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ANALYSIS OF DIFFERENCES IN AUGMENTED RENAL CLEARANCE CASES AND THEIR RELEVANCE TO PHARMACOKINETICS

Master's thesis

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2014 06 11

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SUMMARY

Master Thesis of E. Moser “Analysis of Differences in Augmented Renal Clearance cases and their relevance to pharmacokinetics”, supervisor Prof. R. Mačiulaitis;

Lithuanian University of Health Sciences, Academy of Medicine, Faculty of Pharmacy, Institute of Physiology and Pharmacology – Kaunas.

In recent years, the focus on augmented renal clearance increased as it was found by other researchers to result in subtherapeutic drug dosing concentrations. Accurate assessment of renal function is important for prescribing optimal dosis of pharmaceuticals for ARC patients.

Objective of the work: The purpose of this quantitative retrospective comparative study was to register possible cases of Accelerated renal clearance in patients of Hospital of Lithuanian University of Health Sciences Kaunas Clinics and analyse the differences in assessments of cases of Augmented Renal Clearance and the possible risks of ARC for therapy.

Tasks: To achieve the objective several tasks were raised: 1) to register possible ARC patients cases as assessed by Cocroft-Gault and their possible associated reasons; 2) to analyse differences in three for GFR estimation used equations (Cocroft-Gault, MDRD simplified, and CKD-EPI). 3) determine the risk drugs for changed renal elimination.

Methodology: ARC survey (appendix 1) was filled about patients from various departments of Clinics during the period of 2013 03-04 – 2013 12-20. All patients were selected according serum creatinine values that were 50 µmol/l. or less. Two groups of patients were assigned for analysis: patients were grouped according Cocroft - Gault creatinine clearance values: (1) ARC group A CrCl >130 ml./min and (2) comparative Non-ARC group B CrCl 90-130 ml./min. In the group A were 31 and in the group B - 5 patients included for analysis.

Results: The mean GFR values of the research group were statistically significant: Cockroft-Gault – 164.8±34.50 ml./min., MDRD simplified – 169.7± 39.7 ml./min./1.73 m² and 123.3± 19.9 50 ml./min./1.73 m² by CKD-EPI (p<0.001). The proportion of ARC as assessed by MDRD was 90% and by CKD-EPI – 29 %.

The mean GFR estimations of the comparative group were statistically significantly different: Cockroft-Gault – 101.6 ± 11.34 ml./min., MDRD simplified – 131.2 ± 9.60 ml./min./1.73 m² and by
CKD-EPI – 97.44 ± 9.54 ml./min./1.73 m² (p<0.022). The proportion of non-ARC as assessed by MDRD was 40% and by CKD-EPI – 80%.

ARC was detected in 11 different departments of the Clinics. 29% of ARC cases were detected in ICU as expected (includes neurology and intensive therapy department and Intensive therapy department). Rest of the ARC cases were detected in Non-ICU setting: in surgery departments 32% departments (includes surgery, spinal cord and peripheral nerves surgery and chest surgery departments) and 35.5% in therapeutic departments (endocrinology, obstetrics, gynecology, gastroenterology, hematology and allergy).

The patients who have been detected with ARC had several possible causes associated with ARC and it mostly was –“young age “(< 60 years, in 70.96%). Other possible causes of ARC were found to be associated with 41.93% ”surgery”, “trauma” (chest and brain traumas included) – 22.5%, “diabetes” – 13% and “pancreatitits” – 13%.

The most frequently renally only excreted drugs that are at risk of under dosage if dosed at minimal dosage levels for the patient in an ARC group were: cefuroxime (38.7%) ranitidine (22.5%), KCL (19%) also gentamicine (9.6%).

Conclusions: Based on our study results we can conclude that the ARC as glomerular filtration rate (GFR) more that 130 ml./min. (assessing by Cocroft-Gault was not sufficiently replicated by MDRD and non-ARC – by CKD-EPI.

ARC was detected almost equally in the ICU, non-ICU surgical and non-ICU therapeutic departments as it was expected but also in non-ICU.

The ARC experienced patients had several possible known risk factors associated with ARC, most frequently – young age (below 60 years), surgery and trauma followed by less frequent events of diabetes and cancer.

The most frequently renally only excreted drugs that are at risk of under dosage if dosed at minimal dosage levels for the patient in an ARC group were cefuroxime, and ranitidine followed by gentamicine.

Key words: Augmented renal clearance, ICU, pharmakokinetics, GFR, subtherapeutic dosing.
SANTRAUKA

Elvinos Moser magistro baigiamasis darbas „Skirtumų analizė padidinto inkstų klirenso atveju ir jų svarba farmakokinetiniu požiūriu“, mokslinis vadovas Prof.R.Mačiulaitis, Lietuvos sveikatos mokslų universiteto, Medicinos akademijos, Farmacijos fakulteto, Fiziologijos ir farmakologijos institutus – Kaunas.

Pastaraisiais metais labai išaugo tyrimų apie padidintą inkstų klirensą (PIK), nes pagal keleto tyrejų duomenis šios būklės pasekmė yra subterapinės vaistų koncentracijos. Tikslus inkstų funkcijos nustatymas yra labai svarbus norint parinkti optimalias terapines vaistų dozes padidinto inkstų klirenso pacientams.

