffering from renal insufficiency due to glomerulonephritis is treated in the nephrology unit; he started to receive vancomycin 1000 mg due to Enterococcus faecalis and Corynobacterium spp which are sensitive to vancomycin and resistant to penicillin, gentamicin and ciprofloxacin.

Vancomycin 1000 mg was given IV once a day the first, 2\textsuperscript{nd}, 4\textsuperscript{th} and 5\textsuperscript{th} day, than twice a day on the 8\textsuperscript{th} and 9\textsuperscript{th} day. Vancomycin serum concentrations were measured on the 9\textsuperscript{th} day after the start of the treatment with vancomycin - on the next day after increase of the dose. Concentration was little above of the upper limit - 7.97 mcmol/L (therapeutic range 3.45-6.9 mcmol/L).

CRP, WBC and Neu were monitored regularly and showed a significant improve in the patient’s condition. Urea, diuresis and creatinine serum concentration were also monitored proving the safety of the treatment. The patient’s condition improved and he was discharged.

**Remarks:** Measured concentration is not problematic but is not at the steady state after increase of the dose. It would also more relevant to measure concentration after reaching first steady state (3 to 5 days after start of therapy).

**Patient number 2:** L.B., 32 years old women; 66 kg; admitted to the burn unit due to 3\textsuperscript{rd} degree burns, she is also suffering from acute renal insufficiency. Vancomycin 1000 mg IV once (15.15 mg/kg) each 3 - 4\textsuperscript{th} day was prescribed due to Enterococcus faecalis infection (sensitive to vancomycin and resistant to ampicillin and ciprofloxacin).

Vancomycin was given on the 1\textsuperscript{st}, 4\textsuperscript{th}, 10\textsuperscript{th} and 12\textsuperscript{th} day. Vancomycin serum concentrations were measured twice, on the 4\textsuperscript{th} and the 10\textsuperscript{th} day. Both measurements refer to $C_{\text{min}}$ were too high – 12.99 mcmol/L and 13.13 mcmol/L (therapeutic range: 3.45 – 6.9 mcmol/L).

CRP, WBC and Neu were monitored regularly and showed a significant improve in the patients condition. Urea, diuresis and creatinine serum concentration were also monitored to assess the patient’s safety. The results reflected renal insufficiency (creatinine 397 –
The patient’s condition improved. She was discharged after 17 days of hospitalization.

**Remarks:** Measured concentrations are too high and could be reduced. This would lead to more economical case.

**Patient number 3:** J.Z, a 4 days baby (2964 g) suffering from meningitis admitted into neonates department. Gentamicin 4 mg/kg IV once per day was initiated when the patient’s weight was 2964 g on an everyday basis for a period of 2 weeks. On the 11th day, the patient’s weight was 3330 g, the dose of gentamicin was adjusted.

4 gentamicin serum concentrations were measured: on the 5th (1st $C_{\text{min}}$ measurement), 13th (2nd $C_{\text{min}}$ measurement), and 14th days (1st $C_{\text{max}}$ measurement and 3rd $C_{\text{min}}$ measurement) of therapy. In case of proper measurement (measuring $C_{\text{min}}$ after 6-8 hrs after injection), all three measurements of $C_{\text{min}}$ would be safe (1.41 mcmol/L, 0.35 mcmol/L, and 2.11 mcmol/L) (therapeutic range for $C_{\text{min}}$ is less then 2.1 – 4.2 mcmol/L); while $C_{\text{max}}$ (10.91 mcmol/L) would be in the normal range for standard therapy (effective therapeutic peak: 10.5 – 20.9 mcmol/L) but too low for single dose range (effective therapeutic peak: 42 – 63 mcmol/L).

Efficacy and safety monitoring were barely performed. On the 16th day, the patient recovered and has been discharged.

**Remarks:** First dose might be too high (according to guideline it should be 2.5 mg/kg) but serum concentration is not proving that all results reflect safe therapy. This case also shows the need for measurement of newborns and example of insufficiency to rely on dosage recommendations only.

