A critical review of PK / TD in preventing toxicity

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Cellular and Molecular Pharmacology, Catholic University of Louvain, Brussels, Belgium

8th ISAP Symposium
Developments in Pharmacokinetics and Pharmacodynamics: optimizing efficacy and prevention of resistance
Nijmegen, The Netherlands, July 4th-6th, 2001
A critical review of PK / TD in preventing toxicity

Or, how can we reach efficacy...

without (too much) risk ...
A critical review of PK / TD in preventing toxicity

Or, from the lab ... to the patient...
What is research all about?

- Basic
- Applied
- Clinical

Trying to arrive safely
Antibiotic treatments: What does the clinician want?

“The” drug

Best therapeutic effects

No toxic effect
What did the textbooks say about antibiotic dosages and schedules in the 70’s?

1. Stay above the MIC... \(\text{but how much?}\)

2. Remain around for a while... \(\text{but how long?}\)

3. Hope it works... \(\text{against everything?}\)

4. Hope it is not toxic... \(\text{Sorry, but I can’t do much...}\)
What are we going to discuss?

1. aminoglycosides … (29 slides)
2. macrolides … (5 slides)
3. Fluoroquinolones (3 slides)
4. β-lactams … (8 slides)
5. thanking people… (a lot of slides)
Aminoglycosides in the 70’s ...

- Potent antimicrobials but toxic
  - nephrotoxicity (reversible)
  - ototoxicity (irreversible)

- All very similar biophysical, chemical, microbiological and pharmacokinetic properties, but...
  - variable dosage (3 to 15 mg/kg)
  - variable schedules (1 - 2 - 3 x/day … or even continuous infusion, …

- “necessity” to monitor, but how ??
Aminoglycosides monitoring in the 70’s ...

avoid high peaks
... to reduce toxicity

get sufficiently high trough levels
... to get efficacy

Very small range, isn’t it?

toxicity !!
lack of efficacy
Aminoglycosides toxicity in the 70’s - 80’s ...

Patients with nephrotoxic reaction after treatment with gentamicin

- young volunteers  
  Smith et al, 1982
- random hospital populat.  
  Smith et al., 1980
- critically-ill patients  
  Plaut et al., 1979

All those patients were under close monitoring ...
Aminoglycoside toxicity is not linked to peak ...
What is the (likely) mechanism of aminoglycoside nephrotoxicity?...

AMINOGLYCOSIDE NEPHROTOXICITY CASCADE

1. Drug
2. Accumulation in lysosomes
3. Phospholipidosis
4. Necrosis of tubular cells

and apoptosis

From: Tulkens, 1986 Amer. J Med. 80(Suppl 6B);105-114
Aminoglycoside entry in proximal tubular cells is via brush border binding ...

binding to
- megalin  
  (Moeströp et al., 1995)
- acidic phospholipids  
  (Humes et al, 1983)

  Silverblatt & Kuehen, Kidney Intern., 1979
Aminoglycoside accumulation in the kidney is saturable at clinically meaningful concentrations.* ... 

* Giuliano et al., J. Pharm. Exp. Ther., 1986

This is where patients are in a q8h schedule!!
The once-a-day schedule gives less drug accumulation and less renal alterations in rats.* ...
Shall you now go to humans?
Aminoglycoside once-a-day: the philosophy of one of the first PK / TD clinical trials (1985 ...)

- choose an adapted drug (least toxic)
- patients with low risk
- who need treatment
- do not depart from clinical standards if not part of the hypothesis to test

- “primum non nocere”

- test your hypothesis as correctly as possible
- use surrogate toxicity markers if available and relevant

- netimicin (study #1)
- amikacin (study #2)
- 2 x 40 young patients
- women suffering from PID
- conventional daily doses (N: 6mg/kg; A: 15 mg/kg)
- conventional treatment duration (7 days)
- combine with ampicillin and tinidazole
- randomized
- blinded to evaluators
- phospholipiduria
- high tone audiometry

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phospholipiduria

high tone audiometry
Phospholipiduria can be a surrogate marker of aminoglycoside-induced renal alterations

- St Luc Clinic
- gynaecology
- aminoglycoside plus other drugs

- Bordet Institute
- cancer
- aminoglycoside only
## Pharmacokinetic results (day 7)...

