

The issue of therapeutic equivalence of generic drugs when purchasing drugs

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Conflict of interest

Conflict of interest: nothing to disclose

Introduction

- Similarities between generics
 - What are generics
 - Bioequivalence
 - Scientific research
- Unsimilarities between generics
 - Project
 - Checklist

Generic drugs

Advantage of registration as a generic

- Refer to dossier from reference product
- No clinical tests or clinical trials

FDA: 7.800 generics of total of 10.700
approved pharmaceuticals (73%)

Generic drugs

In comparison to reference product

- Same qualitative and quantitative composition
- Same pharmaceutical form
- Bioequivalence has been demonstrated by bioavailability studies

Bioequivalence

Bioequivalence:

- Pharmaceutically equivalent or pharmaceutical alternatives
- Bioavailabilities (rate and extent) lie within acceptable predefined limits

Bioequivalence

Parameters to be analysed:

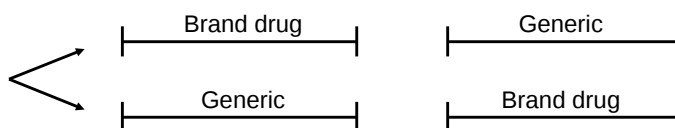
- AUC
- Cmax (when relevant)

Acceptance interval: 90% CI in 80 – 125%

Bioequivalence

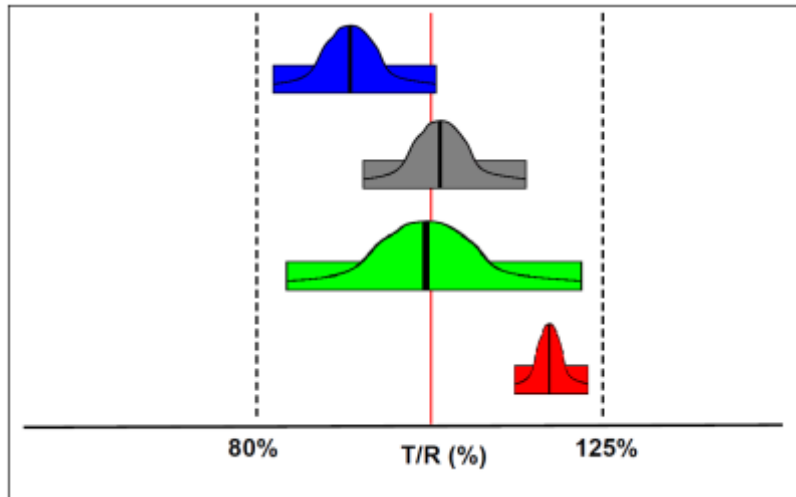
Recommended study design

- Randomised two-period, two-sequence single dose crossover
- Healthy volunteers



In vitro dissolution test

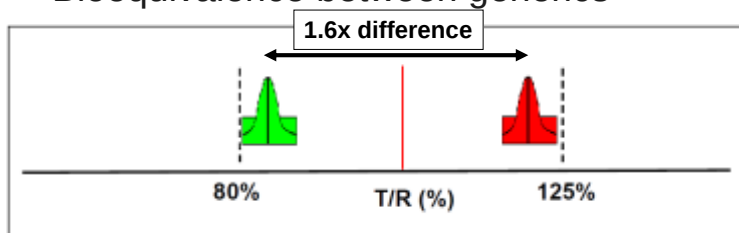
Bioequivalence



Bioequivalence

Limitations:

- Healthy volunteers
- Not right measure for some forms
 - Budesonide, mesalazine, inhalation
- Bioequivalence between generics



Narrow Therapeutic Index Drugs

- Acceptance interval (AUC and Cmax):
90% CI in 90 – 111%

Narrow Therapeutic Index Drugs

- EMEA: must be decided case by case
- Canada: Cyclosporine, Digoxin, Flecainide, Lithium, Phenytoin, ...
- FDA: no formal list: Major drug classes
antiepileptics, antiarrhythmics,
immunosuppressives, anticoagulants,
others...