**Patient number 4:**

R, a 0 day baby; 2534 g; suffering from congenital birth defect – left kidney hypoplasia (creatinine 86 mcmol/L) - is treated for the 1st day with gentamicin 10mg (4 mg/kg) IV infusion for 30 min every 48 hrs. The second day and the 3rd day, the patient received gentamicin 5 mg/kg IV infusion for 30 min. No changes in the patient’s weight during that period.

Gentamicin serum concentration was measured once, on the 3rd day, $C_{\text{min}}$ was 1.33 mcmol/L (safe therapeutic range – less than 2.1 – 4.2 mcmol/L).

CRP, WBC and Neu were monitored regularly. No data about the patient’s outcome.

**Remarks:** Same remark as for 3rd patient.
**Patient number 5:** M.G., a 69 years old women, ~80 kg from Nephrology unit have been diagnosed with sepsis due to S. aureus infection (sensitive to vancomycin and resistant to penicillin and oxacillin); performing every day hemodialysis due to exacerbated chronic renal failure.

On the 1st day she received 0.5 g (6.25 mg/kg) vancomycin IV once per day, on the 2nd and the 4th day she received the same dose twice daily. On the 15th and 20th day, she received vancomycin 1000 g (12.5 mg/kg) IV once per day.

Vancomycin serum concentrations were measured on the 9th (Cmax) and the 19th (Cmin) days; both concentrations were too high: Cmax concentration was 35.56 mcmol/L (therapeutic peak range: 20.7 – 27.6 mcmol/L) and the Cmin was 21.18 mcmol/L (therapeutic range 3.45 – 6.9 mcmol/L).

CRP, WBC and Neu were monitored regularly and showed an improvement in the patient’s condition. Creatinine serum concentration and urea they revealed the kidney’s function (985 – 1049 – 269 – 198 – 535 mcmol/l).

**Remarks:** Measured concentrations are too high and could be reduced. This would lead to more economical case.

**Patient number 6:** N.M., a 22 years old man; ~77 kg; suffering from idiopathic cardiomyopathy and renal insufficiency is empirically treated in the cardiosurgery reanimation unit due to Enterococcus spp. infection (no data about sensitivity and resistance).

He received amikacin 500 mg IV during the first 3 days and vancomycin 1000 mg (13 mg/kg) IV once per day on the 1st, 3rd, 4th, 7th and 13th. Vancomycin serum concentrations have been monitored regularly, 8 measurements were performed. One measurement 6.14 mcmol/L was in the Cmin range (3.45 – 6.9 mcmol/L). No other information regarding applicability of Cmin or Cmax is available but for the other concentrations measured, all of them were or too high than Cmin or to low for Cmax (20.7 – 27.6 mcmol/L). Here are the results: 16.61 – 16.97 – 8.50 – 16.34 – 9.09 – 15.80 – 12.05 mcmol/L.

CRP, WBC and Neu have been monitored regularly showing no improve in the patient’s condition. Urea and creatine serum concentrations also showed no improve in patient’s health.

**Remarks:** Measured concentrations are not interpretable because they might be either too high or too low. Precise interpretation would lead to rational therapy.
**Patient number 7:** I.J, a 36 years old women; ~65 kg; treated in the endocrinology department is suffering from renal insufficiency was diagnosed with sepsis due to Pseudomonas infection and Enterobacter spp. which are sensitive to gentamicin and ciprofloxacin.

Vancomycin 1000 mg (15 mg/kg) IV is prescribed once per day; she receives the dose on 5-7 days intervals, on the 1st, 6th, 11th, 22nd, 30th, 38th and on day number 46. Vancomycin serum concentration have been monitored adequately, 16 measurements of $C_{\text{min}}$ were performed. Where only one measurement was too low: 1.17 mcmol/L (therapeutic range 3.45 – 6.9 mcmol/L). Here are the results of the other measurements: 10.49 – 8.47 – 10.25 – 6.37 – 10.21 – 7.33 – 6.18 – 5.44 – 8.79 - 17.25 – 6.26 – 10.02 – 9.50 – 8.88 – 8.17 mcmol/L.

