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Drug Delivery Trends in Clinical Trials and Translational Medicine: Evaluation of Pharmacokinetic Properties in Special Populations

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Abstract

In spite of the recent advances in technology to optimize the absorption, distribution, metabolism and elimination (ADME) properties of new and promising medicinal products to reduce clinical failures, the investigation of drug disposition in the pediatric and elderly populations continues to be under evaluated. With the increasing prevalence of aging populations world-wide, there is a growing concern from health care providers, regulators and the general public that drug delivery is still less than optimal for the vulnerable patient populations likely to be more sensitive to adverse effects of the new investigational drugs. This review of the ClinicalTrials.gov database revealed a rapidly increasing number of clinical trials and a trend towards wider inclusion criteria of the elderly population in clinical trials over the past 10 years. However, when we summarized trials by drug delivery, biological platforms, and disease categories, less than 10% of these trials included pharmacokinetic evaluation in elderly subjects greater than 65 years of age, and less than 4% included pharmacokinetic evaluation in children less than 17 years of age. Across the various disease areas, the percentage of trials that included pharmacokinetic evaluation in the children and elderly has remained low and is consistently less than the studies that included the younger 18 to 65 age group. Therefore, it is not known whether the right information is being generated from the growing number of clinical trials to guide optimal dosing recommendations in special patient populations.

Keywords

pharmacokinetics; pharmacokinetics/pharmacodynamics; physiological model; population pharmacokinetics/pharmacodynamics; pediatric; elderly; inclusions; ADME; clinical pharmacokinetics

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INTRODUCTION

With the 2007 Food and Drug Amendments Act mandating all drugs, biologics, and devices entering clinical trials be registered at ClinicalTrials.gov, the total number of clinical trials in this centralized database has grown rapidly. In our previous commentaries,^{1,2} we introduced an online resource at *Journal of Pharmaceutical Sciences* (JPharmSci) that provides a summary of clinical trial data into the following key categories: drug delivery systems and technologies, molecular platforms, pharmacokinetic modulations, and disease areas. Through this online resource, readers can also perform in-depth review through links to original sources to examine the demographics of the subjects evaluated in these trials, such as gender or age range of the subjects. In this update, we have reviewed the ClinicalTrials.gov database for the analysis of a trend in the inclusion of elderly and pediatric subjects in studies over the past 10 years.

According to the Center for Disease Control, nearly 40% of patients with diabetes are over the age of 65.³ Specifically, aging populations are often presented with cardiovascular diseases, neurologic disorders, diabetes and metabolic disorders. With the increasing prevalence of aging populations worldwide, there is a growing concern about the inadequate safety and efficacy data available for new medicines in populations over the age of 65, or even over 75 years of age.

Under the traditional drug development paradigm, the drug metabolism, pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of a medicinal product in at-risk special populations is often not evaluated until the dosage or formulation intended for the market has been well defined or the drugs have been approved for marketing. The initial clinical assessment of drug properties, including drug metabolism and pharmacokinetics, is customarily conducted in healthy adults, between 18 and 65 years of age. Furthermore, for most approved drugs, the optimal dosage and formulation are often determined based on PK, safety and efficacy data from clinical studies that exclude special (elderly and pediatric) populations, with the exception of medications that specifically target these populations, such as Alzheimer's and certain types of cancer.

Compared to healthy adults, elderly subjects are typically presented with age-related hemodynamic and physiologic changes,⁴ including diminished metabolic and renal capacity, delayed gastric motility or altered gastric pH, and altered body composition (e.g., increased adiposity or reduced lean body mass). Additional challenges include polypharmacy to address diseases with comorbidities. Therefore, elderly patients are more susceptible to adverse drug effects than a typical healthy adult. Any combination of these age-related issues may lead to unpredictable dose- or time-dependent drug disposition or absorption of oral medications. On the other hand, the pediatric population⁵ present a different set of challenges, mainly due to physiologic and metabolic differences. Due to the concern about long-term effects on childhood development, the current clinical drug development plan tends to avoid testing in pediatric populations. Overall, the current clinical drug development paradigm often does not include pharmacokinetic evaluations for pediatric and elderly populations. Thus, definitive information to support the appropriate dosage or dosing regimen in these special populations may be lacking.

Implementation of several key regulatory initiatives (in the 1990s) for clinical testing of drug candidates in humans have increased efforts to ensure the evaluation of new medicinal entities in the elderly⁶ and pediatric⁷ patient populations. Through the collaborative efforts of regulators, research organizations, and pharmaceutical company scientists, the expected outcomes of these initiatives provide better (data-driven) dosing recommendations in special populations. In this commentary, we reviewed the ClinicalTrials.gov database for emerging trends in clinical trials in the evaluation of special populations.

