Odnos originala i generike i međusobna zamenljivost generičkih lekova / The relation between original and generic medicines and mutual interchangeability of generic medicines

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Definition of generic drugs

• “products which have the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.”

Conditions for marketing authorization of generic drugs

• Bioequivalence study on 12-24 healthy adult males showing that **90% - confidence intervals of ratios** between area under the plasma concentration/time curve (AUC), maximal plasma concentration and time to maximal plasma concentration of generic and original drug after their administration by the same route are somewhere between 80 and 125%.

• More stringent conditions for **drugs with “narrow therapeutic index”** or narrow therapeutic window whose 90% - confidence intervals of AUC ratios with original drugs should fall within much narrower limits – between 90 and 111.11%
Key parameters

- **Drug concentration (mg/l)**
- **Cmax**
- **Cmax/2**
- **Ke = 0.693/T_{1/2}**
- **Tmax**
- **Area under the curve (AUC)**
- **Time (hours)**

**Key parameters**

- **Време (часови)**
- Површина испод криће (ПИК)
- Drug concentration (mg/l)
- Концентрација лека (мг/л)
Problems with bioequivalence concept

- bioequivalence studies are performed in standardized conditions, in healthy volunteers and while they are fasting.
- brand-name and generic drugs could be bioequivalent under fasting conditions, but not after a meal (e.g. case of nifedipine before and after a high-fat meal);
- bioavailability of a drug might not be the same in healthy young males and elderly patients with much co-morbidity

Definition of a “narrow therapeutic index” drug

- the ratio between its least toxic and the least effective concentration is less than two-fold

List of narrow therapeutic index drugs – not yet official

- Anticonvulsants
- Antiarrythmics (quinidine, procainamide, disopyramide, and amiodarone)
- Oral anticoagulants (warfarin in the first place)
- Lithium
- Cardiotonic glycosides
- Theophylline
- Cyclosporine
Comparison of efficacy and safety of original and generic drugs

- Even in the case of narrow therapeutic index drugs efficacy and safety are not significantly different
Problem of “switching”

- Switching from original to generic drug or from one to another generic during an ongoing therapy is frequently accompanied with loss of a disease control
Examples of unfavorable consequences of “switching”

• A study on 975 switched from original to generic warfarin showed decrease of INR for 4.2% and increase in warfarin dose for 26.5%.

• A study on 32 patients showed that switching from original to generic amiodarone was followed by recurrence of arrhythmias. Three patients died.
Examples of unfavorable consequences of “switching”

- the patients who change an anti-convulsant use higher doses and either more frequently visit their doctors or are more often hospitalized
  
  
Examples of unfavorable consequences of “switching”

- The case/control study on 9110 patients who switched from original to a generic anti-convulsant has shown that the switching was associated with increased risk of a seizure-related event (adjusted odds ratio 1.27)
  

- There is higher risk of an epilepsy-related event among patients who switched from original to generic anti-convulsant in comparison to those who did not (odds ratio 1.57).
  
Need to change bioequivalence studies

- bioequivalent anti-convulsants show significant differences in pharmacokinetic parameters which are not routinely used for bioequivalence testing

“Scaled-average bioequivalence testing”

- Even with different lots of the same brand-name anticonvulsant some individuals show high variability of plasma concentrations;
- At first intra-individual variability of study subjects in regard to bioavailability of the reference drug should be established, and then it should be shown that intra-individual variability with the generic product will not go out of these limits.
- With this approach the bioequivalence studies are carried out in three periods on the same subjects (the reference product is administered twice, and the test product once), and the bioequivalence criteria are then scaled to observed variability of the reference product.

Proposal for new design of bioequivalence studies

• Multiple point measurements during the steady-state and estimates of time spent in the therapeutic range are necessary, since only with such data we could make reliable reconstruction of plasma concentration course during the dose interval and estimate true degree of the effect.

Recommendation for the time being

- If a physician and his/her patient decide to use a generic drug as more affordable treatment option, they should do this from the beginning, choosing drug whose presence on the market is stable.
- Switching from brand-name to generic drug or from one to another generic product should be avoided.
- However, if switching is inevitable, it should be done with due care and precautions, in order to minimize possibility of injuries or other adverse consequences of temporary loss of a disease control.