Pharmacoepidemiology
an introduction

Prof dr Toine CG Egberts
Uppsala, May 30 – June 1

bridging molecule and patient environment

Pharmacoepidemiology & Clinical Pharmacology
Clinical Pharmacy
My personal mission

To describe, explain variation in response to drugs (research)

*Passion for unintended effects*

*Inspired by clinical puzzles*

To predict response to drugs for the individual patient i.e. to reduce variability (care)

Today (13.00 – 16.30)

Occurrence relation

Hippocrates’ domains

Study design – part 1

*Lecture – group work – reflection*

*Study papers*

*Design your study*
Why pharmacoepi in drug safety?

Drug evaluation never ends

- Preclinical development
  - Discovery & Screening: 10,000
  - Pre-clinical development: 15-30
- Clinical (I-III)
  - Phase I: 10-15
  - Phase II: 5
  - Phase III: 1
- Phase 4
  - Registration & launch
- Discovery
  - First administration to man: approx. 10-12 years
**People exposed to NCEs at the time of marketing**

*United Kingdom 1987-1989*

<table>
<thead>
<tr>
<th></th>
<th>healthy volunteers</th>
<th>efficacy studies</th>
<th>safety database</th>
</tr>
</thead>
<tbody>
<tr>
<td>all applications</td>
<td>68 (0-619)</td>
<td>861 (41-4906)</td>
<td>1171 (43-15962)</td>
</tr>
<tr>
<td>successful</td>
<td>92 (0-819)</td>
<td>1126 (122-4906)</td>
<td>1480 (129-9400)</td>
</tr>
<tr>
<td>unsuccessful</td>
<td>64 (0-431)</td>
<td>785 (41-4786)</td>
<td>1052 (43-15962)</td>
</tr>
</tbody>
</table>

*Rawlins and Jefferys. BMJ 1991;302:223-5*
What is probability of detection?

*Side effect occurs 1 in 1000.*
What evidence base (trials) is necessary to observe with 95% probability the side effect at least once?

*Evidence base is 1500 patients.*
Side effects with which incidence can be observed at least once with 95% probability?

By the way: what is....?

*An adverse drug reaction / adverse effect*
*A side effect*
*An adverse event*
**Definitions**

*Adverse Drug Event:*
A harmful and unintended event occurring during drug therapy

*Adverse Drug Reaction / Adverse Reaction:*
A harmful and unintended event considered related to drug therapy

*Side Effect:*
An effect other than the intended one

*Medication error*

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**Side effects vs ADRs**

*Case Report*
Reduction of Migrainous Headaches During the Use of Acenocoumarol

E.P. van Puijenbroek, MD; A.C.G. Egberts; J.F.G. Trooster; J. Zomerdiijk, MD

*Not always bad news*

Innovation trigger
e.g. sildenafil, thalidomide
Definitions

Adverse Drug Event:
A harmful and unintended event occurring during drug therapy

Adverse Drug Reaction / Adverse Reaction:
A harmful and unintended event considered related to drug therapy

Side Effect:
An effect other than the intended one

Medication error

Hospital Admissions Related to Medication
The HARM study

Results: Almost 13,000 unplanned admissions were screened, of which 714 (5.6%) were medication related. Almost half (46.5%) of these admissions were potentially preventable, resulting in 332 case patients matched

Arch Intern Med 23 september 2008
Intrinsic vs extrinsic (un)safety

prescribing and use

drug → patient

The time-knowledge curve of NCEs

knowledge (%)

approval
time
Epidemiology

Pr(outcome) = f(determinants)

Pharmacoepidemiology
-drug = outcome (drug utilization)
-drug = determinant (usually)

SSRIs - bleeds in orthopedic surgery

<table>
<thead>
<tr>
<th></th>
<th>serotonergic AD (n=26)</th>
<th>none (n=494)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood transfusion n (%)</td>
<td>6 (10%)</td>
<td>20 (4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Perioperative blood loss</td>
<td>1019 ml</td>
<td>582 ml</td>
<td>0.001</td>
</tr>
<tr>
<td>Postoperative drainage</td>
<td>657 ml</td>
<td>495 ml</td>
<td>0.032</td>
</tr>
</tbody>
</table>

Arch Intern Med 2003;163:2354-8
Selective prescribing of meloxicam

<table>
<thead>
<tr>
<th></th>
<th>meloxicam n=5000</th>
<th>ibuprofen n=5000</th>
</tr>
</thead>
<tbody>
<tr>
<td>recent use NSAIDs</td>
<td>49.8%</td>
<td>7.9%</td>
</tr>
<tr>
<td>recent use H2 blockers</td>
<td>12.4%</td>
<td>4.0%</td>
</tr>
<tr>
<td>recent use proton-pump inh.</td>
<td>11.1%</td>
<td>4.0%</td>
</tr>
<tr>
<td>history of dyspepsia</td>
<td>38.4%</td>
<td>20.3%</td>
</tr>
<tr>
<td>history of peptic ulcer</td>
<td>6.1%</td>
<td>3.1%</td>
</tr>
</tbody>
</table>

*Lanes et al. Pharmacoepidemiol & Drug Saf 2000;9:113-7*
Designing your research

Design (what)
- what do I want to know why?
- Objective and rationale
- Introduction section protocol / paper

Operationalize (how)
- Patients: where (setting), who (in/exclusion), n
- Study design (I.e. trial, case control, follow-up)
- How to measure outcome, determinants, confounders
**Inspiration, transpiration, frustration**

**The occurrence relation**

\[
\text{Determinant(s)} \quad \longrightarrow \quad \text{outcome(s)}
\]

- characteristic/determinant
- exposure
- drugs
- independent variable
- The effect of...

- endpoint
- disease
- adverse effect
- dependent variable
- on....

**Domain:**

the population for which the occurrence relation is of potential relevance in....

Prof dr ACG Egberts
For comparison

P patient

I intervention

C comparison

O outcome

Key message

Consistency of the essential items occurrence relation in:
- Title
- Objective
- Methods
- Primary graph / table
**Assignment 1**

Write down the occurrence relation of the papers
Determinant, outcome, domain

Write down your occurrence relation of interest
The objective of my study is to....
Draw most important graph/table