OVERVIEW OF DRUG DELIVERY FORMULATION TECHNOLOGY IN CLINICAL DEVELOPMENT

We have previously defined drug delivery broadly as physical dosage form, molecular design or approaches utilizing knowledge of metabolism and PK properties.^{1,2} During the development life cycle of a drug, these efforts aim to increase the benefit and minimize the risk of medicinal products by reducing the variability, thus improving the consistency of drug delivery to the target organ systems. The data summarized in the tables and graphs accessible online either at the JPharmSci journal homepage (<http://www3.interscience.wiley.com/journal/117935713/group/home/home.html>) or the database website “Drug Delivery in Clinical Trials Database” (<http://www.abedia.com/dd/>) are by no means comprehensive. Therefore, imbedded links to the ClinicalTrials.gov database are provided for readers who seek additional details. In-depth analyses of the database and associated expert opinions are also provided in these periodic commentaries.

Since early 2000, the ClinicalTrials.gov database became searchable using a limited set of descriptors. The total number of trials increased by an astounding 1260% from 3640 trials reported since January 2000 to 49,527 in January 2008 (Fig. 1 and Tab. 1). The greatest increase was from 2005 to 2006. Since the initial rollout of the JPharmSci “Drug Delivery Clinical Trials Database” in early 2008, there was an additional 69% increase in the total number of clinical trials registered in the database between 2008 and 2010. The growth in the number of clinical trials in the search categories we defined previously (e.g., biologic platforms, drug delivery systems and technologies, or diseases) increased proportionally with the total number of trials in the database (Fig. 1). As of January 2010, there were 83,683 trials listed in the ClinicalTrials.gov database from 172 countries worldwide, of which only 10% (8159) of the total number of trials included descriptors we identified as related to drug delivery system, technology or platform (Tab. 1). However, the number of trials in this category increased 101% between January 2008 and 2010. By contrast, the growth in the number of trials in the Biologics and Vaccines category, for example, is similar to overall growth of 60% over the past 2 years.

EMERGING TRENDS IN DRUG DELIVERY TECHNOLOGIES

Myriads of technological and computational advances have improved the probability of selecting the new molecular entities with safety- and efficacy-favorable PK or ADME (absorption, distribution, metabolism, and elimination) profiles for advancement to first-time-in-human studies with a greater probability of technical success. The battery of advanced computational tools available to scientists in the early phase of drug discovery and

development include *in silico* physicochemical or structural–activity relationship predictors, *in vitro* metabolism and *in vivo* animal models that predict human drug metabolism, absorption, tissue distribution, cellular transport and renal or biliary excretion properties of the drug candidates.⁸

However, the majority of these technologies or models do not take into account the difference in physiological processes and disposition characteristics in elderly⁴ or pediatric populations.⁵ Thus, the inclusion of these subjects for PK/PD characterization of the new medicinal entity in the early stages of drug development is critical to ensure that the final drug product has the optimal properties for minimal risk in these vulnerable patient populations.

We reviewed all available clinical trial information and summarized studies that included PK evaluation in drug delivery, biological platforms, and disease categories defined in our previous commentaries.^{1,2} In-depth analysis of the database on emerging trends in the clinical evaluation of pharmaceutical products for special populations was performed. These data were summarized based on reported inclusion criteria in the protocols for the three predefined age groups: up to 17, over 65, and adults between 17 and 65 years of age. The summary results are presented in Tables 1–4.

Analyses presented in Table 1 revealed that since early 2000 more than 50% of trials included elderly subjects greater than 65 years of age, as shown in the two representative categories: Biologics and Vaccines and the diabetes subcategory under drug delivery systems. This is evidence that investigators and sponsors understand the importance of including elderly subjects into clinical trials for evaluation of safety and efficacy. However, only a small fraction (5%) of these trials included PK assessments. The percentage of trials that included PK evaluation did not significantly increase over the past decade (Fig. 2A and B).

Table 2 presents the analyses of the database as of January 2010 by age groups in select categories of drug delivery system, platform or technologies. Less than 20% of these trials included PK evaluation. Less than 10% included PK evaluation in elderly subjects greater than 65 years of age, and less than 4% included PK evaluation in children less than 17 years of age.

In the analyses of trials that involve pharmacokinetic modulations as an approach to drug delivery (Tab. Table 3), the number of trials that included elderly subjects ranged from 51% to 77%; those that included children ranged from 12% to 24% of the trials. In the past 2 years (since the initiation of the JPharmSci “Drug Delivery Clinical Trials Database”), the percentage of trials that specifically included PK evaluation appeared to be stable (Tab. Table 4).