Darbo tikslas: Šio kiekvieno retrospektyvaus palyginamojo darbo tikslas buvo surinkti duomenis apie padidintą inkstų klirenso PIK atvejus Lietuvos sveikatos mokslų universiteto ligonines Kauno klinikose. Buvo siekiama išanalizuoti sirtumus tarp skirtingų PIK įvertinimo būdų ir įvertinti galimas PIK rizikas terapijai.

Uždaviniai: norint pasiekti užsibrėžtus tikslus šie uždaviniai buvo iškelti: 1) užregistruoti PIK atvejus ir nustatyti jų galimas priežastis. 2) apskaičiuoti GFG trimis skirtingomis formulėmis (Cocroft-Gault, MDRD, CKD-EPI) ir išanalizuoti skirtumus. 3) nustatyti vaistus, kurie gali būti pakitusio inkstų eliminacijos rizikoje.

Metodika: PIK anketa (1 priedas) buvo pildoma apie pacientus iš skirtingų Kauno klinikų skyrių, laikotarpui nuo 2013 04 03 iki 2013 12 20. Visi pacientai buvo parinkti pagal kreatinino kiekį serume – 50 µmol/l. ir mažiau. Dvi pacientų grupės buvo parinktos analizei: pacientai buvo sugrupuoti pagal kreatinino klireną į (1) PIK A grupę – CrCl > 130 ml./min. ir (2) palyginamąją B grupę – CrCl 90-130 ml./min. A grupėje buvo parinktas 31 pacientas ir B grupėje 5 pacientai.

Rezultatai: Vidutinės GFG reikšmės tiriamojo grupėje buvo statistiškai svarbios: pagal Cockroft-Gault – 164.8±34.50 ml./min., MDRD supaprastinta – 169.7± 39.7 ml./min./1.73 m² ir pagal CKD-EPI - 123.3± 19.9 50 ml./min./1.73 m² (p<0.001). PIK proporcija skaičiuojant pagal MDRD buvo 90.3% ir pagal CKD-EPI – 29 %.
Vidutinės GFG reikšmės palyginamojoje grupėje turėjo žymių statistinių skirtumų: Cockroft-Gault – 101.6 ± 11.34 ml./min., MDRD supaprastinta – 131.2 ± 9.60 ml./min./1.73 m² ir su CKD-EPI – 97.44 ± 9.54 ml./min./1.73 m² (p<0.022).

Nepadidinto inkstų klirenso proporcija skaičiuojant pagal MDRD buvo 40%, o pagal CKD-EPI – 80%.

PIK buvo rastas 11 skirtingų Kauno Klinikų skyrių: 29% visų atvejų buvo rasti intensyviosios pagalbos skyriuose (neurologijos ir intensyviosios terapijos skyrius bei intensyviosios terapijos skyrius). Likę PIK atvejai buvo užfiksuoti ne intensyviosios pagalbos skyriuose: chirurgijos skyriuose 32% (chirurgijos, stuburo ir periferinių nervų chirurgijos, krūtinės chirurgijos skyriai) ir 35,5% visų PIK atvejų terapijos skyriuose (endokrinologijos, akušerijos, ginekologijos, gastroenterologijos, hematologijos ir alergijos).

Pacientai, kuriems buvo užfiksuotas PIK, turėjo keletą galimų susijusių su PIK priežasčių dažniausiai tai buvo - „jaunų amžius“ (< 60 metų turėjo 70.9%). Kitos galimos PIK priežastys buvo susietos su „operacija“ (41.9%), „trauma“ (krūtinės ir smegenų traumas buvo įtrauktos) – 22.5% „diabetes“ – 13% ir „pankreatitas“ – 13%.

Dažniausiai vatojami tik per inkstus šalinami vaistai, kurie atsidūrė permažo dozavimo rizikoje buvo: cefuroksimas (38.7%), ranitidinas (22.5%), KCL (19%) taip pat gentamicinas (9.6%).

Išvados: Remiantis tyrimo rezultatais galime apibendrinti, kad PIK kai IFR yra daugiau nei 130 ml./min. (skaičiuojant pagal Cocroft-Gault rezultatai nebuvo reprezentatyvūs naudojant MDRD, o ne PIK grupėje - naudojant CKD-EPI.

PIK atvejai buvo užfiksuoti intensyviosios priežiūros skyriuose ir neintensyvios priežiūros skyriuose. Buvo tikimasi aptikti ligonius IPS, bet PIK atvejų buvo rasta ir kituose skyriuose

Pacientai su PIK taip pat turėjo keletą su PIK asocijuotų rizikos faktorių, kurių dažniausiai buvo „jaunų amžius“ (iki 60 metų), „operacija“ ir „trauma“ bei rečiau pasitaikantys „diabetes“ ir „vežys“. 
Vien tik per inkstus šalinami vaistai, kurių galėjo būti skirtos subterapinės dozės, jei buvo dozuota minimalios dozės lygyje, PIK patientams buvo cefuroksimas, ranitidinas, KCl bei kiek rečiau pasitaikantis gentamicinas.

**Raktažodžiai:** Padidintas inkstų klirensas, intensyviosios terapijos skyrius, farmakokinetika, IFG, subterapinės dozės.
ABBREVIATIONS

ARC – augmented renal clearance
CrCl – creatinine clearance
CKD - a progressive loss in renal function over a period of months or years
GFR – glomerular filtration rate
ICU – intensive care unit
Scr – serum creatinine
DEFINITIONS

Augmented renal clearance – enhanced renal elimination of circulating solutes such as waste products or pharmaceuticals when CrCl $\geq$ 130 ml/min.