<table>
<thead>
<tr>
<th></th>
<th>amikacin ¹</th>
<th>netilmicin ²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>q24h</td>
<td>q12h</td>
</tr>
<tr>
<td>Vd (l/kg)</td>
<td>0.22 ± 0.04</td>
<td>0.24 ± 0.04</td>
</tr>
<tr>
<td>t ¹/₂ (h)</td>
<td>1.52 ± 0.15</td>
<td>1.54 ± 0.23</td>
</tr>
<tr>
<td>AUC(mg*h/L)</td>
<td>119 ± 17</td>
<td>109 ± 18</td>
</tr>
<tr>
<td>peak (ml/L)</td>
<td>55.3 ± 8.8</td>
<td>25.5 ± 1.9***</td>
</tr>
</tbody>
</table>

* p < 0.05  ** p < 0.01  *** p < 0.001

¹ daily dose = 15 mg/kg (1 x 15 mg/kg vs 2 x 7.5 mg/kg per 24h)
² daily dose = 6.6 mg/kg (1 x 6.6 mg/kg vs 2 x 3.3 mg/kg per 24h)
Phospholipiduria (1)

URINARY EXCRETION OF TOTAL PHOSPHOLIPIDS

nmol/g creatinine (Thousands)

- Netilmicin TID
- Netilmicin qD
- Amikacin BID
- Amikacin qD

N q8h
A q24h
Phospholipiduria (2)

URINARY EXCRETION OF PHOSPHATIDYLINOSITOL

nmol/g creatinine (Thousands)

- Netilmicin TID
- Netilmicin qD
- Amikacin BID
- Amikacin qD

N q8h
A q24h
Phospholipiduria: statistical comment ...

- There is a highly significant difference between the two medications (A < N)
- For each variable, there is a highly significant time effect
- The interaction between medication and time is highly significant. The effect of time, however, is not the same for the two medications (N > A)
- The increase, when it occurs, is always faster for the multiple doses schedule (q8h / q12h) than for the once-a-day (q24h) groups

Nephrotoxicity will not be suppressed but delayed ... which is what has been found in most subsequent clinical trials
**Auditory alterations**

no. of patients [over 20 in each group] with lesions* and total no. of frequencies affected

<table>
<thead>
<tr>
<th></th>
<th>low tone (0.25-8 kHz)</th>
<th>high tone (10-18 kHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>amikacin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>q24h</td>
<td>1 (1)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>q12h</td>
<td>0</td>
<td>6 (6)</td>
</tr>
<tr>
<td><strong>netilmicin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>q24h</td>
<td>0</td>
<td>3 (7)</td>
</tr>
<tr>
<td>q8h</td>
<td>2 (3)</td>
<td>8 (9)</td>
</tr>
</tbody>
</table>

* loss of 15dB or more over baseline (max. loss recorded: 30 dB)

this is where most of the toxicity is ...
General conclusions of the first clinical trials ... *

**amikacin** vs **netilmicin**

<table>
<thead>
<tr>
<th></th>
<th>q24h</th>
<th>q12h</th>
<th>q24h</th>
<th>q8h</th>
</tr>
</thead>
<tbody>
<tr>
<td>efficacy</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td></td>
</tr>
<tr>
<td>renal alterations¹</td>
<td>&lt;</td>
<td>&lt;&lt;*</td>
<td>&lt;</td>
<td></td>
</tr>
<tr>
<td>auditory alterations²</td>
<td>=</td>
<td>=</td>
<td>&lt;&lt;*</td>
<td></td>
</tr>
</tbody>
</table>

* highly significant by repeated variance analysis

¹ phospholipiduria
² high tone (10-18 kHz audiometry)

Isn’t that what you want?

- Van der Auwera et al. Pharmacodynamic parameters and toxicity of netilmicin (6 mg/kg.day) given once daily or in three divided doses to cancer patients with urinary tract infection. Antimicrob Agents Chemother (1991) 35:640-647

8th ISAP symposium  July 5th, 2001
But, will once-a-day be effective?

