Estimations of renal function; implications for drug dosing in the elderly

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No conflicts of interest to report
Predictors of outcome and Renal clearance

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Overview

- Pharmacovigilance in the Elderly
- Assessment of Renal Function
- ENCePP/Geriatric Questionnaire Survey
- Dabigatran as an example
- Conclusions
Drug-Related Problems Causing Admission to a Medical Clinic

U. Bergman¹ and B.-E. Wiholm¹,²

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Drug-related problems causing admission to a medical clinic:

16%

Too low effect: 7%
Too high effect: 9%  ADR: 6%
Adverse drug reactions causing hospitalization can be monitored from computerized medical records and thereby indicate the quality of drug utilization

Mia von Euler¹*, Erik Eliasson¹, Gunnar Öhlén² and Ulf Bergman¹

¹Department of Clinical Pharmacology, Karolinska University Hospital, Huddinge, Karolinska Institutet, Stockholm, Sweden, The Regional Adverse Drug Reaction Unit in Stockholm, Sweden
²Department of Emergency Medicine, Karolinska University Hospital, Huddinge, Karolinska Institutet, Stockholm, Sweden
Adverse Drug Reactions (ADRs) causing hospitalisations.
Review of Swedish studies. 2005
Swedish ADR hospitalisation studies


ADR hospitalisations in %


9 %


6 %


14 %


12 %


11 %
Mean AGE in ADR hospitalisations


Types of ADRs

Type A
Predictable from pharmacology of the drug, dose-dependent and preventable

Type B
Bizzare, unpredictable from known pharmacology, and no dose-dependency
% pharmacological (typ A) ADRs


5. Von Euler M, Eliasson E, Öhlén G, Bergman U. Adverse drug reactions causing hospitalisation can be monitored from computerized medical records and thereby indicate the quality of drug utilisation. Pharmacoepidemiol Drug Safe 2006;15:178-184 89 %
Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients.

British Medical Journal 2004;329;15-9

Types of ADRs

Type A
Predictable from pharmacology of the drug, dose-dependent and preventable

95%

Type B
Bizzare, unpredictable from known pharmacology, and no dose-dependency

5%

76% of patients were 65 years or over

How Many ADRs Were Avoidable?

Definitely avoidable 8.6%
Possibly avoidable 63.1%
Not avoidable 28.1%

72 % of ADRs were definitely or possibly avoidable

A major problem in today's (Swedish!) health care, including pharmacotherapy, is the gap between knowledge and clinical practice!


Drugs and Renal Function

Anders Helldén
Ingegerd Odar-Cederlöf
Ulf Bergman

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Renal function and age

![Graph showing renal function and age relationship]
Adverse Drug Reactions and Impaired Renal Function in Elderly Patients Admitted to the Emergency Department
A Retrospective Study

Anders Helldén,¹ Ulf Bergman,¹ Mia von Euler,¹ Maria Hentschke,¹ Ingegerd Odar-Cederlöf¹ and Gunnar Öhlén²

¹ Regional Pharmacovigilance Unit, Division of Clinical Pharmacology, Department of Laboratory Medicine, Karolinska University Hospital, Huddinge, Karolinska Institutet, Stockholm, Sweden
² Department of Emergency Medicine, Karolinska University Hospital, Huddinge, Stockholm, Sweden
Routine measurement of renal function:

S/P-creatinine mikromol/L
S/P-creatinine versus age

P-kreatinin mot ålder

Kreatinin

Ålder

0 100 200 300 400 500 600 700

66 71 74 75 77 79 80 82 84 85 87 90 92 97

66 71 74 75 77 79 80 82 84 85 87 90 92 97

Kreatinin

Ålder

krea

Linjär (krea)
Creatinine clearance versus age according to the Cockcroft-Gault equation

Kreatinininclearance
enligt Cockcroft-Gault

(mL/min)

Ålder

ClCr
Linjär (ClCr)
S/P-creatinine 120 mikromol/L

**Man**
- 25 year
- 100 kg
- 125 ml/min

**Woman**
- 80 year
- 50 kg
- 25-30 ml/min
Renal function in the Elderly

S/P-Creatinine useless
Renal function in the Elderly

Renal Clearance

in absolute value (mL/min)
Renal function in the Elderly

Why absolute value?
(mL/min)

Dose recommendations are based on dose-effect studies using absolute clearance
Estimated renal function

Golden standard:
Iohexol clearance (EMA recommendation 2004)

Estimated GFR based on S/P-creatinine
Cockcroft & Gault \( (CL_{CG}) \)
MDRD4
CKD-Epi

Estimated GFR based on cystatin C
Equations for estimated Glomerular Filtration Rate (eGFR) in adults based on s/p creatinine concentration

Estimated GFR based on S-creatinine

- Cockcroft & Gault \((CL_{CG})\) mL/min  \textit{absolute value}
- MDRD4  mL/min/1,73 m\(^2\)  \textit{relative value (BSA)}
- CKD-Epi  mL/min/1,73 m\(^2\)  \textit{relative value (BSA)}