Anthropometric values – specific dimensions of the body, such as height and weight.

Creatinine clearance – is the volume of blood plasma that is cleared of creatinine per unit time and is a useful measure for approximating the GFR.

Glomerular filtration rate – flow rate of filtered fluid through the kidney.

Intensive care unit – is a special department of a hospital or health care facilities that provides intensive care medicine.
TASKS AND OBJECTIVES OF THE WORK

The aim of this study was to analyse the differences in drug effects in patients with ARC of Hospital of Lithuanian University of Health Sciences Kaunas Clinics.

Tasks:

1. To register possible cases of Accelerated renal clearance in patients of Hospital of Lithuanian University of Health Sciences and determine their possible reasons.

2. Analyse differences in three for GFR estimation used formulas: Cocroft-Gault, MDRD and CKD-EPI.

3. To compare therapies in ARC and Non-ARC groups and determine the risk drugs for changed pharmacokinetics.
1. THEORETICAL BACKGROUND

1.1. Augmented renal clearance

Augmented renal clearance (ARC) became object of many studies in the last few years. This state can be defined as „enhanced renal elimination of circulating solutes (such as waste products or pharmaceuticals), and is quantified by the volume of plasma cleared of a given substance by the kidneys per unit of time ml/min.“. ARC is important especially for critically ill patients as they are in risk of suboptimal drug doses and treatment failure. As Carlier at al. describes, ARC occurs due to pathophysiological changes and the incidence of ARC in critically ill patients is between 30-85% depending on the studied population and the definition of ARC. In Europe accepted definition of ARC corresponds with Creatinine clearance values equal or greater than 130 ml/min. (CrCl ≥130 ml/min.)

According to one of the last years study „ARC is mostly described in critically ill patients in the Intensive Care Unit (ICU) with various incidence rates and no universally accepted aetiology“.3

1.2. Functions of the kidney

To understand the importance of ARC we first need to understand how the kidney functions. The main function of the kidney is excretion of circulating metabolites, toxins and drug substances. Excretion is combined process that consists of glomerular filtration, tubular secretion and reabsorption.4

Kidney also serve homeostatic functions such as the regulation of electrolytes, maintenance of acid–base balance, and regulation of blood pressure (via maintaining salt and water balance). They serve the body as a natural filter of the blood, and remove water soluble wastes.5

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1 Udy A.A. et al., 2010
2 Carlier et al. Critical Care 2013:R84 http://ccforum.com/content/17/3/R84
4 Udy A.A. et al., 2010
5 Robins and Cotran Pathologic basis of disease, 7/E,Elsevier health Sciences 2011 p.910
In case of ARC, these kidney functions are altered compared to expected base line and it further results in accelerated drug substance excretion. But the speed of drug substance excretion is crucial for setting a successful dosage regimen.

1.3. Glomerular filtration rate

To estimate glomerular filtration rate is important for several reasons: either it is renal disease evaluation, setting drug dosage regimen or evaluating renal involvement in some systemic diseases like diabetes melitus. It is important to understand that creatinine is also dependent on muscle mass, age and gender which means that creatinine based GFR calculation might be not always reliable. According Udy et al. the best ways to measure GFR are inulin or iohexol clearance, and radionucleotide studies. Even though these tests provide the most accurate results, they are not available in clinical setting.

1.4. Creatinine – based glomerular filtration rate approximations

1.4.1. Markers of renal function tests

Urea, uric acid, electrolytes, cystatin C and β-Trace Protein all are markers for renal function tests but serum creatinine value is the most commonly used marker in practice.

According the definition „Creatine is a breakdown product of creatine phosphate in muscle, and is usually produced at a fairly constant rate by the body depending on muscle mass“.

Botev et.al. concludes that glomerular filtration rate (GFR) has a paramount diagnostic and staging role for kidney disease patients and is the best index of renal function. Very often used serum creatinine-based formulas in adults for estimated GFR are the Cockroft-Gault (CG) and Modification of Diet in Renal Disease Study (MDRD).

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7 Udy A.A. et al., 2010
1.5. Creatinine clearance

Clearance is a function of glomerular filtration, secretion from the peritubular capillaries to the nephron, and reabsorption from the nephron back to the peritubular capillaries. Clearance is constant in first-order kinetics because a constant fraction of the drug is eliminated per unit time, but it is variable in zero-order kinetics, because the amount of drug eliminated per unit time changes with the concentration of drug in the blood.\(^{10}\)

Creatinine clearance (CrCl) is considered the most practical marker for determining glomerular filtration rate. One of the methods of creatinine clearance estimation is 24-hour urine collection coupled with a serum creatinine measurement. The rate of excretion is calculated by comparing amount of creatinine in plasma to the amount of creatinin in urine over a period of 24 hours. This is one of the ways CrCl can be calculated and it is unfortunately not very often applied in practice because of the practical difficulties (e.g. difficulty to collect urine 24-hours) of this approach. A much more practical way of determining CrCl is estimating the rate of production of creatinine vs. estimating the rate of elimination as it is done in former method. To estimate the rate of production it takes only single measure of serum creatinine. After serum creatinine measure is taken (blood sample is taken to determine serum creatinine) CrCl using different equations can be calculated.\(^{11}\)