CRP, WBC and Neu monitoring was done regularly showing at first an improvement in the patient’s condition than a worsening starting the 22nd day.

**Remarks:** Monitoring reflects proper dosages.

**Patient number 8:** T.B., 72 years old man; 64 kg; treated in the gastroenterology unit, is diagnosed with diverticulitis caused by E. coli, Pseudomonas aeruginosa and Enterobacter spp. infection sensitive to gentamicin and ceftazidim, resistant to ampicillin and cefuroxim.

The patient received gentamicin 240 mg (3.75 mg/kg) IV every second day - on the 1st, 3rd, and 5th day (together with ceftazidim 1000 mg IV daily).

Gentamicin serum concentrations were measured once on day number 5. It was rather little bit too high for $C_{\text{min}}$ (3.90 mcmol/L) (therapeutic range less than 2.1 – 4.2 mcmol/L) but too low for $C_{\text{max}}$.

CRP, WBC, Neu, urea, creatinine serum concentrations were barely monitored.

The patient was forwarded to rheumatology unit, a slight improve was observed in his condition.

**Remarks:** Measured concentrations are not interpretable because they might be either too high or too low. Precise interpretation would lead to rational therapy.
**Patient number 9:** T.N., a 23 days baby; 4812 - 5664 g; treated in neonates department, diagnosed with meningitis, neonatal sepsis due to E. coli (sensitive to ampicillin, cefuroxim, gentamicin).

The patients received cefotaxim 240 mg IV t.i.d and gentamicin 20 mg (4.15 mg/kg) IV once daily for 18 days. $C_{\text{min}}$ of gentamicin was measured once on 11$^{\text{th}}$ day of therapy, it was safe - 0.81 mcmol/L (therapeutic range 2.1 – 4.2 mcmol/L).

Efficacy parameters as CRP, WBC, Neu and the other safety parameters were not monitored. Temperature and weight were observed regularly. The patient is discharged after 3 weeks of treatment. His condition has improved.

**Remarks:** Measured concentrations revealed safe dosage but it would be more prudent to measure after first 3 days.

**Patient number 10:** K, a 3 days baby; 3575 g; is treated in neonates department due to congenital pneumonia, no microbiological culture was performed.

The patient received daily penicillin 350000 IU b.i.d IV and gentamicin 14 mg (4 mg/kg) IV once daily for 7 days. Two measurements of gentamicin serum concentrations were performed on the 5$^{\text{th}}$ day. $C_{\text{min}}$ was safe - 1.11 mcmol/L (therapeutic range lower then 2.1 – 4.2 mcmol/L) and $C_{\text{max}}$ was normal 9.88 mcmol/L (therapeutic pick 8.64 – 17.28 mcmol/L). CRP, WBC and Neu measurements were done regularly and they revealed not sufficient efficacy. The patient was discharged and no improve was observed in his condition.

**Remarks:** Measured concentrations revealed safe dosage but efficacy of dosing can not be judged.

**Patient number 11:** A.N., a 73 years old man suffering from renal insufficiency was admitted into cardiosurgery reanimation unit due to sepsis caused by Serratia marcescens (sensitive to gentamicin, cefotaxim and resistant to ampicillin and cefuroxim).

Tazocin (piperacillin and tazobactam) 2.5g t.i.d and vancomycin 1000 mg IV empirical were both initiated on day number 8. Vancomycin serum concentration $C_{\text{min}}$ measured on the 11$^{\text{th}}$ day was in the normal range 4.3 mcmol/L (therapeutic range 3.45 – 6.9 mcmol/L) CRP, WBC and Neu were monitored regularly the same for creatinine serum concentration (values are 298 – 448 – 402 – 382 mcmol/L) and urea. In general a slight improvement in the patient’s condition was observed.