- cystatin C  mL/min/1,73 m\(^2\)  \textit{relative value (BSA)}
eGFR based on different models cf *Golden standard IOHEXOL*

Woman 86 years, S-creatinine 100 µmol/L, 
weight 40 kg, length 160 cm, BSA 1.37 m²
Renal function estimations and dose recommendations for dabigatran, gabapentin and valaciclovir: a data simulation study focused on the elderly

Anders Helldén,¹ Ingered Odar-Cederlöf,¹ Göran Nilsson,² Susanne Sjövik,³ Anders Söderström,⁴ Mia von Euler,¹,⁵ Gunnar Öhlén,⁶ Ulf Bergman¹,⁷,⁸
Figure 1  Renal function estimated in 790 individuals aged 65 and older by the Cockcroft-Gault equation with uncompensated P-creatinine (creatinine clearance absolute values in ml/min) and modification of diet in renal disease equation 4 (MDRD4) calculated according to the equations in box 1. MDRD4 is given as a relative value (ml/min/1.73 m²; mean±SEM). Uncompensated creatinine denotes S/P-creatinine determined with the ‘old Jaffe’ method.¹³
Based on the literature it seems as there may be a considerable variation internationally.

As our SPCs are now increasingly harmonized in Europe (via EMA) differences in renal function estimates may have clinical implications - particularly in the elderly with physiologically and disease related reduced renal function.
With this background we did a simple pilot survey focusing on Renal Function Assessment Methods available in hospitals in ENCePP member countries in 2012.
Acknowledgment

to the 28 ENCePP centres and hospitals and to the ENCePP office
(Thomas Goedecke, Eeva Rossi and Dagmar Vogl) for the support in doing this questionnaire survey
(13 February - 9 March 2012)
in an excellent way

Predictors of outcome & Renal clearance UB EMA 23.3 2012
Karolinska Institute Survey
ASSESSMENT OF RENAL FUNCTION AS A BACKGROUND TO DRUG TREATMENT IN THE ELDERLY

A. Which of these methods to assess renal function are available and used in daily clinical practice in your hospital?
Mark one or more of the following methods. PLEASE MARK or CIRCLE!

A.1 Serum/Plasma creatinine, enzymatic method
Year the method was introduced: ……………………
Traceable to IDMS (Isotope Dilution Mass Spectrometry)? YES NO
Reference values: in men:…………………………
in women:…………………………
Comments: …………………………………………………………………..

A.2 Jaffe method
Reference values in men:…………………………
in women:…………………………
Comments: …………………………………………………………………...

A.3 Jaffe method adjusted to enzymatic method
(compensated creatinine)
Reference values in men:…………………………
in women:…………………………
Comments: …………………………………………………………………..
Responses from 13 different countries in 'green' (i.e. 12 'ENCePP countries', plus Iceland)

response rate 71% (12/17) or 72% (13/18)
28 responses from 13 countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Questionnaire</th>
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<tbody>
<tr>
<td>BE</td>
<td>1</td>
</tr>
<tr>
<td>DE</td>
<td>3</td>
</tr>
<tr>
<td>DK</td>
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<tr>
<td>EL</td>
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<td>SE</td>
<td>1</td>
</tr>
<tr>
<td>UK</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>28</strong></td>
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</table>

Predictors of outcome & Renal clearance UB EMA 23.3 2012
COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

NOTE FOR GUIDANCE ON THE EVALUATION OF THE PHARMACOKINETICS OF MEDICINAL PRODUCTS IN PATIENTS WITH IMPAIRED RENAL FUNCTION
III.2 Measures of Renal Function

Renal function is usually assessed by measuring glomerular filtration rate (GFR).

A number of exogenous markers for measuring GFR (e.g. 51Cr-EDTA, 99mTc-DTPA, iothalamate, iohexol) and endogenous markers for estimation of GFR (e.g. creatinine, Cystatin C) are available. It is recommended that renal function in pharmacokinetic studies is determined by measuring GFR using accurate well established methods (such as iohexol clearance).
C. Are any of the following GFR (Glomerular Filtration Rate) methods (Golden standard) being used in the elderly in your hospital?

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.1</td>
<td>GFR - Iohexol clearance</td>
<td>2</td>
</tr>
<tr>
<td>C.2</td>
<td>GFR - 51Cr-EDTA clearance</td>
<td>8</td>
</tr>
<tr>
<td>C.3</td>
<td>GFR - 125Iothlamate clearance</td>
<td>0</td>
</tr>
<tr>
<td>C.4</td>
<td>GFR - Inulin clearance</td>
<td>1</td>
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</tbody>
</table>
III.2 Measures of Renal Function

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WHAT ABOUT CLINICAL PRACTICE?
US-FDA Guideline

In the most recent draft guideline from the US-FDA both Cockcroft & Gault and MDRD may be used {FDA, 2010}.