Biosimilars

SAHZ

Highlights of the equivalence of biosimilars

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ISO 9001

Scientific Research

Taber et al.

- Renal transplant patients
- Cyclosporine: Gengraf versus Neoral
- Neoral: jan 1999 – May 2001
- Gengraf: May 2001 – July 2002
- 88 versus 100 patient

Taber et al. Transplantation. 2005; 80:1633–5.

- No differences in 12h CyA concentrations
- More interpatient variability
- 2 fold higher risk of rejection (95% CI 1,26 – 4,9; p=0.008)

Limitations

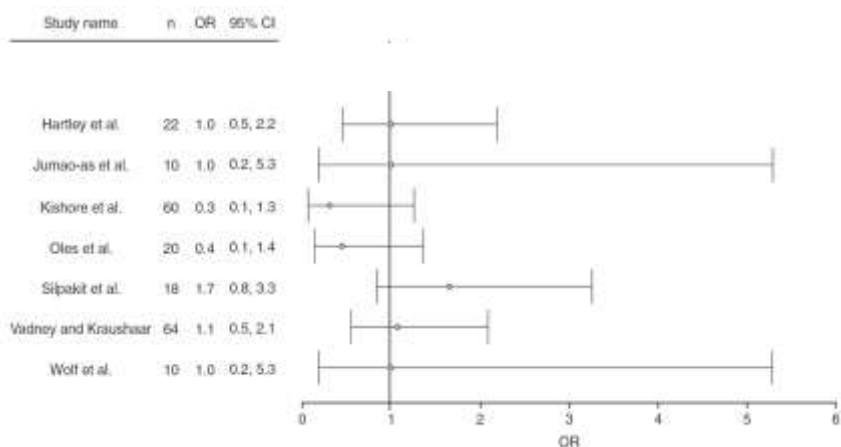
- Historical control group
- Publication bias

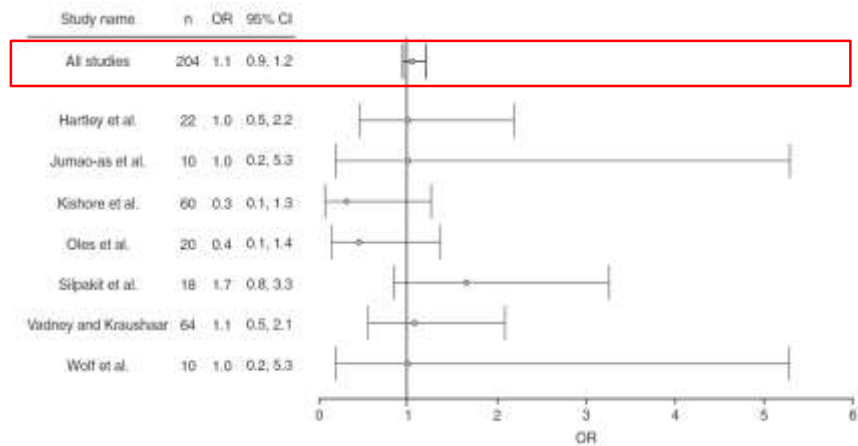
Kesselheim et al.

- Meta-analysis
- RCT's
- Seizure outcomes after switching antiepileptic drugs (Brand-Generic)

Kesselheim et al. Drugs 2010; 70: 605-621.

- Seven RCTs included
 - Carbamazepin (5), Phenytoin (1), Valproic acid (1)
 - Cross-over trial (6), new therapy (1)
- In total 204 patients





Unsilmarities



Project

Goal: to reduce the number of issues after changing between generic drugs

Method: Learn from issues in the past in three hospitals

Storage conditions

Epinephrine 1 mg/ml injection

- Generic A: store 15-25 °C
- Generic B: store 2-8 °C

Problem: Emergency set, Ambulance, etc.