**Remarks:** Measured concentrations revealed effective dosage but it would be more prudent to measure after first 3 to 5 days.
Patient number 12: M.Z., a 71 years old women; ~73 kg treated in the cardiology unit due to a streptococcal endocarditis infection have been switched from cefotaxim to vancomycin 1000 mg (13.70 mg/kg) IV once per day on the 19th day of hospitalization as a switch due to an allergic reaction to beta-lactams. No additional sensitivity and resistant tests were performed.

She received vancomycin on the 1st, 4th, 7th, 10th, 12th, 14th and 17th day. 4 vancomycin serum concentrations referred to C_{min} were measured starting from the 10th day. One measurement was too low (2.9 mcmol/L) and the three other 5.1 – 6.1 – 6.4 mcmol/L were normal (therapeutic range 3.45 – 6.9 mcmol/L)

CRP, WBC, Neu were monitored regularly. The same with creatinine serum concentration (117 – 93 – 106 – 122 – 127 – 125 – 141 mcmol/L) and urea. They showed an improvement in the patient’s condition. She was discharged on the 18th day.

Remarks: Measured concentrations revealed finding of effective dosage but it would be more prudent to measure after first 3 to 5 days.

Patient number 13: G.V., a 23 years old man; ~80 kg; treated in the nephrology unit due to renal insufficiency is suffering from sepsis. No microbiological data are present.

He started to receive vancomycin 1000 mg (12.5 mg/kg) IV once daily empirically on the 5th day. Monitoring vancomycin concentrations from 49th day up to 55th day. After 3 day vancomycin serum concentration was 17.8 mcmol/L. On the 55th day, doctors’ decision was to stop vancomycin treatment.

CRP, WBC, Neu were monitored regularly and showed a significant improve in the patient’s condition.

Remarks: Measured concentrations are not interpretable because they might be either too high or too low. Precise interpretation would lead to rational therapy.

Patient number 14: G.M., a 56 years old women; 74 kg; suffering from renal insufficiency and being dialyzed is treated in the endocrinology department due to a septic and pneumonial infections due to E. coli, S. aureus, Enterobacter faecalis, and Citrobacter freundii.

She received vancomycin 1000 mg (13.5 mg/kg) IV once daily on the 1st, 11th, 18th, 25th, 32nd and 40th day.

Vancomycin serum concentrations were monitored by 10 measurements of C_{min}. First measurement was performed on 5th day. One measurement was too low 3.0 mcmol/L (therapeutic range 3.45 – 6.9 mcmol/L), 5 were a little bit too high; 7.7 – 7.7 – 7.9 – 9.2 –
8.8 mcmol/L, and 4 in the normal range; 6.1 – 5.3 – 6.3 – 6.2 mcmol/L. CRP, WBC and Neu were also monitored regularly showing an improvement in the patient’s condition. No additional safety tests were performed.

Remarks: Measured concentrations are not problematic.

Patient number 15: D.B., a 76 years old women; 52 kg is suffering from septic endocarditis is treated in the cardiology unit. The patient has secondary glomerulonephritis. Microbiological sensitivity and resistance tests were not performed. The patients receives vancomycin 1000 mg (19.2 mg/kg) IV once every 10th day - on the 1st, 10th, 14th, 18th, 22nd, 26th, 30th, 34th, 38th and 42nd. Vancomycin serum concentrations monitoring was performed through 5 measurements of Cmin. 2 measurements were low; 3.2 – 3.2 mcmol/L (therapeutic range 3.45 – 6.9 mcmol/L), and the 3 others were in the normal range; 3.8 – 4.5 – 4.2 mcmol/L. CRP, WBC, Neu were monitored regularly showing an improvement in the patient’s condition. The same with creatinine serum concentration (216 – 204 – 143 – 127 – 126 – 147 – 150 – 136 – 133 – 130 – 135 mcmol/L) and urea, they showed the safety of the treatment. The patient recovered and was discharged.