EMERGING TRENDS IN THERAPEUTIC AREAS

We also analyzed the trends in drug delivery trials according to therapeutic area or disease states. We employed the organ system or disease descriptors in the ClinicalTrials.gov database and nested the searches under drug delivery system descriptors.

A review of drugs under clinical testing from January 2008 to January 2010 revealed emerging patterns in protocol inclusion practice. A surprisingly high number of ongoing clinical trials recruited older subjects over 65 years of age. The percentage of trials that recruited elderly subjects range between 64% (behavioral and mental disorder) and 89% (cancer and cardiovascular diseases) of all trials in each disease category (Tab. 5). The percentage of clinical trials that reported the inclusion of children less than 17 years of age ranged from 15% (cardiovascular diseases) to 33% (AIDS). However, the statistics are misleading as only a small fraction of these trials included PK and absorption, distribution, metabolism, and excretion (ADME) assessment.

As shown in Table 5, cardiovascular disease, an area most highly associated with the aging population, has the highest number of clinical trials, accounting for 30% of trials in the drug delivery category; however, less than 1% included PK evaluations. The general trend we observed in the disease areas is that the percentage of trials that included PK evaluation in the elderly has remained low (<4%) and is consistently less than the studies that included the younger 18–65 age group. Diabetes is another disease of the aging population, with 40–50% of the global population >65 years of age. However, only 1.2% the trials included PK evaluation in the elderly population.

An analysis of the subset of the trials that included PK evaluation, expressed as percent of trials by age group, is shown in Figure 3. Cancer is the disease area with the highest percentage of trials that enrolled elderly patients >65 years of age (87%). Behavioral and mental disorders (40%) and diabetes (44%) are the two disease areas with the lowest percentage of trials that included elderly patients. For children <17 years of age, immune system disorders is the area with the highest percentage of trials (20%) and AIDS has the lowest percentage (14%) of the trials that enrolled children for PK evaluations. Whether such disparity is due to the lower prevalence of children with AIDS than those with immune disorder or some other factors is not clear. Regardless, it is evident that increasing effort is needed to include children in clinical trials for evaluation of PK/ADME, safety and efficacy of medicines that are likely to be used in this population.

Overall, our analyses reflect a significant gap in drug development to support optimal dosing strategies in the elderly and pediatric populations. The misalignment of trends in clinical trials with global concerns associated with the risks in these vulnerable segments of the population will require in-depth evaluations to better understand the root cause of the gap.

Alternative formulations or delivery methods of new medicinal products are often initiated as part of the life cycle development. Investigation of a new drug in special populations such as in the elderly, are often not considered as part of the core clinical program even though the investigation of safety and efficacy of a new drug in the elderly is becoming an important part of the New Drug Application (NDA) package filed with the FDA. However, elderly populations are often excluded in controlled formulation studies. Based on the estimated exposure differences in elderly, when adverse drug reactions occur, the risk is typically mitigated by a simple dose reduction at the cost of clinical benefits. In our opinion, this common practice and the industry guidance for development of drugs for use in special populations are somewhat dated. In fact, the latest guideline of ICH (International

Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) E-7 guidance on studies in geriatrics was published in 1994.⁶ A revision of this guidance, and several other guidance documents in special populations, is pending review (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM189544.pdf>).

Based on the continued expansion and availability of clinical trial data accessible through ClinicalTrials.gov, we have developed the JPharmSci “Drug Delivery Clinical Trials Database,” which is available online for regulatory, pharmaceutical and institutional research scientists. While this high-level summarization of the database identifies a potential gap in drug delivery discovery and clinical development, further refining of the database in the specific drug delivery areas of interest may be useful. It appears that the trend in increasing number of clinical trials did not correspond to increase in knowledge for optimizing the dosing strategy in special populations. A proposal to expand the clinical trial registry to include results of these trials⁹ may provide insights on the impact of drug delivery systems and clinical trial designs to help sponsors and regulators in optimizing dosing or drug delivery strategies that improve drug efficacy and safety.

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Figure 1. Increase in number of trials (total and select categories) registered in the ClinicalTrials.gov database between January 2000 and January 2010 (updated March 15, 2010).

Figure 2. Increase in number of trials in the Biologics and Vaccine (panel A) or the diabetes disease area under the drug delivery (panel B) category, registered in the ClinicalTrials.gov database between January 2000 and January 2010. Total, trials that included elderly >65 years of age and trials that evaluated PK in elderly >65 years of age are shown.

Figure 3.
Percent of clinical trials in different disease areas by age group.

