Dose adjustments in renal failure: Does the Dettli formula need an update moving away from linearity to improve precision medicine?

Wolfgang U. Scholz, Munich

Introduction

CKD (chronical kidney disease) causes deterioration of renal function with reduction of glomerular filtration (GFR). Drugs which are mainly excreted through the kidney have reduced renal elimination (Clrenal) in CKD. For decades dosage adjustments for these drugs have been computed based on GFR and clearance measurement of biomarker serum creatinine (Clcr), respectively, and according to the rule of Dettli (1, 2, 3, 4, 5) where the appropriate dose D compared to the normal dose (Dnorm) may be assessed by the individual elimination fraction Q:

Equation 1) $\quad Q = Qo + (1 – Qo) * GFR\ ml/min\ /\ 100\ ml/min$;

Qo = extrarenal elimination fraction

Equation 2) $\quad D = Dnorm * Q$

Renal clearance based on GFR is not the only mechanism which has an impact on renal drug elimination. There is also tubular secretion.

Problem

The "intact nephron hypothesis" claims that any stage of CKD has quantitatively the same consequences for Clcr or GFR and tubular secretion (Cls). However, that has been questioned as filtration takes place at a different site in the renal system than Cls. GFR and Cls may not go parallel in CKD (5).

The quotient of Clrenal and GFR indicates, if they go parallel or not; it is called RnF (5) (renal to filtration clearance with fraction unbound (fu) neglectable at this time in this context as this constant fu is 1 or close to 1 in most cases).

Equation 3) $\quad RnF = Clrenal / fu * GFR$

There are three possibilities:

a) RnF increases across the range of decreasing GFR

b) RnF decreases across the range of decreasing GFR

c) RnF remain stable across the range of GFR

Chapron et al. (5) evaluated data for 27 drugs and found that RnF showed significant changes of RnF for 13 drugs across the range of falling GFR with RnF decreasing in 10 and increasing in 3 cases.

Regression analysis revealed the following type of equation (5):

Equation 4) $\quad RnF = a + b * GFR$

There are three cases for b:

Case a) $\quad b < 0$: GFR falls more rapidly than Cls

Consequently, Clrenal measured through GFR is too low compared with Clrenal measured based on RnF and GFR. GFR alone therefore underpredicts Clrenal and dose adjustments might lead to subtherapeutic drug plasma levels.

Case b) $\quad b > 0$: Cls falls more rapidly than GFR

Consequently, Clrenal measured through GFR is too high compared with Clrenal measured based on RnF and GFR. GFR alone therefore overpredicts Clrenal, according to Chapron et al on average by 22-48% in patients with CKD 3B (5). The error on relying on GFR measuring Clrenal of the drug is more pronounced the worse CKD and the lower GFR is. Dose adjustments based on Q as a function solely of GFR might lead to high drug plasma levels with the risk of overdosing.

Case c) $\quad b = 0$: GFR and Cls go parallel

-> Clrenal = a * GFR ; Clrenal remains subject to linear functions.

Literature: is available on request
Author and Contact:
Wolfgang U. Scholz
- Founder and Director
  DIT mondial Inc., Wilmington - New York
- CEO, ePrax GmbH, Munich
wscholz@dit-mondial.com

Computing Clrenal through second order function instead of linear function

Chapron et al. do not point out explicitly which type of function might substitute the linear relationship between Clrenal of a drug and GFR. For Clrenal, however, may be concluded equation 5) based on compiling equations 3) and 4):

Equation 5) $\quad Clrenal = RnF * GFR = (a + b * GFR) * GFR = a * GFR + b * GFR^2$

The computation of Q according to equation 1) is then modified as follows:

Equation 6) $\quad Q = Qo + (1 – Qo) * Clrenal / RnF * 100$
or
Equation 7) $Q = Qo + (1 – Qo) * (a + b * GFR) * GFR / (100 * a + 100 * 100 * b)$
or
Equation 8) $\quad Q = Qo + (1 – Qo) * (a * GFR + b * GFR^2) / (a * 100 + b * 100^2)$

Equation 8) is due to the tubular contribution to Q of second order with a graph which may show dependent on b either a concave or convex shape compared to the linear Dettli graph. For case b = 0 the Dettli function remains valid.

Theory

Chapron et al. (5) discuss three considerations one of which is very compelling for explaining the discordance of GFR and Cls and Clrenal respectively in the "b > 0 group". Renal plasma flow distributes 20% to filtration and the remaining 80% to the flow through the capillaries surrounding the tubules. Therefore they conclude that with decreasing GFR the concentration of uremic solutes in the capillary blood flow increases. These uremic solutes may compete with drugs at the tubular transporter systems (e.g. OAT, OCT, MATE2) if their tubular concentrations are elevated. In consequence the secretion of these drugs might be diminished. That would mean that GFR has both a direct and additionally an indirect impact by affecting the tubular secretion on the total Clrenal of drugs where the elimination is subject to filtration as well as to tubular secretion. Furthermore, equation 5) becomes substantially more reasonable and gains substantially more sense when backed up by such theory.

Clinical and Research Consequences

Based on the evaluation of Chapron et al. (5) there is evidence that the hypothesis of the „intact nephron" as well as the theory of the linear Dettli formula to compute dose adjustments of drugs in CKD are frequently not valid. These authors deliver the basis to question the linear relationship between Clrenal of drugs and GFR and consequently emphasize that effective dosing of secreted drugs in patients with CKD requires to include the aspect of renal tubular secretion. Based on their data Equation 8) may be deducted. Thus moving away from linearity to a second order function is possible which helps to describe the relationship between Q, Clrenal and GFR in a more appropriate and more correct manner than using the linear function of Dettli for drugs where the parameters needed beyond GFR are known. Thereby a personalized medicine may be improved and the prevention of overdosing and consecutive adverse effects may be supported, for example in the case of metformin or other drugs depending predominantly on renal elimination with tubular secretion and having a narrow therapeutic index. The clearance of metformin is assumed to be 400ml/min and higher in healthy subjects (6). Applying Equation 8 with a = 2,4 and b = 0,016, estimated values in rough accordance with RnF values of Chapron et al. (5), shows that with falling GFR in the range from 70 - 10 ml/min the individual elimination fraction Q as computed by Dettli will be too high some 10 up to 50%, see also the following graphs for GFR and metformin clearance.
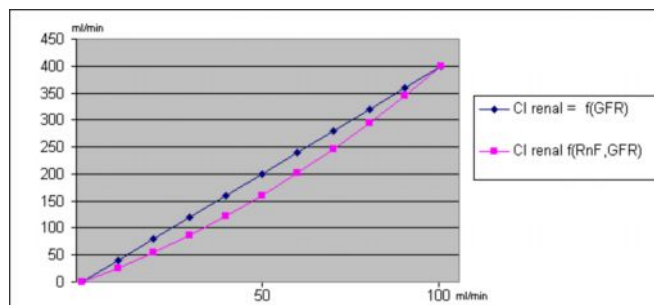
This insight is in contrast to the comprehensive representation of metformin pharmacokinetics by Graham et al (7). More research is needed to elucidate how tubular secretion and its kinetics may develop in CKD and if from such kinetic changes a link to equations 4) and 8) may be deducted and validated causing the need to update the Dettli formula as proposed.