Remarks: Measured concentrations were basis for adjustments.

Patient number 16: P.K., a 65 years old man, suffering from secondary subacute staphylococcal endocarditis is treated in the cardiology unit.

From the first to the day number 10, the patient received gentamicin 240 mg IV, 80 mg infusion 3 times daily and vancomycin 1.0 g twice a day IV.

On the day number 11, gentamicin treatment was stopped; the patient received vancomycin 1.0 g once daily on day number 14, 15, 16 and 19. No gentamicin serum measurements were performed while for vancomycin, 5 serum measurements (Cmin) were performed starting from the 11th day. Here are the results: 17.4 – 10.2 – 8.9 – 5.1 – 2.7 mcmol/L. Cmin was higher in first two measurements (20.7 – 27.6 mcmol/L) and adjustments were done.

CRP and the other hematological parameters were monitored very regularly. Creatinine serum concentrations were monitored adequately. The patient was discharged on the 16th day and doctors recommendation was to proceed with vancomycin 1g IV every 3rd day for 4-6 weeks with careful monitoring of CRP.

Remarks: Measured concentrations were basis for adjustments.
**Patient number 17:** G.Š., a 5 months baby treated in the children’s neurosurgery unit is suffering from congenital hydrocephaly, sepsis. No microbiological data are present.

On the 15th day of hospitalization the patient started receiving empirically vancomycin 50 mg IV 4 times a day; she received for 17 days. On the 7th day, vancomycin serum concentrations were measured (Cmin) and too low concentration was revealed (1.1 mcmol/L). Vancomycin 50 mg IV 4 times a day was initiated again on the 22nd day till the 31st day.

The patient’s condition is improving.

**Remarks:** Measured concentrations revealed finding not sufficiently effective dosage and it would be more prudent also to measure after first 3 to 5 days.

Through this study covering 17 patients over 7 months period, we observed 8 cases (~47%) where pharmacokinetic interventions could be reasonable, 6 cases (~35%) where no additional pharmacokinetic interventions seems reasonable and rest 3 cases are not interpretable.
8. Discussion:

Aminoglycosides and vancomycin were introduced into KMUC approximately 20 years ago. This study of antibiotic consumption during a short period of 3 years provides some important data highlighting consumption and tendencies in tertiary hospital. This is a first study about one of aspects of the rational drug use of antibiotics with narrow therapeutic index. We realized that the consumption tendencies of aminoglycosides and vancomycin do not change essentially during the studied period.

In 2006, 8 hospital units of 28 covered more than 55% of total gentamicin use, 6 hospital units of 23 covered more than 53% of amikacin use. While for vancomycin, 7 hospital units of 24 covered also more than 55% of total DU. Figure 1, 2 and 3.

The intensity of gentamicin consumption in these 8 units does not change essentially during the 3 years, the same with amikacin except for thoracic surgery unit which showed a fast decrease in drug use. Tobramycin manifest in the following manner, a very sharp decrease toward zero in 2005 faced by an increase in use by the urology unit. While with vancomycin the results was variable, a slight decrease in certain departments faced by a rise in others as in head / brain surgery unit. Figure 4, 5, 6 and 7.

Aminoglycosides and vancomycin are drugs with narrow therapeutic range. Therapeutic drug monitoring (TDM) is essential in clinical practice to evaluate efficacy, to avoid toxicity and to reduce drug costs.

Various health care professionals monitor patients to assess their progress with drug therapy. Most commonly this involves doctors, pharmacists and nurses. This requires a systematic approach supported by effective communication and collaboration between the health care professions involved.

Various indicators may be used to monitor a patient’s progress. These include clinical signs, symptoms, biochemical / hematological parameters and certainly serum drug levels for toxic medicaments. Routine laboratory investigations, careful and timeous monitoring of appropriate biochemical / hematological parameters may confirm efficacy and/or prevent drug toxicity.