The importance in clinical practice is to recognize which method the recommendations are based on and to stick to that one when prescribing renal risk drugs.
B. Which of the following calculations/estimations are used in daily practice

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
</tr>
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<tbody>
<tr>
<td><strong>B.1</strong></td>
<td>Creatinine clearance est. (eCer) Cockroft Gault (ml/min)</td>
<td>12</td>
</tr>
<tr>
<td><strong>B.2</strong></td>
<td>MDRD4 (simplified) - eGFR</td>
<td>21</td>
</tr>
<tr>
<td><strong>B.3</strong></td>
<td>CKD-EPI formula - eGFR</td>
<td>5</td>
</tr>
<tr>
<td><strong>B.4</strong></td>
<td>Creatinine clearance Cer measured urine blood 12h/24h</td>
<td>24</td>
</tr>
<tr>
<td><strong>B.5</strong></td>
<td>Clearance calculated from serum Cystatin C</td>
<td>5</td>
</tr>
</tbody>
</table>
Renal function estimations and dose recommendations for dabigatran, gabapentin and valaciclovir: a data simulation study focused on the elderly

Anders Helldén, Ingegerd Odar-Cederlöf, Göran Nilsson, Susanne Sjöviker, Anders Söderström, Mia von Euler, Gunnar Öhlén, Ulf Bergman
Dabigatran as an example

Serious bleedings, even fatal, were reported from Australia, France, Japan and USA with the newly introduced oral antithrombin inhibitor dabigatran

These were mainly seen in elderly patients with renal failure

Dabigatran is predominantly eliminated via the kidneys and it should not be used at a creatinine clearance of less than 30 ml/min. A clearance of 30 to 50 mL/min requires dose reduction

Helldén et al  BMJ Open 2013
Dabigatran as an example

We applied four different equations to estimate renal function

Cockcroft & Gault, uncompensated and compensated P-creatinine (mL/min)

MDRD4 (mL/min/1,73m²)

CKD-EPI (mL/min/1,73m²)

We then calculated the doses of dabigatran that would be prescribed to 790 individuals 65 years and older in Sweden according to the SPC
Dose recommendations in relation to renal function equations used for DABIGATRAN in 790 individuals aged 65 and older in Sweden

Helldén et al  BMJ Open 2013

Dabigatran dosing in the elderly

- **Cockcroft & Gault uncompensated creatinine (mL/min)**: 18% contraindicated, 49% dose 150/220 mg, 11% dose 220/300 mg
- **Cockcroft & Gault compensated creatinine (mL/min)**: 33% contraindicated, 54% dose 150/220 mg, 35% dose 220/300 mg
- **MDRD4 (mL/min/1.73m2)**: 27% contraindicated, 66% dose 150/220 mg, 6% dose 220/300 mg
- **CKD-EPI (mL/min/1.73m2)**: 7% contraindicated, 67% dose 150/220 mg, 25% dose 220/300 mg

Legend:
- Blue: Contraindicated
- Red: Dose 150/220 mg
- Green: Dose 220/300 mg
Patient safety and estimation of renal function in patients prescribed new oral anticoagulants for stroke prevention in atrial fibrillation: a cross-sectional study

Peter K MacCallum, Rohini Mathur, Sally A Hull, Khalid Saja, Laura Green, Joan K Morris, Neil Ashman

Conclusions: Were the MDRD-derived eGFR to be used instead of Cockcroft-Gault in prescribing these new agents, many elderly patients with AF would either incorrectly become eligible for them or would receive too high a dose. Safety has not been established using the MDRD equation, a concern since the risk of major bleeding would be increased in patients with unsuspected renal impairment. Given the potentially widespread use of these agents, particularly in primary care, regulatory authorities and drug companies should alert UK doctors of the need to use the Cockcroft-Gault formula to calculate eligibility for and dosing of the new oral anticoagulants in elderly patients with AF and not rely on the MDRD-derived eGFR.
Conclusions cont.

Renal clearance based on exogenous or endogenous measurements/estimates are only surrogate markers for drug clearance.
Conclusions cont.

For drugs dependent on renal elimination determination of plasma concentrations:

TDM - Therapeutic Drug Monitoring is the best way to optimize drug dosing when there is no useful effect measurement such as blood pressure, pulse, INR etc.

TDM is an underused tool in optimizing the dose for many drugs.
The EMA Guidance on pharmacokinetics in patients with renal function in clinical trials from 2004 is now subject to revision.

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

NOTE FOR GUIDANCE ON THE EVALUATION OF THE PHARMACOKINETICS OF MEDICINAL PRODUCTS IN PATIENTS WITH IMPAIRED RENAL FUNCTION

DISCUSSION IN THE EFFICACY WORKING PARTY: January 2003
TRANSMISSION TO CPMP: March 2003
“The ageing of populations is poised to become the next global public health challenge. During the next 5 years, for the first time in history, people aged 65 years and older in the world will outnumber children aged younger than 5 years.”

See Comment page 484
Questions & Answers

If you don’t ask stupid question
You remain stupid

Alvan Feinstein