Aminoglycosides are concentration-dependent drugs...
Aminoglycoside peak / MIC ratio is predictive of clinical efficacy

Relationship between the maximal peak level / MIC ratio and the rate of clinical response. Vertical bars represent SE values.
How are you going to show that patients will benefit of receiving aminoglycosides once-a-day?

- Proof of concept
  - moderately sick patients
  - success
  - selected severe situations
  - success
  - enlarged population
- Setting the limits
- How large can the benefit be?
- Internal Medicine
- neutropenic patients
  - intensive care
  - neonates
  - nosocomial pneumonia,
  - ...

8th ISAP symposium July 5th, 2001
The worldwide progress of the once-a-day made by clinicians ...

- 1989 - 1993: 14 comparative studies in all major indications showing $\geq$ or $> \text{efficacy}$ and $\leq$ or $< \text{toxicity}$
  - one mini-review in AAC (Gilbert, 1991)
  - one ICAAC symposium
  - FDA petition
  - one re-registration (netilmicin)

- 1993 - 1999: 245 studies ($\geq \text{eff. } ; \leq \text{tox}$) in almost every indication
  - 8 meta-analyses supporting the once-a-day
  - several editorials *
  - inclusion in textbooks **
  - isepamicin is developed and registered once-a-day

* Gilbert, CID, 1997: “there is no need of further studies…”
** In Mandell & assoc. (aminoglycoside chapter) as from 1995
Aminoglycosides in the last 2 years

- Is the once-a-day schedule used?
- Is it good for all indications?
- Do we understand AG toxicity?
- Can we better prevent AG toxicity?
- Other toxicities ...
- Do we still need aminoglycosides?
Is the once-a-day schedule used?


National survey of extended-interval aminoglycoside dosing (EIAD).
Chuck SK, Raber SR, Rodvold KA, Areff D.

- 500 acute care hospitals in the United States
- EIAD adopted in 3 of every 4 acute care hospitals
  - 4-fold increase since 1993
  - written guidelines for EIAD in 64% of all hospitals
- rationale
  - 87.1% : equal or less toxicity (),
  - 76.9% : equal efficacy
  - 65.6% : cost-savings
- dose: > 5 mg/Kg
- 47% used extended interval in case of decline in renal function (38% with Hartford nomogram)
Is the once-a-day schedule good for all indications?

Indications for which questions are still often raised:

- febrile neutropenia (what is the organism ?)
- cystic fibrosis (abnormal $V_d$ and $Cl$)
- endocarditis (synergy)
- “special situations” (like peritoneal dialysis)
- …
Once-a-day schedule in febrile neutropenia ...


Once-daily versus multiple-daily gentamicin in empirical antibiotherapy of febrile neutropenia following intensive chemotherapy.

Bakri FE, Pallett A, Smith AG, Duncombe AS.

- Gentamicin (7mg/kg per day qD vs multiple doses) + azlocillin
- 52 episodes of febrile neutropenia in 28 patients (80.2 % with undocumented cause...)
- response rate 3 x higher in the qD group (p = 0.012)
- NS increase in toxicity

In this clinical context once-daily gentamicin is more effective than a multiple-daily dosing regimen but may be more toxic...
Once-a-day schedule in cystic fibrosis ...

Once daily versus multiple daily dosing with intravenous aminoglycosides for cystic fibrosis (Cochrane Review).
Tan K, Bunn H.

- Two trials (n=70 patients) qD vs tid
- data on Forced Expiratory Volume at one second (FEV1), Forced Vital Capacity (FVC), nutritional status and side effects
- no significant difference in efficacy or in the incidence of ototoxicity and nephrotoxicity

There is a need for an adequately-powered, multicentre, randomised controlled trial assessing qD vs md dosing of AG in cystic fibrosis.
Once-a-day schedule in endocarditis ...

Pharmacotherapy 2000 Sep;20(9):1116-9
Tam VH, Mckinnon PS, Levine DP, Brandel SM, Rybak MJ.