The use of serum drug levels is the mostly appropriate for such antibiotics with narrow therapeutic index and a well-defined target serum concentration range. Targeting particular drug levels by the application of pharmacokinetic principle can often result in a quicker and safer route to efficacy than that achieved by clinical assessment alone. That’s exactly was TDM is all about.

The intensity of serum concentration measurements for vancomycin in 2006 was rather low (1/84 DDDs) as well as for gentamicin (1/1516 DDDs). In ideal scenario at
least 2 measurements should be performed (one at the beginning and one after 3-5 days of gentamicin use and after saturation for vancomycin) and figures calculated show clear insufficiency in serum concentration monitoring intensity. 60-70% of improper gentamicin and vancomycin dosing (Figure 8 and Figure 9) and 42-55% of improper valproic acid, carbamazepine and digoxin dosing (figure 10, 11 and 12) reveals high need for intensifying TDM.

Through the study of the 17 patients, pharmacokinetic interventions could be reasonable in approximately half of the cases, while in the rest, no additional pharmacokinetic interventions seems reasonable and some of these cases were not interpretable.

Focus to monitor rationality of antimicrobial therapy employing serum concentrations measurements is expanding while extend is not sufficient and should be intensified through targeted interventions by promoting blood measurements starting with the highest consumers.
CONCLUSIONS

Aminoglycosides and vancomycin uses are evaluated for three consecutive years starting from 2004. Through this study, we showed that:

1. No essential changes in the mean consumption of aminoglycosides and vancomycin during the 3 years;

2. Comparing the DDD/100OBDs data year-on-year revealed the no statistically significant changes of each investigated antimicrobial’s use during the three years. Numerical lowering of tobramycin use was observed between 2004 and 2005 although without statistical significant difference.

3. One fourth to one third of highest consuming units in hospital are using more than half of total investigated antimicrobials during 2006.

4. The antimicrobials utilization tendencies of the highest consuming units were very variable without clear general tendencies.

5. During 2006 monitoring of gentamicin and vancomycin serum concentrations were considered to be insufficient.

6. The 60-70% of all measurements showed the improper dosing of these antibiotics. These serum concentrations data were less adequate then other highly toxic medicaments (valproic acid, carbamazepine and digoxin).

7. A cohort study of 17 cases of treatment with antibiotics regarding the pharmacokinetic monitoring over 7 months reveals rather limited approach to monitor intensively efficacy and safety of aminoglycosides and or vancomycin with pharmacokinetic methods.
RECOMMENDATIONS

Antimicrobial therapy shall approach the rationality by improving the pharmacokinetic monitoring. This can be achieved through:

1. A better strategy in antimicrobial use in the main consumer units.

2. Intervention of skilled clinical pharmacists in monitoring efficacy and safety of the treatment starting from highest consuming hospital units with focus on more intensive monitoring, especially by intensifying serum concentrations.

3. Measure serum drug level after first 3 to 5 days since antimicrobial initiation.

4. Intensify drug and organ function monitoring specially in patients at higher risk of drug intoxication.
Evaluation of needs for pharmacokinetic (PK) monitoring of aminoglycosides and vancomycin in tertiary hospital.

**Background and Objectives:** Tendencies in Drug Use (DU) of highly toxic drugs—such as aminoglycosides and vancomycin and level of Rational Drug Use (RDU) is unknown in Lithuania. Our goal was to evaluate the first experiences in serum concentration measurements (Sc) of vancomycin & gentamicin, monitor patients receiving these antimicrobials and explore the practicality of using defined daily dose (DDD) in measuring their consumption tendencies.

**Design:** DU study based on hospital pharmacy and hospital administrative databases; consumption in DDD per 100 occupied bed daily (100OBD) during 2004–6 and highest consumers of aminoglycosides and vancomycin in 2006. Evaluation of Sc in 2006. Monitoring assessment of 17 patients over 7 months. Data were processed with SPSS 16.0 using descriptive and comparative statistics for nonparametric values (Mann-Whitney test).

