Dose-response relationships in clinical pharmacology.
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EFFECT OF AGE ON THE DOSE RESPONSE CURVE

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INTRODUCTION

The development of clinical pharmacology has permitted a better understanding of the various factors influencing drug kinetics and drug response, thus permitting a more rational and safer therapeutic approach.

Among the various factors, age does surely play an important role both for drug disposition and sensitivity to drugs. It is in fact well known that the different physiological variables important for drug kinetics undergo continuous changes from birth to old age, and that receptor sensitivity and density do vary with age.

Drug responses may hence be modified by age. This should be taken into consideration not only when treating patients of various age groups but, also and more specifically, during the development of new pharmacological agents.

In fact in general drug ranging studies for either safety or pharmacodynamic and therapeutic effects are conducted, and dose/response curves established, in healthy young volunteers and middle aged patients. However the percentage of drug exposed individuals is lower in these age ranges while the higher percentages are found in Pediatric and Geriatric groups.

The need of a more correct definition of the dose/response curves in various age groups, together with a more refined kinetic analysis has been stressed by several Regulatory Bodies (1,2,3,4).

It is today evident that no new pharmacological agent should be put on the market without a precise definition of the optimal doses, not only for middle aged patients but also for geriatric patients. Depending on the class of the drug, studies in children should also be envisaged and carried out.

In the next pages I will try to illustrate the reasons for which a definition of the dose/response curve in various age groups is not only desirable but necessary.

PEDIATRIC PATIENTS

Existing data indicate that wide differences in drug pharmacokinetics may be found not only between neonates and adults, but also between preterm newborns, fullterm newborns, infants and children.(5,6,7).

As a rule, the absorption of an orally administered drug is poor and highly variable in neonates. In contrast, with a suitable formulation, optimal absorption may be achieved by rectal route. A wide variability in the rate and degree of resorption is observed following intramuscular administration. This is a consequence of the variations in muscle blood flows, of the reduced motor activity and the marked vasomotor instability.

In contrast, absorption and resorption of drugs are very effective in infants and young children, with peak concentrations higher and earlier than in adults.

The binding of acidic drugs to plasma proteins is usually reduced in neonates and infants, with higher concentrations in target organs as a possible result. On the contrary binding of weak bases may be increased in children (7).

The biotransformation of drugs, in the absence of exposure to enzyme inducers during gestation, is greatly reduced in the first two weeks of life.

A dramatic increase mainly affecting phase I reactions, usually occurs at approximately 15 or 18 days of life, the metabolic rate may exceed at 2 or 3 months of life 2-3 fold that in adults (6,7)

At birth, the renal function is globally reduced (glomerular filtration, tubular secretion), with as a result a limited capacity for eliminating drugs up to the age of 6-8 months (6,7).

In the neonate and the infant several pathologic conditions such as hypoxia, altered renal or gastrointestinal functions, heart failure, respiratory distress syndrome, etc., have very significant consequences on the pharmacokinetics of drugs and on their toxic and therapeutic effects. As a rule, all these conditions are responsible for a further decrease in the already low clearance capacities.

The maturing of physiological functions, which have a significant influence on drug pharmacokinetics, is neither a homogeneous process nor a predictable one, especially when certain pathological condition exists.

In addition to the described paharmacokinetic differences, which may partially explain a modified dose/response curve, differences in therapeutic and toxix thresholds in plasma drug concentrations between infants and children, and children and adults have been reported for theophylline, antipileptic, cardiovascular and psychotropic drugs (7-8-9-10-11)

In the light of the above it is evident that the definition of the correct dosage in a neonate and in an infant is a very difficult task. Such a difficulty is further increased by the low specificity of signs and symptoms that may be encountered in these two age groups.

In my opinion more than a classical dose/response curve which appears as rather questionable both on practical and ethical grounds, therapeutic drug monitoring appears as the indispensable tool for these two age groups.

Meaningful dose/response curves may on the contrary be more easily obtained in grow-up children, where in general the kinetic inter-individual variability is considerably reduced and the response profile is more homogeneous. In our experience the dose/response curve in children is steeper than in adults and if expressed on a mg/kg basis is shifted to the right of the curve observed in middle aged patients.

ELDERLY PATIENT

The pharmacological treatment of the elderly patient represent a therapeutic problem which, over the last decade has reached a totally unexpected dimension with important social, medical and economical implications (1,12).

According to the WHO (1), the prevalence of chronic illness increases 7 fold from the age group of 15-34 years (9 %) to the age group of 65-74 years (67 %). Concomitantly, disability and number of days of hospital increase. The number of concurrent illness increases also with age (13,14,15).