1.6. Cockcroft-Gault equation

In 1976, Cockcroft and Gault introduced a equation comprising several anthropometric variables. Anthropometric values included in the formula were gender, age, weight and they help compensate for the inadequacies of creatinine level as a marker of glomerular filtration rate (GFR).\(^{12}\)

Derivation included the relationship found between age and 24-hour creatinine excretion/kg in 249 patients aged 18–92. Values for Ccr were predicted by this formula measured in 236 patients. The formula gave a correlation coefficient between predicted and mean measured Ccr·s of 0.83; on

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\(^{11}\) Walker, R., and Cate Whittlesea. Clinical pharmacy and therapeutics. Elsevier Health Sciences, 2011

average, the difference between predicted and mean measured values was no greater than that between paired clearances.13

\[
GFR \text{ (mL/min/1.73 m}^2\text{)} = (A \times (140 - age)) \times \frac{\text{weight}}{\text{Cre}}
\]

Where A: 1.23 for male, 1.04 for female

Table 1. Cockroft-Gault equation

The advantage of this approach is that the time-consuming and error-biased collection of 24 hour urine can be skipped, whereas the results are of similar quality.

The weakness of this approach is that it tends to be imprecise especially in cases of acute renal failure, unstable renal function, strong edema or adipositas.14

1.7. Modification of diet in renal disease equation (MDRD)

This equation was created to simplify prediction of GFR and included only demographic and serum variables. Independent factors associated with a lower GFR included a higher serum creatinine concentration, older age, female sex, nonblack ethnicity, higher serum urea nitrogen levels, and lower serum albumin levels.15 The strength of this formula is a higher accuracy because of respecting more GFR-relevant factors of the patient.

The Equation was developed in 1999 by Levey et al. was meant to replace the commonly used Cockroft-Gault equation, but did not gain much success in practice. „The principal objective of MDRD was to study the effect of dietary protein restriction and strict BP control on the progression of

13 Cockcroft D.W., Gault M.H., Departments of Medicine, Queen Mary Veterans’ Hospital, Montreal, Quebec, and Memorial University, St. John’s, Newfoundland Nephron 1976;16:31–41, Available at: http://www.karger.com/Article/Abstract/180580
14 cf: http://www.biomedizin.de/service/medizinische formeln/gfr_nach_cockgroft_gould/
chronic kidney disease (CKD)\textsuperscript{16}. Several studies reported that MDRD formula underestimates GFR in patients who do not have renal disease.\textsuperscript{17} Additionally, it might lead to erroneous results and should therefore be avoided in these patient groups: children under , pregnant women, extreme muscle mass (bodybuilder), extraordinary length of body, quickly changing renal function, overweight, underweight, vegetarian diet.\textsuperscript{18} 

According Verhave et al who studied 850 patients, GFR estimation while using MDRD was about 10\% underestimated\textsuperscript{19}

\[
GFR \ (\text{mL/min/1.73 m}^2) = 175 \times (S_{cr})^{-1.154} \times (\text{Age})^{-0.203} \times A
\]

\[
A: \ 0.742 \text{ if female or } 1.212 \text{ if African American}
\]

<table>
<thead>
<tr>
<th>Table 2. Modification of diet in renal disease equation (MDRD)</th>
</tr>
</thead>
</table>

1.8. Chronic kidney disease epidemiology collaboration equation (CKD-EPI)

In May 2009 a Chronic Kidney Disease Epidemiology collaboration formula was published with the expectation of more accurate GFR estimation possibilities.

Instead of creatinine, this formula focuses on the filtration of cystatin C. The formula is superior in accuracy especially for patients in first stage of impaired renal function.

Even though this formula showed decrease in bias it remained imprecise. The coefficients in the formula represent average effects observed in the population used to develop the equations and exclude patients at the extremes of muscle mass (including frail elderly, critically ill, or cancer patients), those with unusual diets, and those with conditions associated with reduced secretion or extra-renal elimination of creatinine.\textsuperscript{20}

\begin{itemize}
  \item Andrew S., et al. Journal of the american society of nephrology, available at: http://jasn.asnjournals.org/content/10/11/2426.full
  \item Mai T. Et al. Misapplications of Commonly Used Kidney Equations: Renal Physiology in Practice; George Washington University Medical Center, 2150 Pennsylvania; Available at : http://cjasn.asnjournals.org/content/4/3/528.full#ref-3
  \item http://www.bioscientia.de/de/service/medizinische-formeln/gfr_mdrd/#
\end{itemize}
GFR = 141 X min(Scr/κ, 1)^a X max(Scr/κ, 1)^-1.209 X 0.993^{Age}

where: X 1.018 [if female] X 1.159 [if black]

Table 3. Chronic kidney disease epidemiology collaboration CKD-EPI equation

Figure 1. Accuracy of the CKD-EPI and MDRD equations to estimate GFR for the validation data set (N=3896). Both panels show the difference between measured and estimated (y-axis) vs. estimated GFR (x-axis).

1.9. Normal GFR values

According UK Renal Association, GFR over 90 ml/min 1.73 m² is normal unless there is other any evidence of kidney disease. In case GFR is less than 90 ml/min 1.73 m², patient might be diagnosed with I degree chronic kidney disease (CKD).

