Is Phase I safe ?

Michel SIBILLE

and

French Club Phase I

Safe ?

- YES… based on the available data
- BUT… there are risks:
  1. Non accurate methods or non compliance
  2. New risks for future
- AND… two questions

The available data

Safety in Phase I and
Experimental research

Levinski NG NEJM 2002, 347: 759

« I was unable to identify a comprehensive list of deaths of normal volunteers in the United States…»

Questions:

- Number of volunteers ?
- Number of deaths & serious adverse events ?

Number of healthy volunteers
Phase I and Experimental Research

- ***US***: NIH alone, 5510 HV *Lemonick TIME 22.4.2002.*
- ***France***: 2002-4, # 6-10000 *Club Phase I register-AFSSAPS*
- ***UK***: 92-2001, # 9-10000 *AICRC register*

→ ***Worldwide grand total ≥ 100000 per year***

Last 30 years	N of subj	Phase I	Experimental research	Reference		
Cardon 1976	934000	+	+	NEJM 1976, 295: 650		
Zarafonetis 1978	29162	+	+	CPT 1978, 24: 127		
Royle 1986	27424	+	+	Br J Clin Pharm, 86, 21: 548		
Orme 1989	8163	+	+	Br J Clin Pharm, 89, 27: 125		
Rosenzweig 1993	1228	+		CPT 1993, 54: 578		
Huic 1996	885	+		Therapie, 1996, 51: 410		
Herman 1997	440	+		Eur J Clin Pharm, 1997, 53: 207		
Sibille 1992-98-03	1901	+		Eur J Clin Pharm, 1992, 42: 389 Eur J Clin Pharm, 1998, 54: 13		
UK AICRC 1992-2001	92510	+		-		
Club Phase I 2004	5523	+		-		

Last 30 years	N of subj	Phase I	Exper research	**Serious Adverse events**	**Per thousand**
Cardon 1976	934000	+	+	**38**	**0,04**
Zarafonetis 1978	29162	+	+	**65**	**2,2**
Royle 1986	27424	+	+	**13**	**0,5**
Orme 1989	8163	+	+	**48**	**5,5**
Rosen 1993	1228	+		**0**	
Huic 1996	885	+		**0**	
Herman 1997	440	+		**0**	
Sibille 1992-98-03	1901	+		**8**	**3**
UK AICRC 1992-2001	92510	+		**209**	**2,2**
Club Phase I 2004	5523	+		**25**	**4**

Serious Adverse Events

France: Club Phase I register
Whole year survey on 2004

Number of subjects: 5523

Serious AEs: 25 (4 ‰)

- No life threatening, no disability
- Related to tested drug : 9

  Non related to tested drug : 16

Last 30 years	N of subj	Phase I	Exp. Res.	**Deaths**
Zarafonetis	29162	+	+	**1**
Royle	27424	+	+	**1**
Sibille	1901	+		**3**
UK AICRC	92510	+		**3**
Club Phase I + Personal Update	5523	+ +	+	**1** **5**

Total = 14

Deaths in Phase I and experimental research

N°	Year	Country	Phase I	Exp. Researc	Reference
1	1980	US	X		Hastings - Center, 1980, 10:5
2	1985	Ireland	X		Lancet, 1985, I:93
3	1985	UK	X		BMJ, 1985, 290:1359
4	1999	US	X		No publication
5	2004	US	X		Indianapolis Star, 10 Feb. 2004
6	1992-2001	UK	X		AICRC Survey
7	1992-2001	UK	X		AICRC Survey
8	1992-2001	UK	X		AICRC Survey
9	1978	US		X	CPT, 1978, 24:127
10	1996	US		X	NY State Dpt of Health - 96 Press release
11	2000	Australia		X	Med. J. Aust, 1998, 168 (9):449
12	2001	US		X	Science, 2001, 293, 5532:1013
13	2002	US		X	Arterioscler. Thromb. Vasc. Biol. 2002, 22:1046
14	2004	France		X	Club Phase I French register

1. Supposedly healthy, but anorexia nervosa with severe potassium depletion; Interaction with tested drug
   Treatment: **lithium and methyl paratyrosine**
2. Supposedly healthy, but psychotic who received the day before a depot I.M. injection of flupenthixol

   Treatment: **antiarrhytmic**, death by probable drug interaction.