**Main outcomes measures:** Annual consumptions of gentamicin, amikacin, tobramycin and vancomycin according to DDD/100OBD; intensity of gentamicin & vancomycin monitoring (as per number of DDDs) and proportions of abnormal Sc; Evaluation of the rationality level of antimicrobial’s therapy in a cohort of 17 patients.

**Results:** Mean (±SE) DDD/100OBD values of gentamicin (240mg) were 3.67±0.69 (median 1.31; CI95% 2.29-5.06) in 2004; 4.53±1.87 (median 0.86; CI 95% 0.79-8.27) in 2005, and 4.24±0.82 (median 1.05; CI95%2.60-5.88) in 2006. Mean (±SE) DDD/100OBD values of amikacin (1000mg) were 0.55±0.17 (median 1.22; CI95% 0.23-0.88) in 2004; 0.44±0.13 (median 1.03; CI 95% 0.18-0.69) in 2005, and 0.52±0.13 (median 1.08; CI95%0.27-0.78) in 2006. Mean (±SE) DDD/100OBD values of tobramycin (240mg) were 0.03±0.02 (median 0.14; CI95% 0.00-0.07) in 2004, 0.006±0.003 (median 0.03; CI95% 0.00-0.01) in 2005. Corresponding values of vancomycin (2000mg) were 0.55±0.17 (median 0.10; CI95% 0.21-0.89) in 2004, 0.50±0.14 (median 0.16; CI95% 0.22-0.79) in 2005, and 0.53±0.14 (median 0.11; CI 95% 0.26-0.80) in 2006. Numerical changes during 3 years period statistically were not significantly different.(p>0.05) One fourth (6/23) to one third (9/28) of highest consuming units in hospital are using more than half (55%) of total investigated
antimicrobials during 2006. Intensity of Sc were 1/1516 DDDs for gentamicin and 1/84 DDDs for vancomycin. Sc Vanco: 3/28 (11%) too low, 10/28 (36%) normal, and 15/28 (53%) too high; Sc Genta: 5/17 (30%) too low, 5/17 (30%) normal, and 7/17 (40%) too high. 8 cases of 17 patients (~47%) PK interventions could be reasonable, 6 cases of 17 (~35%) no additional PK interventions seems reasonable and 3 cases of 17 are not interpretable.

**Conclusion:** Intensity of aminoglycosides and vancomycin consumption does not change essentially during last 3 years; one fourth to one third of highest consuming units used more than half of total investigated antimicrobials; Clear insufficiency in serum concentration measurements; PK intervention could be reasonable in half of the studied cases.

**Keywords:** Rationality, defined daily dose, intervention, antimicrobial therapy.
Toksiškų vaistų, tokių kaip aminoglikozidų ir vankomicino, bei racionalus vaistų vartojimo tendencijos Lietuvoje dar nėra pakankamai žinomos. Mūsų darbo tikslas buvo nustatyti ir įvertinti aminoglikozidų ir vankomicino suvartojimo KMU klinikose tendencijas, gentamicino ir vankomicino koncentracijas kraujo serume (KKS), bei įvertinti 17 stebėtų pacientų gydymo šiais antibiotikais atvejus.


Vidutinis gentamicino (240mg) suvartojimas 2004m. (±SE) DDD/100OBD buvo 3.67±0.69 (median 1.31; CI95% 2.29-5.06); 2005m. 4.53±1.87 (median 0.86; CI 95% 0.79-8.27); 2006m. 4.24±0.82 (median 1.05; CI95%2.60-5.88). Amikacino (1000mg) buvo 0.55±0.17 (median 1.22; CI95% 0.23-0.88) 2004m.; 2005m. 0.44±0.13 (median 1.03; CI 95% 0.18-0.69), ir 0.52±0.13 (median 1.08; CI95%0.27-0.78) 2006m. Tobramicino (240mg) buvo 0.03±0.02 (median 0.14; CI95% 0.00-0.07) 2004m, 0.006±0.003 (median 0.03; CI95% 0.00-0.01) 2005m. Vancomicino (2000mg) buvo 0.55±0.17 (median 0.10; CI95% 0.21-0.89) 2004m, 0.50±0.14 (median 0.16; CI95% 0.22-0.79) 2005m, ir 0.53±0.14 (median 0.11; CI 95% 0.26-0.80) 2006m. Statistiškai reikšmingų antibiotikų suvartojimo pokyčių trių metų laikotarpyste nenustatyta. (p>0.05).

