A framework for quantifying the influence of adherence and dose individualisation

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Adherence

• Adherence is of importance for both noncommunicable diseases and infectious diseases to achieve therapeutic success
• Adherence to cardiovascular treatment in low- and middle-income countries is similar to that observed in high-income countries
• It has been shown that within one year almost 50% of patients with hypertension stopped taking their medications
The concept of forgiveness

• Forgiveness is the property of a drug that signifies the likelihood of therapeutic success with imperfect adherence

\[ F = D - I \]

\( F \) is forgiveness
\( D \) is duration of effect
\( I \) is dose interval

• When the duration of effect exceeds the dose interval then the drug is considered forgiving

Relative forgiveness

- Relative forgiveness (RF) accounts for both variability in PKPD parameters and adherence behaviour

\[ RF = \frac{P_{ip}/(1 - P_{ip})}{P_p/(1 - P_p)} \]

$RF$ is relative forgiveness

$P_{ip}$ is the probability of therapeutic success with imperfect adherence

$P_p$ is the probability of therapeutic success with perfect adherence

- Values close to one indicate that the drug is forgiving with imperfect adherence

Assawasuwannakit et al, CPT Pharmacometrics Syst Pharmacol 2015; 4: 204-11
A priori and a posteriori forgiveness

Before dose individualisation

\[ \frac{P_{ip}/(1 - P_{ip})}{P_{p}/(1 - P_{p})} \times P_{prior} \]

• \( P_{prior} \) is the probability of therapeutic success before dose individualisation

• \( P_{prior} = P_p \)

After dose individualisation

\[ \frac{P_{ip}/(1 - P_{ip})}{P_{p}/(1 - P_{p})} \times P_{post} \]

• \( P_{post} \) is the probability of therapeutic success after dose individualisation

• \( P_{post} \geq P_{prior} \)

Aim

- To illustrate *a priori* and *a posteriori* forgiveness of drugs
  - adherence is of primary importance
  - dose individualisation is of primary importance

**Atorvastatin**
- Cholesterol reduction
- LDL monitoring

**Omeprazole**
- Heart burn
- Patient feedback
Atorvastatin PKPD model

- Three dose levels considered were 10 mg/day, 40 mg/day, and 80 mg/day
- $P_{post} = 0.72^*$ based on LDL monitoring
- The model was adapted from Narwal et al. and Kim et al.


Figure adapted from Narwal et al, Clin Pharmacokinet 2010; 49: 693-702; Kim et al, Basic Clin Pharmacol Toxicol 2011; 109: 156-63
Omeprazole PKPD model

- Three dose levels considered were 10 mg/day, 20 mg/day, and 40 mg/day.
- $P_{post} = 1$ is defined here since it is not practical to monitor pH in clinical routine, and it is expected that negative reinforcement would act as a tool for dose individualisation.
- The model was adapted from Puchalski et al.

Figure adapted from Puchalski et al, J Clin Pharmacol 2001; 41: 251-81
Simulations: imperfect adherence

2 drugs → 3 dose levels → 10 levels of missing doses

1, 10, 20, 30, 40, 50, 60, 70, 80, and 89 missing doses of 90
Simulations: imperfect adherence

2 drugs

3 dose levels

10 levels of missing doses

1, 10, 20, 30, 40, 50, 60, 70, 80, and 89 missing doses of 90

60 scenarios
Simulations: imperfect adherence

2 drugs

3 dose levels

10 levels of missing doses

1, 10, 20, 30, 40, 50, 60, 70, 80, and 89 missing doses of 90

5000 patients × 60 scenarios
Simulations: perfect adherence

2 drugs

3 dose levels

Perfect adherence

90 doses were taken

5000 patients ×
Determining successful profiles

- Successful profiles: at least 60% of steady state trough LDL concentrations or pH values has to meet the therapeutic criterion ($S_i = 0$ or $1$)
- Therapeutic criteria:
  - atorvastatin: an LDL lower than 2.6 mmol/L
  - omeprazole: a pH higher than 4
- $P_{ip} = \frac{1}{5000} \sum S_i$, with imperfect adherence
- $P_p = \frac{1}{5000} \sum S_i$, with perfect adherence
**A priori and a posteriori forgiveness**

Before dose individualisation

\[ \frac{P_{ip} / (1 - P_{ip})}{P_{p} / (1 - P_{p})} \times P_{prior} \]

- \( P_{prior} \) is the probability of therapeutic success **before** dose individualisation
- \( P_{prior} = P_{p} \)

After dose individualisation

\[ \frac{P_{ip} / (1 - P_{ip})}{P_{p} / (1 - P_{p})} \times P_{post} \]

- \( P_{post} \) is the probability of therapeutic success **after** dose individualisation
- \( P_{post} \geq P_{prior} \)

A priori and a posteriori forgiveness

atorvastatin 40 mg

omeprazole 20 mg
Discussion

**Atorvastatin**
- A disease modifying drug (a silent factor)
- Dose individualisation provides a higher probability of therapeutic success irrespective of the underlying adherence

**Omeprazole**
- A symptomatic relief drug (a non-silent factor)
- Dose individualisation predominates at low levels of missed doses
- Adherence is the primary factor of interest for those who are poorly adherent
Conclusions

• The concept of *a priori* forgiveness and *a posteriori* forgiveness provides a quantitative measure that allows the influence of adherence to be disentangled from dose individualisation

• This could be used to provide clear guidelines about the relative importance of each in clinical practice
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