3. Aplastic anemia (8 months after study)
   Treatment: **midazolam**

4. Anaphylactic shock or arrhythmia and inaccurate resuscitation; patient volunteer with mild renal insufficiency
   Treatment: **Antibiotic by iv route**

5. Suicide: hanged herself in the Clinical Research Lab.
   Treatment: **duloxetine**

6. Unknown cause*;* **placebo**, one day after study inhoused period

7. Cardiac arrest, predosing period

8. Car accident, one week after study

9. Cerebrovascular haemorrhage, placebo

10. Rochester case: **Overdose of lidocaine**- local anaesthetic used in bronchial fibroscopy

11. Australian case; **Overdose of lignocaine**- local anaesthetic used in bronchial fibroscopy

12. The Johns Hopkins'case: cough then respiratory breakdown

Treatment: **inhaled hexamethonium (unauthorized drug)**

13. Cleveland case: Severe vomiting, hypertension, confusion, acute aspiration pneumonia

Methionine overdose (# 10 fold, proven by PK data).
Subject already participant in another 'WACS' study using vitamin C and betacarotene.

14. Lung cancer, study on biomarker

Analyse causes…

… suggest safety rules

N°	Last 30 years: 14 identified cases of Deaths in Healthy Volunteers	Study and/or drug	Hazard or accident
	PHASE I STUDIES		
1	Supposedly healthy, but anorexia nervosa with severe potassium depletion; Source of interaction with tested drug : Treatment: **lithium and methyl paratyrosine.**	X	
2	Supposedly healthy, but psychotic who received the day before a depot I.M. injection of flupenthixol; Source of drug / drug interaction to tested drug;Treatment: **antiarrhytmic**, death by probable drug interaction.	X	
3	Aplastic anemia (8 months after study); Treatment: **midazolam.**	X	
4	Anaphylactic shock or arrhythmia and inaccurate resuscitation; patient volunteer with mild renal insufficiency; Treatment: **Antibiotic by iv route**	X	
5	Suicide: hanged herself in the Clinical Research Lab. Treatment: **duloxetine**	X	
6	Unknown cause (Alcohol ?); placebo, one day after study inhoused period		X
7	Cardiac arrest, predosing period		X
8	Car accident; one week after study		X
	EXPERIMENTAL RESEARCH:		
9	Cerebrovascular haemorrhage; placebo treatment		X
10	Rochester case: **Overdose of lidocaine**-local anaesthetic bronchial fibroscopy	X	
11	Australian case; **overdose of lignocaine**-local anaesthetic bronchial fibroscopy	X	
12	The Johns Hopkins'case: cough then respiratory breakdown; Treatment: **inhaled hexamethonium** (unauthorized drug);	X	
13	Cleveland case: Severe vomiting, hypertension, confusion, acute aspiration pneumonia related to methionine overdose (# 10 fold, proven by PK data). Subject already participant in another study 'WACS' using vitamin C and betacarotene.	X	
14	Lung cancer; study on biomarker	X	
17		**10**	**4**

The Causes & *the safety rules*

10 non accidental deaths

A/ Screening default : 3 (psychiatric abn. 2)

1. *Qualified process and staff*
2. *Special scrutiny on volunteers already known by team (4/10 deaths)*
3. *Use of REMEDI to detect previous drug consumption (Rapid Emergency Drug Identification Ann. Biol. Clin. 1993, 51, 611)*

The Causes & *the safety rules*

10 non accidental deaths

B/ Study conduct default 7/10

- *Continuous presence of a qualified physician in CPU*
- *Conservative safety rules regarding :*
  - *Drug use*
  - *Procedure implementation*
  - *Unexpected and /or severe AE*

The Causes & *the safety rules*

10 non accidental deaths

DRUGS 7/10

- Parallel drugs: 4
- Overdose: 3 (local anaesthetics (2) and additive (1))
- Non authorized drug: 1

Suggested preventive action:

Special scrutiny …

Special scrutiny
Donna Shalala NEJM, 2000, 343: 808

1. Non authorized substance
2. Non tested (parallel) drug required for specific studies
   ie local anaesthetic….

at least same requirements as for the tested drug:

- Extensive literature review: describe risks
- Rules & limitations for use, in the protocol

The Causes & *the safety rules*
Population

A/ Elderly: 5/14 or 3/10 non accidental

Well known increase of disease risk in parallel to age & also decrease of resistance capacity

Suggested preventive action:

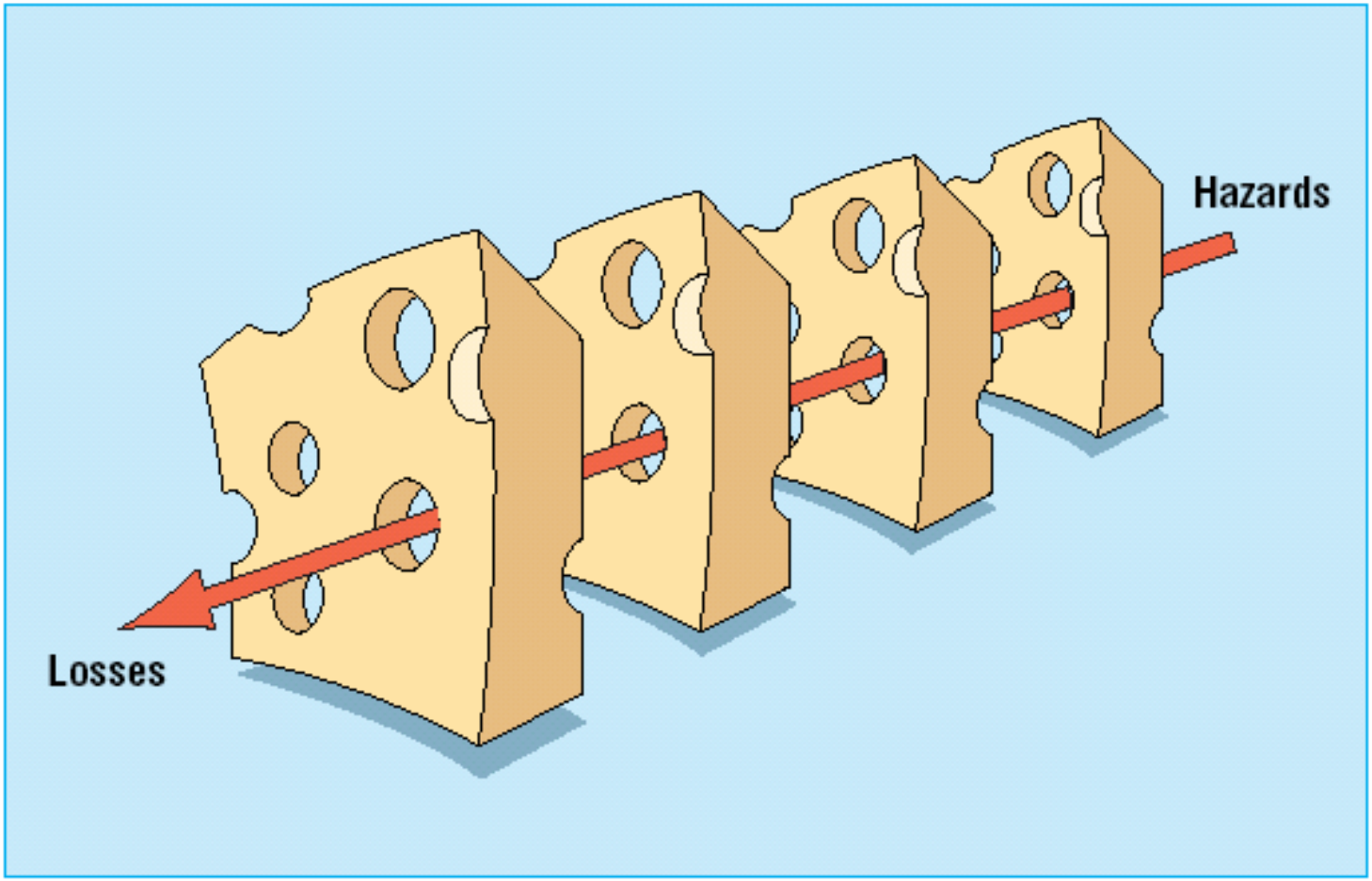
- *More comprehensive screening process in elderly.*
- *Limitation on non benefit studies in healthy elderly & conservative approach if MTD required in elderly*

The Causes & *the safety rules*
Population

B/ Women: 7/10 non accidental deaths

Why ?

- *Inclusion of women in first-in-man ?*
- *Special scrutiny on protocols in women to make continuous risk assessment*



The Swiss cheese model of how defences, barriers, and safeguards may be penetrated by an accident trajectory

The causes & potential factors

10 DEATHS RELATED TO STUDY AND / OR DRUG								
N°	Screening	Subject working with or known by study staff	Study conduct	Drug overdose	Unauthorized drug	Elderly	Woman	Number of
1	X	X	X				X	**4**
2	X	X						**2**
3								**.**
4			X			X		**2**
5			X				X	**2**
10			X	X			X	**3**
11		X	X	X			X	**4**
12		X	X		X		X	**4**
13			X	X			X	**4**
14	X						X	**3**
Total	3	4	7	3	1	1	7	