6 - 9 skyriai iš 23 – 28 suvartijo daugiau kaip 55% šių antibiotikų. Gentamicino KKS buvo tiriamos 1/1516 DDDs, vankomicino - 1/84 DDDs. 3/28 (11%) vankomicino KKS per žemos; 10/28 (36%) tinkamos; 15/28 (53%) per aukštos. Gentamicino KKS - 5/17 (30%) per žemos, 5/17 (30%) tinkamos, ir 7/17 (40%) per aukštos. Nustatyta, jog 8 atvejais iš stebėtų 17 pacientų (~47%), galima farmakokinetinė intervencija; 6 atvejais – ne (~35%), o 3 atvejai buvo neinterpretuojami.

Aminoglikozidų ir vankomicino esminių suvartojimo pokyčių per trejus metus nenustatyta. KKS tyrimų skaicius lyginant su šių antibiotikų suvartojimu nepakankamas. Pusei stebėtų ligonių atvejų galima farmakokinetinė intervencija.

Racionalumas, nustatyta dienos dozė (DDD), farmakokinetika, intervencija, antimikrobinė terapija.
Annex 1: LEIDIMAS ATLIKTI BIOMEDICININĮ TYRIMĄ

2005-05-04 Nr. BE-229

Biomedicininių tyrimo pavadinimas: Neracionalaus antimikrobinių vaistų vartojimo priežasčių apžvalginis intervencinis tyrimas.

Pagrindinis tyrejas: Doc. Romalda Mačiulaitis

Biomedicininių tyrimo vieta: Kauno medicinos universiteto klinikos

Istigas pavadinimas: Eivenių 2, 50009 Kaunas

Adresas:

Isgyvena:

Kauno regioninio biomedicininių tyrimų etikos komiteto posėdžio, įvykdytose 2005m. gegužės 3 d. (protokolo Nr. 72 2005) sprendimu pritaraita biomedicininių tyrimo vykdytiui.

Medžiagos eksperimento vykdymui būtų reikalingas (1) nėrdant informuoti Kauno regioninį biomedicininių tyrimų etikos komiteto aplink visus asmenybes atvejus, susijusius su studijos vykdymu, (2) užduotis su dirbtinių medžiagų sustatymo ir išvadų aptarnavimu bei (3) per mėnesį po studijos užbaigtąms, patiekal galutinį įvertinimą ir eksperimentus. 

| Nr. | Vardas Pavarde | Verklos sritys | Darbas išvadavimo
|-----|----------------|----------------|-------------------|
| 1   | Doc. Irena Marchiūtė | anestežologija | tarp
| 2   | Doc. Romalda Mačiulaitis | klininė farmakologija | tarp
| 3   | Prof. Nikolajus Bakšienė | pediatrija | tarp
| 4   | Prof. Algirdas Mikša | farmakologija | nė
| 5   | Doc. Tarvelis Nediūnas | chirurgija | tarp
| 6   | Danutė Zagurskienė | slauga | nė
| 7   | Laimu Ventiliauskaitė | pektoterapija | tarp
| 8   | Doc. Marta Rūbinienė | žemės ūkis | nė
| 9   | Egle Vilhelminienė | vadyba | tarp

Irena Marchiūtė

Pirmiinkė
References:


47. Moellering RC Jr, Krogstad DJ, Greeblatt DJ. Pharmacokinetics of vancomycin in