EVALUATION OF DRUG TOXICITY IN
CLINICAL TRIALS: A BIASED
MISCONCEPTION

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PROVOCATIVE QUESTIONS

„The responsible conduct..clinical research”
What is the most important meaning?

- Is it concordance with GCP?
- Is it agreement with one of the ICH?
- Is it in concordance with human rights?

As an average physician or a member of society
I may not be interested in GCP, ICH, or other
PROBABLE ANSWER

The basic interest in Responsible Conduct of Clinical Research comes from the expectation that such clinical research will deliver sound results showing that drug under study is safe and effective and society may approve it for common usage and I can take it.

Is it ethical problem?

Yes, because if the problem of drug evaluation to be used by JS and other Europeans is approached unethically the chances that I will be poisoned (and other Euro) are high.
IS IT ETHICAL APPROACH?

The activity that at the end produces right and good things for every member of the society (i.e. safe & effective medicines) is ethical. The opposite is unethical. The Q. is whether it is unethical because people (Pharma, Sponsors, etc) are bad, want to cheat results so their product will appear safe & effective or the procedures on which clinical research is based are not good enough.

Much is discussed about misconduct, falsification, etc. However, I will focus on inadequacy of some basic rules of clinical research.
DATA ON VIOXX

- COX-2 inhibitors marketed for arthritis:
  - rofecoxib approved on May 21, 1999
  - MSD withdrew the drug on September 30, 2004
- 80 mln pts had taken rofecoxib
- last year sales: up to $ 2.5 billions
- it took FDA almost 2 yrs (Feb 8, 2001) to discuss the possible harm
- MSD: $ 100 mln/yr on advertising
- Topol: ..”sales valued over safety..”
TRAGEDY OF VIOXX

- rofecoxib: NNT to prevent GI event, 125; NNH for thrombotic event, 103
  (Vigor study, NEJM 2000)
- in 2600 pts with colon polyps, 3.5% on rofecoxib had MI or stroke as compared to 1.9% on placebo
- NNH (number needed to treat to have MI or stroke) is: 1/(0.035-0.019) = 62.5 pts!
  (JAMA 2001)
TOPOL’S POINT OF VIEW (NEJM 2004)
WHAT IS WORSE...

The effect of rofecoxib is a class effect shared by:
- Celecoxib (approved for arthritis and polyposis)
- Parecoxib
- Valdecoxib

with celecoxib widely used with FDA Panel statement:

„For upper GI safety and also for global safety there does not appear to be any meaningful advantage for Celebrex”
WHAT IS EVEN WORSE …

There are several examples from the past. The following drugs were withdrawn because of “unexpected” (it is always unexpected) toxicity:

- Cerivastatin – rhabdomyolysis (120 deaths)
- Alosteron – ischemic colitis (over 50 deaths)
- Cisaprid – cardiotoxicity (some deaths)

(These examples are from recent years)
I personally do not think that the cause of these tragedies is due to greediness of Pharma, Sponsor, etc, or to ambition of PI or „small” ghost authors but rather to inadequacy of rules governing clinical trials.

In the case described here an inadequacy of evaluation of safety is suspected. This lesson should force us to think it over and learn from the past experience and try to modify future.
SOME MAY THINK THAT THIS TASK IS TOO DIFFICULT BUT THE BIG LEADER SAID:

"I would not say that the future is necessarily less predictable than the past. I think the past was not predictable when it started."

(Donald Rumsfeld)
TYPE OF THE STUDY

For producer to register drug (for the good of the society) the confirmatory trial is needed.

ICH E9 II.A.2.1.2:
Trial content, Confirmatory

..“to provide firm evidence of efficacy and safety..”

Trial ..“be sufficient to answer each key clinical question relevant to the efficacy or safety claim clearly and definitively”

What is the producer claim?
There are two basic types most often used for registration purposes:

- non-inferiority (n-in) control: active treatment
- Superiority, control: placebo

There is no time to discuss n-in type and the case of superiority is simpler.
SUPERIORITY TRIAL

H₀: T – P ≤ O
Hₐ: T – P > O

O

T – P
T, tested; P, placebo

Efficacy:
stat. sign. difference when H₀ could be rejected

Safety:
producer does not want to reject equivalence
with placebo (his claim: drug is not sign.
different from placebo, tox is „comparable”)


PROBLEMATIC ISSUES

Aim: toxicity of drug is comparable to placebo

- level of acceptance: „moving target“ (depends on disease, often switch to OTC)
- sample size (min. no. of participants: increases possibility of type II error, i.e. not detecting toxicity when in fact it is present)
- what about toxicity of placebo? (This is the way to show that the drug is „comparable“ to placebo. Since all drugs are poisons – Paracelsus - in order to show „comparability“ toxicity of placebo must be increased)
TOXICITY OF PLACEBO: EXAMPLE

New hypotensive agent, blindness is limited:
- usually tested in hypertensive clinic
- most common drugs: ACE inhibitors (all of them are inducing cough)
- neither pt nor physician is aware of trea but when somebody coughs immediately ADR is assigned (“of course must be due to medicine”)
- when code is broken, cough appears common ADR in placebo group
- placebo-ADRs are trea- and disease- specific

(Weihrauch & Gauler, 1999)
IS PLACEBO TOXIC?

- Participants recruited for the study are in fact „active volunteers” they want to be treated they do not anticipate that the treatment will be harmful (in that case they would not agree to be in).
- Pts do not assume up-front that the treatment will induce harm – such pts do not enter study.
- Perhaps placebo is not toxic at all and the common practice to subtract placebo toxicity from that of drug’s is not correct?
<table>
<thead>
<tr>
<th>Compliance:</th>
<th>Propranolol</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 75%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of pts (% of dead)</td>
<td>72 (4,2)</td>
<td>57 (7,0)</td>
</tr>
<tr>
<td>&gt; 75%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of pts (% of dead)</td>
<td>1 009 (1,4)</td>
<td>1 037 (3,0)</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>3,1</td>
<td>2,5</td>
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</tbody>
</table>
"The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods" = no placebo trials

In VIGOR trial rofecoxib was compared not with placebo but with naproxen. When the data revealed increased frequency of cardio events in rofecoxib group, authors contended that this is due to protective effect of naproxen!
CONCLUSIONS

- Attempts to concentrate on efficacy are often at the expense of safety
- Failure to detect toxicity against placebo does not provide the proof that drug is not toxic
- Placebo toxicity, both qualitatively and quantitatively can be assessed only against no-treatment
- Placebo-induced toxicity needs reevaluation
THANK YOU!
“As we know, there are known knowns; there are things we know we know. We also know there are known unknowns; that is to say we know there are some things we do not know”