Analysis of 401 NEPharm consultations requested for drug dose adjustment in kidney patients

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with support from
Franz Maximilian Rasche, Benjamin Boesler, Belal Awad, Ruth Renz and Tim Seewoester

Nephrology

Disclosures
Sponsored by Novartis and Alexion

Which drugs make the biggest problems?

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiinfectiva</td>
<td>46%</td>
</tr>
<tr>
<td>Zydostatika</td>
<td>25%</td>
</tr>
<tr>
<td>Antihypertensiva</td>
<td>12%</td>
</tr>
<tr>
<td>Anidriabekta</td>
<td>10%</td>
</tr>
<tr>
<td>Andere</td>
<td>7%</td>
</tr>
</tbody>
</table>

NEPharm inquiries 2002 – 2012

- **Cases**: N = 401
- **Mean age of patients**: 57 +/- 17 years
- **e-mail**: 92%
  - **fax**: 6%
  - **post mail**: 2%
- **On dialysis or dialysis started**: 85% 10%
- **CKD**: 15%
  - **mean GFR**: 45 +/- 19 ml/min
**NEPharm Drug Consultations**

Dose adjustment

Zytostatika bei Dialyse

YES =>

- Actinomycin D
- Arsentrioxid
- Bleomycin
- Capecitabin
- Carboplatin
- Carmustin
- Cisplatin
- Cladribin
- Clofarabin
- Cyclophosphamid
- Cytarabin
- Chlorambucil
- Dacarbazine
- Daunorubicin
- Doxorubicin
- Epirubicin
- Etoposid
- Fludarabin
- Gemcitabin (dFdU-M)
- Hydroxyurea
- Idarubicin
- Ifosfamid
- Irinotecan
- Lenalidomide
- Melphalan
- Mitomycin
- Methotrexat
- Oxaliplatin
- Pemetrexed
- Procarbazine
- Topotecan

NO =>

- Anastrozol
- all trans Retinol
- Anagrelid
- Asparaginase
- 5-Azazitidin
- Azathioprin
- Bevacizumab
- Bortezomib
- Busulfan
- Cetuximab
- Docetaxel
- Doxorubicin PEG
- Epirubicin (fren 7%)
- Erlotinib
- 5-Fluorouracil
- Gefinitib
- Gentuzumab
- Imatinib
- Leuprolrelin
- Mechloreotamin
- Megestrol
- 6-Mercaptopurin
- Mitoxantron
- Nilotimib (?)
- Paclitaxel
- Procarbazine
- Rituximab
- Sorafenib
- Sunitinib
- Thalidomide
- Tamoxifen
- Terezol
- Topotecan
- Trastuzumab
- Vinblastin
- Vincriustin
- Vorexibin


**Anti-cancer drugs and **\textbf{KIDNEY}

- **Platinderivate:** *Cisplatin* / *Carboplatin* / *Oxaliplatin*
- **Antimetabolite:** 5-FU / Gemcitabin / *Pemetrexet* / 6-Mercaptopurin
  - Capecitabin / *Methotrexat* / Azathioprin
- **Vinca-Alkaloide:** Vinorelbin / Vincristin / Vinblastin
- **Taxane:** Docetaxel / Paclitaxel
- **Anthrazykline:** Doxorubicin / *Daunorubicin* / Epirubicin / *Idarubicin*
- **Antikörper:** Bevacizumab / Cetuximab
- **TK-Inh:** Erlotinib / Sorafenib / Sunitinib
- **Alkylantien:** Cyclophosphamid / *Ifosfamid* / Treosulfan
  - *Dacarbazin* / Procarbazin
- **Antibiotika:** *Bleomycin* / *Mitomycin*
- **Topoisomerase-Inh:** *Etoposid* / Irinotecan / Topotecan

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**NEPharm database**

**PubMed search**
- Identification of papers (manually)
- Data extraction
- Data input
- Control of errors

**NEPharm (Ulm)**
- Pharmacokinetic Datenbase \(T_{1/2}, Cl, Vd\)
- Form: Access
- Number: >90’000 Parameter values for >30’00 Drugs from >10’000 papers

Keller F, Frankewitsch T, Zellner D, Simon S, Czock D, Giehl M.  
\textit{Standardized structure and modular design of a pharmacokinetic database.}  
Dettli Dose Adjustment \( AUC = \text{const.} \). 

Referee’s comments:
Referee: I

Comments to the Author
From academic perspective, this manuscript is fairly good but in real life (clinical setting) it has no practical application. In a clinical setting, a treating physician has neither time nor the ability to calculate the duration of effect as proposed by the authors. The physicians will ultimately adjust the dose based on a patient’s response and may increase or decrease the dose accordingly.