- To date, no case reports or clinical trials have examined its utility in human enterococcal endocarditis.
- A patient with right-sided endocarditis caused by Enterococcus faecalis was successfully treated by once-daily gentamicin.
- Clinical and bacteriologic cures of this patient raise questions as to whether enterococcal endocarditis should still be regarded as contraindication to ODA.

The clinical utility of ODA in this disease deserves further investigation.
Once-a-day schedule in peritoneal dialysis ...

Adv Perit Dial 2000;16:280-4

Use of bolus intraperitoneal aminoglycosides for treating peritonitis in end-stage renal disease patients receiving continuous ambulatory peritoneal dialysis and continuous cycling peritoneal dialysis.
Mars RL, Moles K, Pope K, Hargrove P.

- 6 patients -- 5 mg/kg tobramycin -- 6 continuous nightly cycles with daytime dwell
- $t_{1/2} = 29.3 \pm 3.5$ h
  (therapeutic blood levels persisted for 72-96 hours)
- no change in audiograms at 17 days
- no clinical oto/vestibular toxicity,
- cost-effective,
- convenient strategy for patients and nursing staff.
Do we understand aminoglycoside nephro- and oto-toxicity and its relation to dosage?

- **apoptosis ...**
  - is this the cause of the toxicity at clinical doses?
- **impairment of Mrp2 et PgP efflux systems**
  - does the cell get indirectly intoxicated?
- **interaction with NMDA receptor**
  - can we dissociate activity and toxicity?
Mimicking human clinical dose in animals

TABLE 1. Experimental groups, conditions of treatments, and relevance to the clinical use of aminoglycosides

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/kg)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Duration (days)</th>
<th>Fold increase over:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clinical dose&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>10</td>
<td>4–10</td>
<td>~2</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>4–10</td>
<td>~4</td>
</tr>
<tr>
<td>Netilmicin</td>
<td>10</td>
<td>4–10</td>
<td>~1.7</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>4–10</td>
<td>~3.3</td>
</tr>
<tr>
<td>Amikacin</td>
<td>40</td>
<td>10</td>
<td>~2.7</td>
</tr>
<tr>
<td>Isepamicin</td>
<td>40</td>
<td>10</td>
<td>~2.7</td>
</tr>
</tbody>
</table>

<sup>a</sup> Twice-a-day schedule (daily dose split into two administrations at 12-h intervals). This schedule (or even a three-times-a-day schedule) was long considered mandatory for aminoglycosides but is known to increase toxicities at both low and high doses in animals (38, 52). Data for patients are less definite, even though a trend toward less toxicity is commonly observed with a once-a-day schedule (21, 48).

<sup>b</sup> Suggested maintenance doses for an adult patient with an estimated creatinine clearance of 90 ml/min (20) (gentamicin, 5.1; netilmicin, 6; and amikacin, 15 mg/kg, respectively) or based on the registered dosage in Belgium and many other countries for isepamicin.

<sup>c</sup> Based on estimated ratio of areas under the serum concentration-time curve, AUC ratio, using the dose ratio defined in footnote b and assuming apparent half-lives of ~30 min in rats and ~120 min in humans (β-elimination phases).
Evidence of apoptosis in proximal tubular cells: TUNEL staining

gentamicin 10 mg/kg, 10 days

El Mouedden et al., 2000
The severity of AG-induced regeneration (top) and apoptosis (bottom) at “clinical doses” varies among derivatives ...

DNA specific radioactivity

TUNEL (+) nuclei (no./sq mm)

El Mouedden et al., 2000

ct = control
gm = gentamicin (10mg)
nt = netilmicin (10 mg)
is = isepamicin (40 mg)
am = amikacin (40 mg)
Aminoglycosides inhibit Mrp2 and P-glycoprotein-mediated fluorescein-labelled methotrexate transport in killifish proximal tubular cells

controls

amikacin
50 μM or ~ 25 mg/L

gentamicin
10 μM or ~ 5 mg/L

Most frequent antibiotic-pumps in eucaryotes (1/2)

**Multiple Drug Resistance** (MDR also known as PgP)

### TOPOLOGY

### MECHANISM

### ANTIBIOTICS

- tetracyclines
- fluoroquinolones
- erythromycin
- lincosamides
- rifampicin
- chloramphenicol
- aminoglycosides