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21 From Annual Internal Medicine Journal 2009;150:604-612,

22 British kidney association website: http://www.britishkidney-pa.co.uk/patient-info
Table 4. Degrees of CKD according CrCl value

Values of kidney function tend to differ from particular population and individuals so it is difficult to accurately define the process. Normal (GFR) values are about 130 ml/min in young women and men. It is important to mention that these values decline with increasing age.  

In the table below, the normal values of GFR (ml/min) are grouped according the gender and age parameters, calculated using Cockroft-Gault formula:

<table>
<thead>
<tr>
<th>Age</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 - 29</td>
<td>72 - 100</td>
<td>94 - 140</td>
</tr>
<tr>
<td>30 - 39</td>
<td>71 - 121</td>
<td>59 - 137</td>
</tr>
<tr>
<td>40 - 49</td>
<td>50 - 102</td>
<td>76 - 120</td>
</tr>
<tr>
<td>50 - 59</td>
<td>50 - 98</td>
<td>67 - 109</td>
</tr>
<tr>
<td>60 - 69</td>
<td>45 - 75</td>
<td>54 - 98</td>
</tr>
<tr>
<td>70 - 79</td>
<td>37 - 61</td>
<td>49 - 79</td>
</tr>
<tr>
<td>From 80</td>
<td>27 - 55</td>
<td>30 - 60</td>
</tr>
</tbody>
</table>

Table 5. From: Thomas L., Labor und Diagnose

One study reports that Cockroft-Gault formula for indirect estimation of GFR does not give precise results, this formula gonna be used in this study because unavailability of other better GFR estimation methods.

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Thomas L., Labor und Diagnose; 6. Auflage 2005; Figure available at: http://www.bioscientia.de/de/service/medizinische-formeln/gfr_nach_cockroft_gould
1.10. Possible reasons of ARC

As ARC is comparatively new phenomenon, not many studies and researches have been made to find out the possible reasons of it.

Researcher Andrew Udy made several studies in this topic and as possible associated ARC reasons excluded:

I. Younger Age (<60 years)
II. Pregnancy
III. Sepsis
IV. Trauma
V. Surgery or neurosurgery
VI. Neutropenia
VII. Burns injury
VIII. Cystic fibrosis

These eight possible associated reasons of ARC have not been extensively studied and could become a topic of future research.

1.11. Setting an appropriate dosage regimen for the ARC patients

Most of drug dosing regiments derive from data that is taken from healthy volunteers. Ill patients that have different pathophysiology than healthy ones and require different dosing schedules.

ARC patients are the ones that are mostly in need for better adjusted therapeutic dosage regimen, because:

1. patients with ARC have increased GFR, which means renally excreted drugs are excreted faster than normal without fully exerting their effect, which strongly indicates for dosage adjustment;

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25 Kuzminskis V. et al., Comparison of methods for evaluating renal function, Department of nephrology, LUHS, 2006, Article available at: http://vddb.library.lt/fedora/get/LT-eLABa-0001:J.04~2007~ISSN_1010-660X.V_43.SUPPL_1.PG_46-51/DS.002.0.01.ARTIC
2. even though therapeutic drug monitoring (TDM) is more often available, case studies report that subtherapeutic doses of β-lactam antibiotics, especially meropenem, have been detected in 48% of the patients and even 80% of them had ARC.  

Study made by Baptista J. et al.(2011) associated ARC with subtherapeutic serum vancomycin concentrations, especially on the first three days of treatment period. Another case study made by Tröger U. et al. concluded that patients with present ARC needed much higher meropenem dosages compared to empirical dosage regimen.

1.12. Only renally excreted drugs

Most of drugs are renally excreted. Drugs that are excreted mainly renally are in the main risk to fail in reaching therapeutic dosages of ARC patients. It is important to detect such drugs in ARC patients’ prescriptions and consider possible dosage changes for these drugs. Some of such drugs are: penicillins, cephalosprins, aminoglycosides, tetracycline, ranitidine, cimetidine, porcainamide, digoxin, lithium, diuretics, gentamicine, beta blockers.

26 Carlier M. et al. Critical care 2013, 17: R84 Available at: http://ccforum.com/content/17/3/R84
29 http://www.gpnotebook.co.uk/simplepage.cfm?ID=-1321926612
2. METHODOLOGY

2.1 ARC patient surveys

**Objective:** Patients of Hospital of Lithuanian University of Health Sciences Kaunas Clinics who had ARC.

**Patient selection and amount:** Patients of Hospital of Lithuanian University of Health Sciences Kaunas Clinics who had serum creatinine concentrations 50 mc mol/l or less were selected. Patient selection was performed by Kaunas Clinics data base software. Accordingly, data from medical history books of these patients and prescribed medications journals were filled in ARC patient surveys (appendix 1) during the period of 2013 03 04 – 2013 12 20.

The permission of Bioethics Center was given. (appendix 2).

In total 31 patients with ARC (CrCl > 130 ml./min.) and 5 patients in comparative group (CrCl 90-130 ml./min.) were taken for analysis. All of the analysed patients had Scr values lower than 50 mc mol./l.

**Metodology:** To evaluate if patients have ARC survey was made. Survey consists of general information part which include data about: department, doctors` name, date of hospitalisation, patients code, gender, weight, health status, age, blood pressure, pulse and breathing rate.

Second part of the survey includes data about patients used medications, dosages and dosage changes made, creatinine test results, creatinine clearance calculations and table of possible reasons of ARC. According the survey data (specifically according Cockroft-Gault equation results) patients were grouped to ARC or comparative groups. To decide whether patient belongs to ARC group estimation of GFR rate was calculated using CrCl as the marker.