I disagree with the authors that “the time of effect duration is a proportional function of the elimination half-life”. In reality, pharmacokinetic half-life can be entirely different than the pharmacological half-life. A drug can have a very short half-life but its pharmacological effect can be much longer than the elimination half-life. For example, selegiline (an adjunct to levodopa) has a half-life about 2 hours but this drug is given every 24 hours. Similarly, diazepam has a long half-life (approximately 40 hours) but is given 2 to 3 times a day for the treatment of anxiety. This phenomenon will be true for a good majority of drugs.

In disease states such as renal or hepatic impairment, the dose adjustment is made based on the AUC not on the elimination half-life. The regular practice is to reduce the dose based on increase in the AUC but keep the dosage interval similar to healthy subjects.

\[
Cl = \frac{D}{AUC}
\]

for \( \rightarrow \ Tau = \text{const.} \rightarrow D = D_{\text{norm}} \cdot \frac{Cl}{Cl_{\text{norm}}} \)

= Dettli rule 1

General Kunin approach \( C_{\text{peak}} = \text{const.} \).

Kunin CM.
A guide to use of antibiotics in patients with renal disease.

\[
D = D_{\text{start}} \left[ 1 - \exp \left( -0.693 \cdot \frac{\ Tau}{T_{1/2}} \right) \right]
\]

\[
Tau = \frac{T_{1/2}}{0.693} \cdot \ln \left( \frac{C_{\text{peak}}}{C_{\text{trough}}} \right)
\]

for \( \rightarrow C_{\text{trough}} = \text{const.} \rightarrow Tau \geq T_{1/2} \)

= Dettli rule 2

for \( \rightarrow C_{\text{trough}} = \frac{1}{2} \cdot C_{\text{peak}} \rightarrow Tau = T_{1/2} \)

= Kunin rule
Clinical course of haemodialysis patients with malignancies and dose-adjusted chemotherapy.

**Table 1. Administered doses compared with the dose proposals calculated by the dose adjustment rules of Dettli and Giusti/Hayton**

