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

Limitations:
- Healthy volunteers
- Not right measure for some forms
  - Budesonide, mesalazine, inhalation
- Bioequivalence between generics
  - 1.6x difference
Bioequivalence

Narrow Therapeutic Index Drugs

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

Bioequivalence

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

Highlights of the equivalence of biosimilars

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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

Scientific Research

• 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
Scientific Research

<table>
<thead>
<tr>
<th>Study name</th>
<th>n</th>
<th>OR</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>All studies</td>
<td>204</td>
<td>1.1</td>
<td>0.9, 1.2</td>
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<tr>
<td>Hartley et al.</td>
<td>22</td>
<td>1.0</td>
<td>0.5, 2.2</td>
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<td>Jumaão et al.</td>
<td>10</td>
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<td>Kishore et al.</td>
<td>60</td>
<td>0.3</td>
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<td>Gles et al.</td>
<td>20</td>
<td>0.4</td>
<td>0.1, 1.4</td>
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<tr>
<td>Siipakat et al.</td>
<td>18</td>
<td>1.7</td>
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<td>Sadovy and Krausheie</td>
<td>64</td>
<td>1.1</td>
<td>0.5, 2.1</td>
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<td>Wolf et al.</td>
<td>10</td>
<td>1.0</td>
<td>0.2, 5.3</td>
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Unsimarities
**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
• USA: Trade Dress Law
• Not allowed to make similar appearance
• Differences in appearance:
  - Mistakes
  - Adherence

Coffeine for neonates

Coffeine base: Mw = 194 g/mol
  • Start dose 10 mg/kg/day sid,
  • Maintenance dose 2,5 - 5 mg/kg/day sid

Coffeine citrate: Mw = 386 g/mol
  • Start dose 20 mg/kg/day sid,
  • Maintenance dose 5 - 10 mg/kg/day sid
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

Generic A: Powder for solution

Generic B: Concentrate for solution 38 mg/ml

421 mg/ml ethanol 96%

1.8 m2 x 1250 mg/m2 = 2250 mg
2250 mg / 38 mg/ml = 59 ml concentrate
59 ml x 421 mg/ml = 24 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

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
How to prevent these issues?

Checklist!

Or

E-mail: mbecker@sahz.nl

Checklist (1/3)

Topics

- Packaging
  - Unit packaging, flask, etc.
  - Flag labels, leaflet
  - Similarity with other presentations
- Storage conditions & shelf life
- Barcoding
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
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- Patricia van den Bemt (Erasmus MC)
- Arnold Vulto (Erasmus MC)
- Stijn Koolen (SAHZ)
- Ruud van der Hoeven (SAHZ)

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