Modelling is seldom used to describe pharmacokinetics in phase I clinical trials

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Objective: To investigate the way pharmacokinetics (PK) is described and reported in phase I clinical trials through a bibliographic study.

Methods

Article selection

- PubMed search, with criteria :
  - in title: "phase I" or "phase 1"
  - in title, abstract, keywords: pharmacokinetic*
  - limited to English language
  - published in 2005 or 2006
- selection of 60 papers for each year
  - random sample
  - full text obtained through online librairies, mail service or direct contact
- 40 papers read by both authors

Data abstraction form

Relevant information extracted using a data abstraction form, built using the guidance for PK studies in humans [1]:

- general characteristics, including address, affiliation, journal, pathology, drugs tested, and study objectives
- study design, including number of subjects, number of dose levels, dose escalation procedures, patient selection procedures
- PK analysis, including number of subjects included in PK, description of the sampling times, analysis methods, PK variables reported

Statistical analysis

- descriptive statistics
- data management and statistical analyses using R

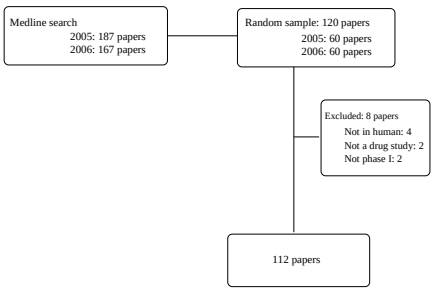

Figure 1: *Flow-chart of the selection process.*

Results

General results

Item		N (%)
Year	2005	56 (50%)
	2006	56 (50%)
Country	North America	66 (59%)
	Europe	33 (29%)
	Asia	9 (8%)
	other	4 (4%)
Pharmaceutical industry*	yes	51 (46%)
	no	61 (54%)
Pathology	cancer	103 (92%)
	infectious disease	3 (3%)
	other	6 (5%)
Population	adults	104 (93%)
	children or adults	1 (0.9%)
	children/young	7 (6%)
Subjects	patients	104 (93%)
	healthy volunteers	8 (7%)
Study objective**	MTD	78 (70%)
	DLT	13 (12%)
	PK	90 (80%)
	dose	3 (3%)
	toxicity	42 (38%)
	efficacy	25 (22%)
	other	5 (4%)
Number of subjects	median [range]	24 [8-151]

Table 1: *Characteristics of the 112 papers read in the present study.*
** the answer 'no' means 'no' or 'not reported'*
*** multiple answers are possible.*

- pharmaceutical industry present in about half of the papers
  - item recorded based on the affiliations and addresses provided
  - probably underestimates actual proportion of phase I studies performed by the pharmaceutical industry (publication bias?)
- overwhelming majority of papers dealing with cancer patients (92%)
  - although not explicitely selected in the search
  - phase I studies maybe more codified in oncology
- objectives
  - PK explicitely stated in the objectives for 80% of the studies
  - determination of the maximum tolerated dose (MTD) or dose-limiting toxicities (DLT) also frequently stated (consistent with the large number of studies in oncology)

Pharmacokinetic study

Item		N (%)
Description of PK	yes	93 (83%)
	partial	6 (5%)
	no	13 (12%)
Multiple occasions	yes	78 (70%)
	no	34 (30%)
Analysis method	Descriptive	13 (12%)
	Non compartmental method (NCA)	73 (65%)
	Non linear regression (RNL)	7 (6%)
	Population approach (POP)	5 (4%)
	NCA and RNL	4 (4%)
	NCA and POP	1 (0.9%)
	Not reported	9 (8%)
Model built	yes	18 (16%)
	NR for PK, yes for PD	1 (0.9%)
	no	93 (83%)
Relationship PK/toxicity	no	96 (86%)
	yes	10 (9%)
	not applicable	6 (5%)
Relationship PK/efficacy	no	94 (84%)
	yes	12 (11%)
	not applicable	6 (5%)
PK variables*	Observed concentrations	12 (11%)
	Cmax, Css, Cmin,...	73 (65%)
	AUC by NCA	85 (76%)
	CL by NCA	58 (52%)
	Additional NCA parameters	59 (53%)
	PK model parameters	8 (7%)
	Other	22 (20%)
	none reported	7 (6%)

Table 2: *Characteristics of the pharmacokinetic study.*
** multiple answers are possible.*

- description of the design usually available in methods
  - description incomplete or missing in 17% of the papers
  - a majority of studies involve sampling on several occasions
  - extensive sampling
- statistical methods
  - modelling used in around 15% of the studies
  - non-compartmental approaches used in 2/3 of the studies
  - results purely descriptive in 12%
  - software often not reported
- results
  - less standardised as the methods section
  - often missing information
  - PK results usually reported separately from clinical results
  - only 10 papers study the relationship PK-toxicity, and 12 the relationship PK-efficacy

Combination therapies

Item		N (%)
Single drug	yes	61 (54%)
	no	51 (46%)
Interaction study (n=51)	yes	10 (20%)
	no	41 (80%)
Double escalade (n=51)	yes	17 (33%)
	no	34 (67%)
PK studied for associated drugs (n=51)	yes	23 (45%)
	partial	4 (8%)
	no	24 (47%)
Interaction studied (n=51)	yes	9 (18%)
	partial	12 (24%)
	no	30 (59%)

Table 3: *Multiple or single drug.*

- 45% involve at least 2 drugs
- dose escalation for all drugs in only 1/3 of these studies

Discussion

Main findings:

- mostly studies in oncology
  - search bias: "phase I" only in title
    - but previous search with "phase I" anywhere in title, keywords and abstract led to similar results, and resulted in a larger percentage of excluded papers
  - publication/reporting bias
    - time pressure
    - phase I studies in oncology mostly performed in patients, maybe more likely to involve academia and be published?
  - definition of phase I in different fields
- modelling seldom used
  - some consequences
    - multiple occasions available in 70% of the studies but interoccasion variability seldom studied
    - loss of data from patients considered not evaluable for NCA
    - PK results for different doses reported separately and not related
    - relationship between PK and efficacy or toxicity rarely investigated
  - added value of modelling
    - modelling approaches useful for decision purposes [2]
    - modelling helps the drug approval process [3]
    - the critical path initiative suggests a better integration of all information (including PK) during drug development [4]

Study limits:

- selection not exhaustive (randomised sample)
  - pilot study, will be extended
- based on available information
  - focus on study reporting through published information

References

[1] Food and Drug Administration. *Guideline for the format and content of the human pharmacokinetics and bioavailability section of an application*. 1987. URL http://www.fda.gov/CDER/GUIDANCE/old071fn.pdf

[2] L. Aarons, M. O. Karlsson, F. Mentré, F. Rombout, A. van Peer, and invited COST B15 Experts. Role of modelling and simulation in Phase I drug development. *European Journal of Pharmaceutical Sciences* **13**:115–22 (2001).

[3] V. Bhattaram, C. Bonapace, D. Chilukuri, J. Duan, C. Garnett, J. Gobburu, S. Jang, L. Kenna, L. Lesko, R. Madabushi, Y. Men, J. Powell, W. Qiu, R. Ramchandani, C. Tornoe, Y. Wang, and J. Zheng. Impact of pharmacometric reviews on new drug approval and labeling decisions - a survey of 31 new drug applications submitted between 2005 and 2006. *Clinical Pharmacology and Therapeutics* **81**:213–21 (2007).

[4] Food and Drug Administration. *Innovation or stagnation: critical path opportunities report*. Rockville, Maryland, USA, 2006. URL http://www.fda.gov/oc/initiatives/criticalpath/reports/opp_report.pdf

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