Look alikes



Appearance



Appearance

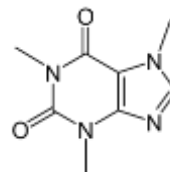
- USA: Trade Dress Law
- Not allowed to make similar appearance
- Differences in appearance:
 - Mistakes
 - Adherence



Coffeine for neonates

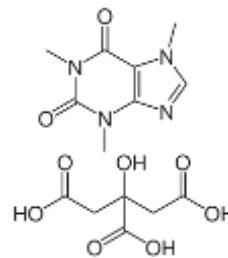
Coffeine base: $M_w = 194 \text{ g/mol}$

- Start dose 10 mg/kg/day sid,
- Maintenance dose 2,5 - 5 mg/kg/day sid



Coffeine citrate: $M_w = 386 \text{ g/mol}$

- Start dose 20 mg/kg/day sid,
- Maintenance dose 5 - 10 mg/kg/day sid



Coffeine for neonates

Hospital A:

neonate treated with coffeine citrate (Peyona) 20
mg/kg daily

Transfer to our hospital:

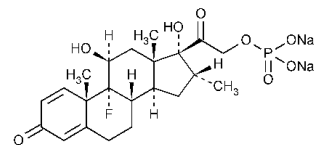
Physician prescribes coffeine 20 mg/kg daily

Is coffeine base

Seen during medication surveillance: once double
overdose of coffeine

Salt forms

Similar product dexamethason:



Product A:

Dexamethason disodium phosphate 5 mg

Product B:

Dexamethason 3.8 mg (as dexamethason
disodium phosphate)

Gemcitabine

Gemcitabine

Generic A: Powder for solution



Generic B: Concentrate for solution 38 mg/ml

Gemcitabine

Generic B: Concentrate for solution 38 mg/ml
421 mg/ml ethanol 96%

$1.8 \text{ m}^2 \times 1250 \text{ mg/m}^2 = 2250 \text{ mg}$
 $2250 \text{ mg} / 38 \text{ mg/ml} = 59 \text{ ml concentrate}$
 $59 \text{ ml} \times 421 \text{ mg/ml} = 24 \text{ gram ethanol}$

Is 2 to 2,5 glasses of beer!



Propranolol

Propranolol for children

Syprol oral solution 2 mg/ml
orange/tangerine flavour containing: ethanol
0.12 %v/v

Propranolol

4 year old child, 17 kg, 2 mg/kg/day

17 ml Syprol per day

0,12% = 0,95 mg/ml

17 ml x 0,95 mg/ml = 16 mg ethanol per day

1/1000th glass of beer

$$\frac{1}{1000} \times$$



Checklist!

¹MI, intermuscular; I, intrafascial; N, intraneural; SC, subcutaneous; WB, water for injection, as other detail.

Checklist (2/3)

- Excipients
 - Gluten, benzyl alcohol, propylene glycol, ethanol, paraben, sulphite, wheat starch
- Compatibility with devices

Checklist (3/3)

- Split tablets
- Taste (oral liquids)
- Administration (route)
- Preparation
 - Ampoule, flask
 - Powder, concentrate
 - Solvent

Implementation

- Our hospital:
 - Contracting 800 products
 - Switching on average 70 products
- Use checklist
 - After selecting drug
 - Before contracting
 - Check by hospital pharmacist

Conclusion

- Although all legislation, still a lot of differences
- Use checklist to avoid unexpected issues
- Patient safety and costs
- Important role for the hospital pharmacist!
- For checklist: mbecker@sahz.nl

- Hylke Jan Kingma (SAHZ)
- Nicole Hunfeld (Erasmus MC)
- Patricia van den Bemt (Erasmus MC)
- Arnold Vulto (Erasmus MC)
- Stijn Koolen (SAHZ)
- Ruud van der Hoeven (SAHZ)

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