NEPHROTOXICITE DES AMINOSIDES

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Est-il possible de prédire l'évolution d'un processus néphrotoxique au cours d'un traitement par aminoglycoside ?

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Aminoglycoside Nephrotoxicity: Modeling, Simulation, and Control

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Modèle pharmacocinétique

Deux compartiments

- $$\frac{dQ_{S(t)}}{dt} = i_{(t)} - [(K_i + K_s \cdot CCr_{(t)}) \cdot (1 - k_{reabs}) + k_{cp}] \cdot Q_{S(t)} + k_{pc} \cdot Q_{P(t)}$$
- $$\frac{dQ_{P(t)}}{dt} = k_{cp} \cdot Q_{S(t)} - k_{pc} \cdot Q_{P(t)}$$

*i(t) is the AG infusion rate ($mg.h^{-1}$) during a 30 minute infusion,
K_i is the AG non renal elimination constant (h^{-1}),
K_s is the AG renal elimination constant ($min.ml^{-1}.h^{-1}$),
$CCr_{(t)}$ is the creatinine clearance value ($ml.min^{-1}$),
k_{reabs} is the AG tubular reabsorption constant (h^{-1}),
k_{cp} is the transfer constant from the central compartment to the peripheral compartment (h^{-1}),
k_{pc} is the transfer constant from the peripheral compartment to the central compartment (h^{-1}),
$Q_{P(t)}$ is the AG amount in the peripheral compartment (mg).*

Modèle d'accumulation rénale

Michaelis Menten

- $$\frac{dQ_{C(t)}}{dt} = V_{max} \cdot \frac{Q_{S(t)}}{k_M + Q_{S(t)}} - k_1 \cdot Q_{C(t)}$$

*V_{max} is the maximal accumulation rate in the renal cortex ($mg.h^{-1}$),
$Q_{S(t)}$ (mg) is the AG serum amount (mg),
k_M is the AG serum amount for which accumulation rate is equal to $V_{max}/2$ (mg),
k_1 is the AG elimination constant from the renal cortex (h^{-1}).*

Modèle d'effet suite à l'accumulation

de Hill

- $Q_{C(t)} < Q_{min} \rightarrow$ ...
- $Q_{C(t)} > Q_{min} \rightarrow$ $E_{(t)} = \frac{E_{max} \cdot Q_{C(t)}^{\gamma}}{Q_{50}^{\gamma} + Q_{C(t)}^{\gamma}}$

*Q_{min} is the AG renal cortex amount under which no effect is observed (mg),
E_{max} is the maximal accumulation effect observed (mM),
$Q_{C(t)}$ is the AG renal cortex amount, Q_{50} is the AG renal cortex amount for which $E_{(t)}$ is equal to $E_{max}/2$ (mg),
γ is the Hill sigmoidicity coefficient (no unit).*

Modèle de filtration glomérulaire

Clairance de la créatinine estimée (Jelliffe/Jelliffe) plus

- des variations circadiennes sinusoidales
- le feedback tubulo-glomérulaire

- $$CCr_{(t)} = CCr_0 - \frac{CCr_{max} \cdot E_{(t)}^{\delta}}{E_{50}^{\delta} + E_{(t)}^{\delta}} + \eta \cdot sin\left(\frac{2\pi t}{24} - \frac{2\pi}{3}\right)$$

*CCr_0 is the creatinine clearance value at the beginning of the treatment ($ml.min^{-1}$),
CCr_{max} represents the maximal decrease of creatinine clearance ($ml.min^{-1}$),
E_{50} is the accumulation effect value (mM) for which $CCr_{(t)}$ is equal to $CCr_{max}/2$,
δ is the Hill sigmoidicity coefficient (no unit).*

Effets sur la créatinine sérique

Production musculaire (cf J & J)

Elimination rénale

$$\frac{dSCr_{(t)}}{dt} = k_2 - \frac{CCr_{(t)}}{Vol} \cdot SCr_{(t)}$$

*k_2 is the muscular creatinine production constant ($mg.h^{-1}$),
$CCr_{(t)}$ is the creatinine clearance value ($ml.min^{-1}$)
Vol is the volume of distribution of creatinine (liters).*