**Statistical analysis:**

Received data was typed in standard Excel summary table and evaluated statistically using appropriate software that helped to find correlations between two groups that were compared. Microsoft Excel and SPSS 17.0 software was used for analysis. Various parameters were calculated in order to analyse the data: mean values(X±SD) of (age,weight,pulse, GFR using three formulas), percentages of (departments,diseases, possible ARC reasons, GFR estimations differences, renally excreted drugs. Values of GFR estimations (using all three formulas) were analysed statistically using non-parametric statistical Friedmans’ test (p value was calculated that points differences of two compared populations, if p <0,05 two compared populations have a significant statistical differences.
3. RESULTS

In 31 patient ARC was detected (analysed group) and 5 patients were selected as comparative group. 55% of ARC group were women. Average age of A group were 49 ±15.67 years, comparative - 74±7.26 years. Mean weight was: A - 71.7 ±11.08 kg, and comparative - 64.4 ±7.98 kg. Average blood pressure were: A group - 128±20.81/79±12.05, B - 118±28.02/68±14.83 mmHg. The average variables of both groups are shown below in Table 6.

<table>
<thead>
<tr>
<th>Variables (average) :</th>
<th>ARC group A (n=31)</th>
<th>Comparative group B (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49 ±15.67</td>
<td>74±7.26</td>
</tr>
<tr>
<td>Gender (f./m.)</td>
<td>55% f.</td>
<td>100% f.</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.7 ±11.08</td>
<td>64.4 ±7.98</td>
</tr>
<tr>
<td>Blood pressure (systolic/diastolic mmHg)</td>
<td>128±20.81/79±12.05</td>
<td>118±28.02/68±14.83</td>
</tr>
</tbody>
</table>

Table 6. Means of different variables in both groups.

ARC was detected in 11 different departments of the Clinics. 29% of ARC cases were detected in ICU as expected (includes neurology and intensive therapy department and Intensive therapy department). Rest of the ARC cases were detected in Non-ICU setting: in surgery departments 32% departments (includes surgery, spinal cord and peripheral nerves surgery and chest surgery departments) and 35.5% in therapeutic departments (endocrinology, obstetrics, gynecology, gastroenterology, hematology and allergy). Data is shown in the Figures 2 and 3 below.
The patients who have been detected with ARC had several possible causes associated with ARC and it mostly was –“young age “(< 60 years, in 70.9%). Other possible causes of ARC were found to be associated with 41.9% ”surgery”, “trauma” (chest and brain traumas included) – 22.5%, “diabetes” – 13% and “pancreatitis” – 13%.
Figure 4. Possible associated ARC causes in % (n=31)

Less frequent conditions included stroke, burn, tetanus, nephritis, cholangitis, cystic fibrosis and vein embolism.

Patients of comparative group who have no ARC were hospitalized because of the surgery 80% or burns injury 20%.

The mean GFR values of the research group were statistically significant: Cockroft-Gault – 164.8±9.54 ml./min., MDRD simplified – 169.7± 9.60 ml./min./1.73 m² and 123.3± 11.34 ml./min./1.73 m² by CKD-EPI (p<0.001). The proportion of ARC as assessed by MDRD was 90% and by CKD-EPI – 29 %.

The mean GFR estimations of the comparative group were statistically significantly different: Cockroft-Gault – 101.6 ± 11.34 ml./min., MDRD simplified – 131.2 ± 9.60 ml./min./1.73 m² and by CKD-EPI – 97.44 ± 9.54 ml./min./1.73 m² (p<0.022). The proportion of non-ARC as assessed by MDRD was 40% and by CKD-EPI – 80%.

Comparing the therapies of both groups not many similarities were found. The only renally excreted drug that both groups take is ranitidine: in ARC group – 22.5%, comparative – 20%.
Figure 5. Comparison of GRF estimations according to three different formulas.

Comparing group B, results of MDRD formula have statistically greater significance (p=0.022). Results of both groups were compared using non-parametric statistical Friedmans’ test calculating with all three formulas.

As shown in the Table 6. The differences of the results of the equations are statistically significant. In ARC group, calculating with CKD-EPI formula the results have smaller statistical significance (p<0.001).

<table>
<thead>
<tr>
<th>Groups:</th>
<th>Mean rank</th>
<th>Asymp. Sig. (p value)</th>
<th>Chi -square</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARC group (A)</td>
<td>GFR according MDRD simplified</td>
<td>2.55</td>
<td>&lt;0.001</td>
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<tr>
<td></td>
<td>GFR according</td>
<td>2.45</td>
<td></td>
</tr>
</tbody>
</table>

Number of the patient

GFR approximations in ml./min.

![Graph showing GFR approximations](image-url)
<p>| | | | | |</p>
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<thead>
<tr>
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<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Cocroft-Gault</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR according CKD-EPI</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparative group (B)</td>
<td>GFR according MDRD simplified</td>
<td>3</td>
<td>0.022</td>
<td>7.6</td>
</tr>
<tr>
<td></td>
<td><strong>GFR according Cocroft-Gault</strong></td>
<td><strong>1.60</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>GFR according CKD-EPI</strong></td>
<td><strong>1.40</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 7.** Comparison of both groups using non-parametric statistical Friedmans` test.