Van Bambereke et al., Biochem. Pharmacol. 2000
Most frequent antibiotic-pumps in eucaryotes (2/2)

Multidrug Resistance Proteins (Mrp1 - Mrp2)

**TOPOLOGY**

**MECHANISM**

**ANTIBIOTICS**

- fluoroquinolones
- β-lactams
- tetracyclines
- macrolides

Van Bambke et al., Biochem. Pharmacol. 2000
Mrp2 is inactivated by nephrotoxins through Ca\(^{2+}\)-induced endothelin release and PKC activation ...
Polyamines → Activation of the NMDA receptor → cochleotoxicity

AG and NMDA receptor ...

<table>
<thead>
<tr>
<th></th>
<th>EC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>MIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-ethyl-apramycin</td>
<td>3.2*</td>
<td>32</td>
</tr>
<tr>
<td>apramycin</td>
<td>3.9</td>
<td>4</td>
</tr>
<tr>
<td>cyclocarbonyl-apramycin</td>
<td>19</td>
<td>8</td>
</tr>
</tbody>
</table>

Activation of the NMDA receptor by apramycin (■) and phthalimidoapramycin (●). Scott et al., Eur. J. Pharmacol. 387:1-7, 2000

* ~ 2 mg/L
azithromycin (10 mg/L) causes a phospholipidosis in cultured fibroblasts within 2-3 days


... because it interacts with phospholipids
Phospholipidosis induced by macrolides…
Implication for drug early evaluation?

Long-term (7 days culture) exposure
to low doses (0.03 to 10 mg/l) of azithromycin…

Morphology at 0.1 mg/ml:

Biochemistry:

- Cathepsin B activity $>$ 1 mg/l
- Phospholipid content $>$ 5 mg/l
- Cholesterol content $>$ 10 mg/l

Van Bambeke et al, JAC, 1998
Phospholipidosis induced by macrolides…
Implication for drug early evaluation?

\[
\frac{C_c}{C_e} \approx 100
\]

\[
\frac{C_c}{C_e} \approx 1000
\]

Increase in phospholipid cellular content

Van Bambeke et al., 1998
Toxicodynamic models for the discovery of cellular alterations induced by macrolides

Long-term therapy with azithromycin ...

lymphocyte of a patient treated with azithromycin 1200 mg once-a-week during several weeks

Y. Van Laeyhem & F. Van Bambeke, unpublished
Toxicodynamic models for the discovery of cellular alterations induced by macrolides

Unsuspected effects …

Accumulation of cholesterol… (filippin staining)

Impairment of endocytosis… (horseradish peroxidase uptake)

… in relation with azithromycin accumulation

The fluoroquinolones in 3 slides ... or evidencing efflux

non linear accumulation kinetics ...

receptor mediated uptake

diffusion

facilitated uptake

Ce
Cc
Evidencing active efflux ...

accumulation à low concentration

uptake is defeated by active efflux
Evidencing active efflux ...

accumulation at large concentrations ...

facilitated uptake

saturation of efflux!
Active efflux of ciprofloxacin

Ciprofloxacin accumulation is facilitated upon increase of its extracellular concentration

extracellular [ciprofloxacin] - 2h incubation at 37°C

Michot et al., ICAAC 2000
Now, the $\beta$-lactam antibiotics:

- time-dependent antibiotics
- little or no influence of the concentration once above a threshold ($4 \times$ the MIC for most organisms)

Influence of drug concentration on listericidal activity *in vitro*

Percent of $C_{\text{max}}$ reachable in serum in humans

Why wouldn’t you try a continuous infusion?

A high peak is unnecessary...