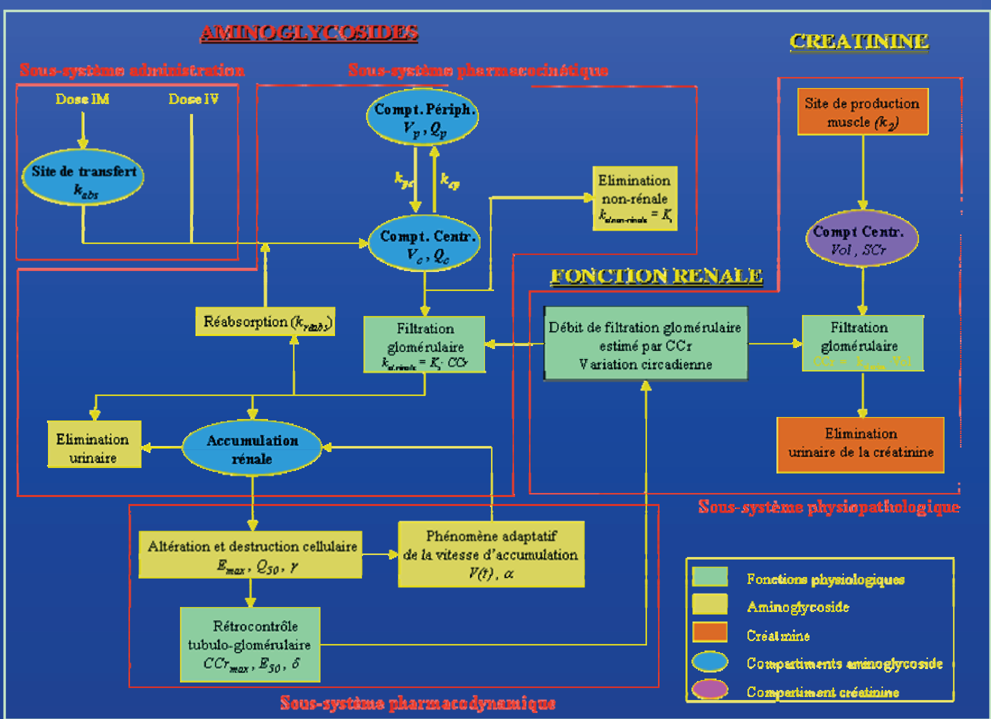
Simulations

Matlab ® - Simulink ®

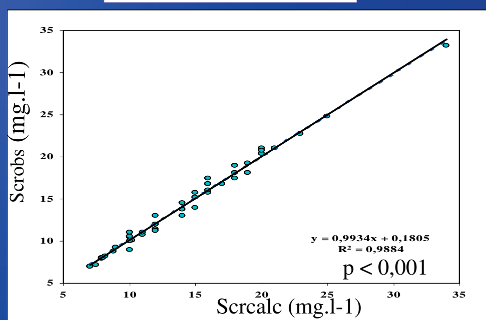
- Valeurs des paramètres

K_i (h^{-1})	K_s ($min.ml^{-1}.h^{-1}$)	V_d ($l.kg^{-1}$)	k_{cp} (h^{-1})	k_{pc} (h^{-1})	$k_{réabs}$ (%)
0.05	0.00257	0.25	0.03798	0.013	0.05

V_{max} ($mg.h^{-1}$)	k_M (mg)	k_1 (h^{-1})	Q_{min} (mg)	E_{max} (mM)	Q_{50} (mg)	γ (no unit)	CCr_{max} ($ml.min^{-1}$)	E_{50} (mM)	δ (no unit)	η ($ml.min^{-1}$)	k2 ($mg.h^{-1}$)	Vol (liters)
1	15	0.06	10	100	50	2.5	20	33.5	6	10	60	5



Pour les 8 patients :



Pour un patient :