The most frequently renally only excreted drugs that are at risk of under dosage if dosed at minimal dosage levels for the patient in an ARC group were: cefuroxime (38.7%) ranitidine (22.5 %), KCL (19%) less frequently gentamicine (9.6%). Results shown in the Figure 6 below.

Comparing the therapies of both groups not many similarities were found. The only renally excreted drug that was found in both groups is ranitidine: in ARC group – 22.5%, in comparative – 20%.
Figure 6. Percentage of drugs mostly used in ARC group
4. CONCLUSIONS

1. Based on our study results we can conclude that the ARC as glomerular filtration rate (GFR) more than 130 ml./min. assessing by Cocroft-Gault was not sufficiently replicated by MDRD and non-ARC – by CKD-EPI.

2. ARC was detected almost equally in the ICU, non-ICU surgical and non-ICU therapeutic departments as it was expected but also in non-ICU.

3. The ARC experienced patients had several possible known risk factors associated with ARC, most frequently –“young age“ (below 60 years), “surgery“ and “trauma“ followed by less frequent events of “diabetes“ and “cancer“.

4. The most frequently renally only excreted drugs that are at risk of under dosage if dosed at minimal dosage levels for the patient in an ARC group were cefuroxime, and ranitidine followed by gentaminiceicine and KCl.
5. DISCUSSIONS

Results of this study suggests:

- that ARC patients are not only present in ICU but can also be detected in other therapeutic departments (in our study detection of ARC cases in ICU and non-ICU was almost equal)
- this study correspond with the opinion that „ARC phenomenon is a significant event in patients in any hospital department“ of Minkutė R. et al. study (2013).
6. RECOMMENDATIONS

More profound and longer ARC cases study may be suggested in the future in order to:

- fully evaluate possible reasons of ARC and gain deeper understanding about its etiology.
- be able to make better drug therapy analysis between ARC and non-ARC groups.
- Find out more precisely which drugs are in risk of changed pharmacokinetics.
- avoid subtherapeutic drug doses, which is especially important when ARC is present.
- Drugs like: KCL, ranitidine, cefuroxime and gentamicine are in risk of underdosing and a more precise study should be made about them.
REFERENCES:


2. Carlier et al. Critical Care 2013:17:R84 http://ccforum.com/content/17/3/R84


5. Robins and Cotran Pathologic basis of disease, 7/E, Elsevier health Sciences 2011 p.910


12. Grubb A. Et al. , A cystatin C-based formula without anthropometric variables estimates glomerular filtration rate better than creatinine clearance using the Cockcroft-Gault formula, Scandinavian Journal of Clinical and Laboratory investigation 2005;65(2):153-62.,Available at :
13. Cockcroft D.W., Gault M.H. , Departments of Medicine, Queen Mary Veterans’ Hospital, Montreal, Quebec, and Memorial University, St. John’s, Newfoundland Nephron 1976;16:31–41 , Available at :
http://www.karger.com/Article/Abstract/180580
4. cf: http://www.bioscientia.de/de/service/medizinische-formeln/gfr_nach_cockgroft_gould/#
17. Mai T. Et al. Misapplications of Commonly Used Kidney Equations: Renal Physiology in Practice; George Washington University Medical Center, 2150 Pennsylvania; Available at : http://cjasn.asnjournals.org/content/4/3/528.full#ref-3
http://www.ajkd.org/article/S0272-6386(05)00625-6/abstract
21. From Annual Internal Medicine Journal 2009;150:604-612,
22. British kidney association website: http://www.britishkidney-pa.co.uk/patient-info
23. Thomas L., Labor und Diagnose; 6. Auflage 2005; Figure available at :
http://www.bioscientia.de/de/service/medizinische-formeln/gfr_nach_cockgroft_gould
24. Kuzminskis V. et al., Comparison of methods for evaluating renal function, Department of nephrology, LUHS, 2006, Article available at: http://vddb.library.lt/fedora/get/LT-eLABa-0001:J.04~2007~ISSN_1010-660X.V_43.SUPPL_1.PG_46-51/DS.002.0.01.ARTIC


## 8. APPENDIXES

1 Appendix. ARC patient survey

Augmented renal clearance (ARC) survey No. ______

_____________

Date of the first observation

### I. General information

<table>
<thead>
<tr>
<th>Clinic, department</th>
<th></th>
<th>Doctor`s name</th>
<th>Patient`s case history No.</th>
</tr>
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<tbody>
<tr>
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</table>

<table>
<thead>
<tr>
<th>Patient’s code</th>
<th>Disease code</th>
<th>Date of hospitalization</th>
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<tr>
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</table>

<table>
<thead>
<tr>
<th>Gender (M/F)</th>
<th>Height</th>
<th>General health status</th>
<th>Blood pressure</th>
<th>Pulse rate</th>
<th>Breathing rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Weight</td>
<td></td>
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</tbody>
</table>

### 2. Diagnosis (main condition, complications)

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</tbody>
</table>
II. Data about kidney damage

<table>
<thead>
<tr>
<th>Initial creatinine conc. (Cre)</th>
<th>Creatinine clearance was calculated: (Cockcroft Gault: CrCl=(A × (140-age) × weight)/Cre A: 1.23 - male, 1.04 - female)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td>MDRD</td>
</tr>
<tr>
<td></td>
<td>CKD-EPI</td>
</tr>
</tbody>
</table>