Table 1

Number of Clinical Trials Reported Between 2000 and 2010

Date	Number of Trials in Each Category				% of Category Included Age >65		% of Category Included PK in Age >65	
	Total Trials	Biologics and Vaccine	Diabetes	Drug Delivery	Drug Delivery in Diabetes	Biologics and Vaccine	Drug Delivery in Diabetes	Biologics and Vaccine
January 2000	3640	672	314	73	2	65	50	2.5
January 2001	5616	950	522	115	7	69	71	2.4
January 2002	7002	1256	669	158	12	73	83	2.1
January 2003	8606	1480	819	203	14	74	86	2.4
January 2004	10,294	1779	1020	264	25	74	76	2.6
January 2005	12,103	2069	1196	306	29	74	79	3.1
January 2006	25,090	3109	2294	1500	105	69	78	3.1
January 2007	36,025	4212	3393	2593	185	66	77	3.4
January 2008	49,527	5419	4838	4059	293	66	77	3.9
January 2009	66,591	7049	6515	6064	431	66	78	4.6
January 2010	83,683	8745	8121	8159	565	65	75	5.1

Table 2

Trials Evaluating Drug Delivery Categories (Updated January 1, 2010)

Search Terms	Total	% of Total Included PK	% Trials Included PK in Age 18–65 (n)	% Trials Included PK in Age <17 (n)	% Trials Included PK in Age >65 (n)
Dosage form or formulation	10,371	17	16% (1611)	2.4% (247)	9.0% (935)
Biologics or vaccine	8745	7.0	6.6% (578)	1.5% (130)	5.1% (442)
Drug delivery device, technology or system	8159	2.1	2.1% (170)	0.2% (13)	1.3% (102)
Route of administration	437	1.5	15% (64)	3.2% (14)	10% (44)

Table 3
Pharmacokinetic-Based Trials as Percent of Total in Each Category (Updated January 1, 2010)

Search Terms	% of Trials in Drug Delivery (n=8159)		% Trials Included Age 18–65 (n)		% Trials Included Age <17 (n)		% Trials Included Age >65 (n)	
	Total							
Drug transport modulator	163	2.0	98% (159)		16% (26)		51% (83)	
Metabolic inhibitor	1497	18	98% (1469)		10% (149)		77% (1151)	
Drug interactions	1354	17	92% (1239)		24% (331)		52% (706)	
Metabolic induction	334	4.1	96% (322)		17% (57)		53% (178)	
Active metabolite	222	2.7	95% (212)		12% (27)		57% (126)	

Pharmacokinetic-Based* Drug Interaction Trials as Percent of Total in Each Category Reported Between 2008 and 2010

Table 4

Search Terms	% Trials Included PK		% Trials Included PK in Age 18–65		% Trials Included PK in Age <17		% Trials Included PK in Age >65	
	2008	2010	2008	2010	2008	2010	2008	2010
Drug transport modulator	33	30	32	30	4.9	5.6	12	14
Metabolic inhibitor	13	10	13	10	1.7	1.7	6.8	6.8
Drug interactions	37	33	36	33	2.5	4.2	13	16
Metabolic induction	11	12	10	12	1.5	1.2	3.0	4.7
Active metabolite	58	56	56	54	4.1	5.9	31	11

*Trials that specifically included “pharmacokinetics” as a search descriptor.

Table 5
Trials Evaluating Drug Delivery by Disease Category and Age Groups (updated January 1, 2010)

Search Terms	Total	Trials Included PK (%)	% Trials Included PK in Age 18–65 (n)	% Trials Included PK in Age <17 (n)	% Trials Included PK in Age >65 (n)
Cardiovascular diseases	2437	33 (1.4%)	1.3% (32)	0.1% (3)	0.7% (18)
Central nervous system	1545	45 (2.9%)	2.8% (43)	0.3% (5)	1.4% (21)
Cancer	939	31 (3.3%)	3.3% (31)	0.2% (2)	2.9% (27)
Behaviors and mental disorders	889	17 (1.9%)	1.7% (15)	0.2% (2)	0.7% (6)
Immune system	781	35 (4.5%)	4.4% (34)	0.9% (7)	2.7% (21)
Infection	688	26 (3.8%)	3.6% (25)	0.4% (3)	1.9% (13)
Digestive system	609	18 (3.0%)	3.0% (18)	0.3% (2)	2.1% (13)
Diabetes and endocrine	565	16 (2.8%)	2.8% (16)	0.0% (0)	1.2% (7)
AIDS	132	7 (5.3%)	5.3% (7)	0.8% (1)	3.0% (4)