10 DEATHS RELATED TO STUDY AND / OR DRUG									
N°	Screening	Subject working with or known by study staff	Study conduct	Drug overdose	Unauthorized drug	Elderly	Woman	**Preventable**	
								Yes	No
1	X	X	X				X	**X**	
2	X	X						**X**	
3									**X**
4			X			X		**X**	
5			X				X	**X**	
10			X	X			X	**X**	
11		X	X	X			X	**X**	
12		X	X		X		X	**X**	
13			X	X		X	X	**X**	
14	X					X	X	**X**	
Total	3	4	7	3	1	1	7	**9/10**	**1**

First Conclusion

- Is Phase I safe ?
  - YES … only 10 non accidental deaths / 30 years & > 100,000 volunteers per year
  - YES … only ONE non preventable death
  - YES… IF … safety rules are accurate & respected

Safe ?

- YES… based on the available data
- BUT… there are risks:
  1. Non accurate methods or non compliance
  2. New risks for future
     - Experimental medicine
     - Conflict-of-interest
- AND… two questions

Future of Clin Pharm is Experimental medicine

IN DRUG RESEARCH, THE GUINEA PIGS OF CHOICE ARE, WELL, HUMAN.

« Researchers repeated the experiment 70 times: a healthy volunteer would receive a chemical injection, then be left alone to ride out an artificially induced panic attack…. Each volunteer was put through the same test a few days later, but this time most of them first received an experimental antianxiety drug… »

The New York Times Aug.4, 2004 by Andrew Pollack

Special scrutiny

- Criterion 1: Initial translation of scientific advances into humans
- Criterion 2: Risk for significant harm and no potential for direct medical benefit
- Criterion 3: Ethical questions about research for which there is no authoritative consensus

Carol LEVINE Ann Intern Med 2004,140:220

Conflict-of-interest

Do exist ! Not avoidable !

Could be financial & direct but also indirect – research activities or publishing activities

- USA, from 80 to 2000, industry's share in biomedical research increases from 32% to 62%
- Phase I, by nature, is sponsored by industry

Best proposals

- Fully disclose nature and extent of relationships
- Publish all results

JE Bekelman,	**JAMA, 2003, 289:454**
EA Boyd	**Acad Med 2003,78:769**
NG Levinski	**NEJM 2002,347:759**

Safe ?

- YES… based on the available data
- BUT… there are risks:
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- AND… two questions

Repeat participation among healthy research volunteers

- Only one at a time
- Exclusion period after a research study participation
- Limitation in the total amount of money to avoid « professionalism »
  - Follow-up after study
  - Volunteer registry

French Law **Volunteer National file**

Carl LTishler **Perspec. Biol. Med. 2003, 46, 508**

Long term follow-up & volunteer register

Feasibility ?

Restricted to

- Repeat participation
- Multiple dose protocols
- Probability of risks

  ie Psychotropic drugs

  Immune system activity

Levinski NG NEJM 2002, 347: 759

« I was unable to identify a comprehensive list of deaths of normal volunteers in the United States.

The FDA requires reports of deaths during clinical trials of investigational drugs, but the information is not made public. »

Last risk: holding back information

Ex: A new drug in a new class with big unexpected new risk → mandatory reporting from investigator → sponsor → agencies

But: * no publication by investigator
* holding back information by sponsor & agencies

Thus: * scientific handicap
* risk on second drug in class
* ethically questionable custom

Make available the research results Bekelman JAMA 2003,289,454

« All investigators and sponsors undertaking human participants research should …make available all research results from completed trials in a comprehensive, publicly accessible registry »

Rennie *Fair conduct and fair reporting trial*
JAMA 1999,282:1766

Horton *Time to register randomised trials*
Lancet 1999, 354: 1138

Mc Cray *Better access to information about clinical trials*
Ann Med Intern 2000, 133:609

Conclusions and/or recommandations

1. Safe…yes, if safety rules respected
2. Special scrutiny on emergent risks: experimental medicine including « parallel drugs » used for pharmacodynamics or risky procedure
3. Long term follow-up in restricted conditions

…/…

4. Share experience and knowledge

Proposal for Phase I & Experimental Research

Per country or Europe,

- Create a register on Deaths & Serious AEs
  (life threatening, disability …)
- Independent organism or Health authorities
- Give access to such register*

* Take care of confidentiality

HEALTHY VOLUNTEERS
Club Phase I register France - 2004

	Men	Women	
Young	4312	783	
Elderly	169	259	
Total	4481	1042	5523

Serious AEs
Club Phase I register France 2004

	Men		Women		
	Young	Elderly	Young	Elderly	
Related	5	-	-	4	9
Non related	9	2	1	4	16
	14	2	1	8	25