1. Currently used medication (data is written during the first day of investigation, changes made– in case dosing changed, since when and how long)

<table>
<thead>
<tr>
<th>Name, dosing, changes made and date</th>
<th>Name, dosing, changes made and date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>13.</td>
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<tr>
<td>2.</td>
<td>14.</td>
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<td>3.</td>
<td>15.</td>
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<tr>
<td>4.</td>
<td>16.</td>
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<td>5.</td>
<td>17.</td>
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<tr>
<td>6.</td>
<td>18.</td>
</tr>
</tbody>
</table>
2. Laboratory test results *(In case of ARC data is registered starting from the beginning of ARC!)*

<table>
<thead>
<tr>
<th>Date</th>
<th>Result and comment</th>
<th>Date</th>
<th>Result and comment</th>
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</thead>
<tbody>
<tr>
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<tr>
<td>4. Laboratory data to evaluate the impact of ARC</td>
<td>Laboratory tests/data, efficiency</td>
<td>Laboratory tests/data, safety</td>
<td></td>
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<tr>
<td>Date</td>
<td>Result and comment</td>
<td>Date</td>
<td>Result and comment</td>
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</tbody>
</table>

5. Possible reasons for ARC

<table>
<thead>
<tr>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger age (&lt;60 years)</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Surgery or neurosurgery</td>
</tr>
<tr>
<td>Neutropenia</td>
</tr>
<tr>
<td>Burns injury</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

6. Patient belongs to group:

<table>
<thead>
<tr>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARC (CrCl &gt;130 ml/min.)</td>
</tr>
<tr>
<td>Control group (CrCl 90-130 ml/min.)</td>
</tr>
<tr>
<td>Not included to investigation (CrCl &lt; 90 ml/min.)</td>
</tr>
</tbody>
</table>
2. Appendix. Permission from Bioethics center

KAUNO REGIONINIS BIOMEDICININIŲ TYRIMŲ ETIKOS KOMITETAS
LSMUL KK. Fiziologijos ir farmakologijos institutas (Klinikinės farmakologijos padalynys. Eivenių g 2, LT-50009 Kaunas.
tel. (+370) 37 32 68 89; el. paštas: kaunorbtek@lsmuni.lt

LEIDIMAS ATLIKTI BIOMEDICININĮ TYRIMĄ

2013-07-22 Nr. BE-2-35

Biomedicininio tyrimo pavadinimas: "Farmakoterapių problemų ir neracionalaus vaistų vartojimo paplitimio, priežasčių ir valdymo galimybių tyrimo programa"

Protokolo Nr.: 5
Data: 2013-01-21
Versija: 1
Asmens informavimo forma bei Informuoto asmens sutikimo forma data: 2013-06-13
Pagrindinis tyrėjas: Prof. Dr. Romaldas Mačiulaitis
Biomedicininio tyrimo vieta: LSMUL Vš Kauno klinikos
Adresas: Eivenių g. 2, LT-50009, Kaunas

Išvada:
Kauno regioninio biomedicininio tyrimų etikos komiteto posėdžio, jvykusio 2013 m. liepos 2 d. (protokolo Nr. 75/2013) sprendimu pritarta biomedicininio tyrimo vykdymui.

Mokslinio eksperimento vykdytojai jsipareigoja: (1) nedelsiant informuoti Kauno Regioninį biomedicininį Tyrimų Etikos komitetą apie visus nenumaty tus atvejus, susijusius su studijos vykdymu, (2) iki sausio 15 dienos - pateikti metinį studijos vykdymo apibendrinimą bei, (3) per mėnesį po studijos uzbaigimo, pateikti galutinį pranesimą apie eksperimentą.

Kauno regioninio biomedicininio tyrimų etikos komiteto nariai

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<th>Nr.</th>
<th>Vardas, Pavardė</th>
<th>Veiklos sritis</th>
<th>Dalyvavovo posedyje</th>
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<td>1.</td>
<td>Prof. Romaldas Mačiulaitis</td>
<td>Klinikės farmakologija</td>
<td>taip</td>
</tr>
<tr>
<td>2.</td>
<td>Prof. Edgaras Stankevicius</td>
<td>Fiziologija, farmakologija</td>
<td>ne</td>
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<tr>
<td>3.</td>
<td>Doc. Eimantas Peicius</td>
<td>Filosofija</td>
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<tr>
<td>4.</td>
<td>Dr. Ramunė Kasperavičienė</td>
<td>Kalbotyra</td>
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<td>5.</td>
<td>Med. dr. Jonas Andriuškevičius</td>
<td>Chirurgija</td>
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<td>7.</td>
<td>Prof. Skaidrius Milauskas</td>
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<td>8.</td>
<td>Med. dr. Rokas Bagdonas</td>
<td>Chirurgija</td>
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</tr>
<tr>
<td>9.</td>
<td>Egle Vaizgeliene</td>
<td>Visuomenės sveikata</td>
<td>taip</td>
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</tbody>
</table>

Kauno regioninis biomedicinių tyrimų etikos komitetas dirba vadovaudamasis etikos principais nustatytais biomedicininio tyrimo Etikos įstatyme, Helsinkio deklaracijoje, vaistų tyrinėjimo Geros klinikines praktikos taisyklemis.

________________________________

Kauno regioninis biomedicinių tyrimų etikos komitetas
Pirmininkas

Prof. Romalda Mačiulaitis