S. Carryn, SBIMC/BVIKM, 2000

8th ISAP symposium July 5th, 2001
Continuous infusion of ceftazidime in ICU (3 g/day)

<table>
<thead>
<tr>
<th></th>
<th>Intermittent (n=17)</th>
<th>Continuous (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C max (mg/ml)</td>
<td>106.5 (34.6)</td>
<td>18.2 (6.5)</td>
</tr>
<tr>
<td>C min (mg/ml)</td>
<td>10.3 (16.0)</td>
<td>16.5 (5.7)</td>
</tr>
<tr>
<td>C mean (mg/ml)</td>
<td>3.2 (2.5)</td>
<td>17.4 (6.1)</td>
</tr>
<tr>
<td>$T_{1/2}$ (h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC 0-24h</td>
<td>777.4 (474.6)</td>
<td>419.7 (141.5)</td>
</tr>
<tr>
<td>Cl (ml/min)</td>
<td>142.5 (58.7)</td>
<td>133.2 (37.0)</td>
</tr>
</tbody>
</table>

PK / PD in action …
continuous infusion of β-lactams:
the case of ceftazidime (4g / day) in Intensive Care Units

\[ C_{ss} = \frac{K_o}{Cl} \]

serum concentration

Clearance *

Infusion rate

27 [µg/ml] = \( \left\{ \frac{2.77 [mg/min]}{102 [ml/min]} \right\} \times 10^3 \)

Targeted level for MIC’s up to 6-8 mg/L …
PK / PD in action …
continuous infusion of β-lactams:
the case of ceftazidime (4g / day) in Intensive Care Units

mean : 26.6 ± 15.0 (n = 93; min = 7.6; max = 62.4)

Servais, Laterre & Tulkens, unpublished
But is it safe?
Ceftazidime stability studies ... 25°C

Ceftazidime stability at 25°C

Range of tolerance

Servais & Tulkens, AAC, in press
But is it safe?
Ceftazidime stability studies ... 37°C ...

Ceftazidime stability at 37°C

Legend:
- ⬤ 4%
- ■ 6%
- ▲ 8%
- ○ 10%
- □ 12%

Range of tolerance

Servais & Tulkens, AAC, in press
Degradation products of ceftazidime

Servais & Tulkens, 11th ECCMID, 2001
Degradation pathways of ceftazidime (24h in aqueous media)

\[
\text{[(2–amino–4-thiazolyl) (1–carboxy–1–methyletoxy) imino] acetyl–ethanal.}
\]

* < 50 mg from an amount of 4 g in 24h at temp < 25°C

Servais & Tulkens, AAC, in press
Pharmacodynamics ...

It’s a brilliant idea....

But don’t forget toxicity...
Toxicodynamics ...

There is still MUCH work...

Novel antibiotics

Intracellular infections

Efflux modulators
- in bacteria
- in eucaryotes
Thanking people … *

Research is a lonely exercise but its true value is directly related to the collaborative activities it leads to...
Aminoglycosides...

Starting very basically in the early 80’s...

G. Laurent
M.B. Carlier
R. Brasseur
J.M. Ruysschaert
Aminoglycosides...
The once-a-day story...

In the late 80’s...

S. Ibrahim
P. Maldague
L. Giurgea
F. Renoird
M.C. Cambier
G. Laurent
D. Beauchamp

and

F. Clerckx-Braun * (FATC)
J. Donnez (St Luc)
M.P. Mingeot *
P. Lambricht
R. Wagner
B. Rollmann (CHAM)
P. Herman (SP-Belg.)
M.E. De Broe (UZ-UIA)
G. Verpooten (UZ-UIA)
A. Giuliano (UZ-UIA)
B. Kaufman (VUB)
B. Derde * (VUB)
The β-lactams, the macrolides, the fluoroquinolones, etc...

C. Renard
M. Leto *
C. Bruno
F. Van Bambeke *
S. Burton
C. Dupriez
J.M. Michot *
H. Chanteux *
Y. Ouadrhiri
H. Servais *
S. Carryn *
E. Viaene

I. Dab (UZ-VUB)
B. Byl (ULB-Erasme)
P.F. Laterre (St-Luc)

...
But ISAP made it all possible … when we were still youngs and serious...

- Population pharmacokinetics
- Tissue concentrations
- Efficacy/toxicity ratios
- Postantibiotic effect...
- Intracellular pharmacodynamics and toxicity

* AUIC
And also when as young but less serious...

toxicity isn’t that bad...

http://www.isap.org
And now, en route to the future ...

To a bright future...