<table>
<thead>
<tr>
<th>Drug</th>
<th>$B_{\text{admin}}$</th>
<th>$B_{\text{norm}}$</th>
<th>$B_{\text{Dettli}}$</th>
<th>$D_{\text{Giusti}}$</th>
<th>$T_1/2\text{norm}$ (h)</th>
<th>$T_1/2\text{Dettli}$ (h)</th>
<th>$f_{\text{admin}}$ (%)</th>
<th>$D_{\text{admin}}/D_{\text{Dettli}}$ (%)</th>
<th>$D_{\text{admin}}/D_{\text{Giusti}}$ (%)</th>
<th>$D_{\text{admin}}/D_{\text{norm}}$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carmustine</td>
<td>60°</td>
<td>60°</td>
<td>6°</td>
<td>5.9°</td>
<td>1.5</td>
<td>1.6</td>
<td>1.4</td>
<td>1.0</td>
<td>100</td>
<td>98</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>6°</td>
<td>6°</td>
<td>6°</td>
<td>8.9°</td>
<td>1.6</td>
<td>1.6d</td>
<td>1.0</td>
<td>1.0</td>
<td>100</td>
<td>98</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>9°</td>
<td>9°</td>
<td>9°</td>
<td>8.9°</td>
<td>1.6</td>
<td>1.6d</td>
<td>1.0</td>
<td>1.0</td>
<td>100</td>
<td>98</td>
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<tr>
<td>Cisplatin</td>
<td>48°</td>
<td>60°</td>
<td>31.7°</td>
<td>31.8°</td>
<td>137</td>
<td>239</td>
<td>171</td>
<td>145</td>
<td>80</td>
<td>90</td>
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<td>Cyclophosphamide 11.25°</td>
<td>15°</td>
<td>10.9°</td>
<td>12.8°</td>
<td>6.0</td>
<td>8.5</td>
<td>14.5</td>
<td>106</td>
<td>87</td>
<td>75</td>
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<td>Cyclophosphamide 13°</td>
<td>13°</td>
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<td>12.8°</td>
<td>6.0</td>
<td>8.5</td>
<td>14.5</td>
<td>142</td>
<td>90</td>
<td>100</td>
<td></td>
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<tr>
<td>Cyclophosphamide 600°</td>
<td>600°</td>
<td>423.3°</td>
<td>512.9°</td>
<td>6.0</td>
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<td>555.6°</td>
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<td>Cyclophosphamide 1000°</td>
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<td>1709.6°</td>
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<td>14.5</td>
<td>142</td>
<td>90</td>
<td>100</td>
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<tr>
<td>Cytarabine</td>
<td>20°</td>
<td>200°</td>
<td>177.3°</td>
<td>176.0°</td>
<td>2.0</td>
<td>2.2</td>
<td>2.2</td>
<td>120</td>
<td>113</td>
<td>144</td>
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<td>Daunorubicin</td>
<td>45°</td>
<td>60°</td>
<td>48.5°</td>
<td>51.6°</td>
<td>16.2</td>
<td>20.1</td>
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<td>75</td>
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<td>Doxorubicin</td>
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<td>7°</td>
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<td>17.5</td>
<td>20.8</td>
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<td>86</td>
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<tr>
<td>Etosaxel</td>
<td>3°</td>
<td>90°</td>
<td>87°</td>
<td>86.8°</td>
<td>5.1</td>
<td>5.3</td>
<td>3.8</td>
<td>40</td>
<td>40</td>
<td>39</td>
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<tr>
<td>Doxorubicin</td>
<td>5°</td>
<td>50°</td>
<td>40°</td>
<td>43.7°</td>
<td>17.5</td>
<td>20.8</td>
<td>17.5</td>
<td>12.7</td>
<td>89</td>
<td>86</td>
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<tr>
<td>Etoposide</td>
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<td>25°</td>
<td>158.1°</td>
<td>158.0°</td>
<td>5.1</td>
<td>8.1</td>
<td>38.6</td>
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<td>158</td>
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<td>S-Fluorouracil</td>
<td>423°</td>
<td>423°</td>
<td>311.7°</td>
<td>389.8°</td>
<td>0.2</td>
<td>0.3</td>
<td>8.3</td>
<td>136</td>
<td>109</td>
<td>100</td>
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<tr>
<td>S-Fluorouracil</td>
<td>480°</td>
<td>480°</td>
<td>352.0°</td>
<td>440.2°</td>
<td>0.2</td>
<td>0.3</td>
<td>8.3</td>
<td>136</td>
<td>109</td>
<td>100</td>
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<tr>
<td>S-Fluorouracil</td>
<td>600°</td>
<td>600°</td>
<td>440.9°</td>
<td>550.3°</td>
<td>0.2</td>
<td>0.3</td>
<td>8.3</td>
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<td>109</td>
<td>100</td>
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<tr>
<td>S-Fluorouracil</td>
<td>650°</td>
<td>650°</td>
<td>440.9°</td>
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<td>0.3</td>
<td>8.3</td>
<td>136</td>
<td>109</td>
<td>100</td>
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<tr>
<td>S-Fluorouracil</td>
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<td>2600°</td>
<td>1910°</td>
<td>2380°</td>
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<td>0.3</td>
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<td>109</td>
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<td>Idarubicin</td>
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<td>5°</td>
<td>9.5°</td>
<td>9.4°</td>
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<td>63</td>
<td>64</td>
<td>60</td>
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<tr>
<td>Melphalan</td>
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<td>30°</td>
<td>19.0°</td>
<td>19.0°</td>
<td>1.1</td>
<td>2.9</td>
<td>36.7</td>
<td>158</td>
<td>158</td>
<td>100</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>8°</td>
<td>10°</td>
<td>9.5°</td>
<td>9.4°</td>
<td>40.7</td>
<td>43.3°</td>
<td>6.0</td>
<td>84</td>
<td>85</td>
<td>80</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>100°</td>
<td>100°</td>
<td>100°</td>
<td>100°</td>
<td>0.12</td>
<td>0.12</td>
<td>0.12</td>
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<tr>
<td>Vincristine</td>
<td>0.4°</td>
<td>0.4°</td>
<td>0.4°</td>
<td>0.4°</td>
<td>2.7</td>
<td>3.2</td>
<td>12.0</td>
<td>111</td>
<td>114</td>
<td>100</td>
</tr>
<tr>
<td>Vincristine</td>
<td>0.4°</td>
<td>0.4°</td>
<td>0.4°</td>
<td>0.4°</td>
<td>2.7</td>
<td>3.2</td>
<td>12.0</td>
<td>111</td>
<td>114</td>
<td>100</td>
</tr>
<tr>
<td>Vinorelbine</td>
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<td>30°</td>
<td>17°</td>
<td>24.9°</td>
<td>36.3</td>
<td>44.2°</td>
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<td>119</td>
<td>108</td>
<td>91 ± 16</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>119 ± 30</td>
<td>108 ± 26</td>
<td>91 ± 16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Proposed Dosing N = 401**

- **Initiate or intensify hemodialysis**
- **Daily hemodialysis for 4 successive days**

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Platin derivatives and kidney dysfunction

Proposal:
- Standard dose
- 2 – 12 h later Hemodialysis
- Daily for 4 days HD


Carboplatin in non-small cell lung carcinoma N = 41
Ruth Renz, Christian Schumann, Franz Maximilian Rasche
Conclusion

Dose adjustment
The optimum might be chosen
– between Dettli
– and Kunin
Based on pharmacodynamic considerations