Recent estimates indicates that more than 50 % of drug consumption is by the elderly and polytherapy is present in more than 80 % of the cases (1,12,16,17).

In parallel we have been confronted with a dramatic increase in the prevalence of ADR in the elderly (1,16,18,19).Furthermore, not only the prevalence of ADR but also the severity is increased in the elderly with higher life threatening risks (20,21).

The causes conditioning such change in the incidence and severity of ADR in the elderly are multiple : alteration in homeostatic processes, preferential distribution in blood flow, changes in receptor sensitivity etc.

However the most important cause is probably the fact that for many drugs presently prescribed to elderly people, there is an astonishing lack of specific information on their pharmacokinetics and pharmacodynamic profile, on their dose/response curve, on their efficacy and safety profile in the geriatric patient.

Within this frame several Regulatory Authorities have put forward specific guidelines for drug development in the elderly (1,2,3,4). Such a request is totally legitimate, very sound and necessary, however when the issue is considered at pragmatic level the problem appears as a really difficult one.

Characteristics of the elderly

The elderly is currently defined as an individual aged 65 and over. This rather vague definition is totally meaningless, and the population so defined cannot be regarded as an homogeneous one.

In fact the "elderly population" defined by the chronological criterium is constituted by a wide spectrum of subjects going from the totally independent subject living alone in the community, to the mildly dependent relying on day care or day hospital, to the bed-ridden polymedicated institutionalized demented patient. (22)

The current definition of the elderly population needs to be completed by an overall assessment of physical and mental health, activity of daily living and co-medications in order to be able to characterize relevant sub-groups of elderly patients, who may respond quite differently to drugs.

It is generally accepted that the process of ageing is accompanied by a constant progressive involution of physiological functions (23). However this involution process is not uniform and is totally unpredictable with respect to both its onset and its rate of development. Surely it is not dependent on chronological age.

Several physiological variables (Fig. 1.) important for drug kinetics undergo this involutionary process (1,24,25,26,27,28).

CHANGES IN PHYSIOLOGICAL VARIABLES IMPORTANT FOR DRUG KINETICS INDUCED BY AGING

- Gastric emptying time = ↘
- Gastric pH = ↗
- Intestinal motility = ↘
- Splanchnic blood flow = ↘
- Absorbing surface = ↘

MODIFIED DRUG ABSORPTION

- Liver microsomal enzyme activities = ↘
- First pass effect = ↘
- Glomerular filtration = ↘
- Tubular secretion = ↘
- Tubular resorption = ↘
- Urinary pH = ↗
- Urinary volume = ↘

REDUCED DRUG ELIMINATION (METABOLISM . EXCRETION)

- Total body water = ↘
- Adipose tissue = ↗↘
- Plasma albumine = ↘
- Plasma globulins = ↗
- Red blood cells = ↘
- Distribution volume = ↗ ↘
- Cardiac output = ↘
- Hepatic blood flow = ↘
- Renal blood flow = ↘
- Cerebral blood flow = →↘
- Vascular permeability = ↘

ALTERED DRUG DISTRIBUTION WITH PREFERENTIAL UPTAKE IN VITAL ORGANS (HEART-BRAIN)

Figure 1.

Is generally assumed that they may play an important role in the modified response to drugs observed the elderly. However their role has probably been over-emphasized and the other factors such as alterations in the homeostatic processes, preferential blood flow to vital organs (such as heart and brain) and alteration of receptor sensitivity (16,17,23,29,30,31,32,33) should be taken into consideration.

Ageing and/or pathological processes affect homeostatic mechanisms involved in the regulation of main physiological functions (43) leading to a decreased functional reserve of the systems involved. We may recall as examples the decreased in baroreflex sensitivity, the decrease in efficiency of the autonomic nervous system, of the body water regulatory mechanism, or of the control of ventilation (33,34,35).

The impairment in homeostatic mechanisms may lead to :

- a decreased capability to adapt to less than optimal situations with consequent increased sensitivity to environmental factors and thus increased interindividual variability.
- a possibility of paradoxical responses (36,37).

The alteration of homeostatic capabilities may hence allow the expression of side effects which in younger individuals are easily compensated by an efficient homeostasis. An example is given by the orthostatic hypotension due to vasodilators or CNS agents, which is frequently magnified in the elderly.

Furthermore, the specificity and sensitivity of signs and symptoms is altered in the elderly (38,39).

In fact, if in middle aged or young patients a sypmtom is generally ascribable to one specific disease, in the elderly the same symptom may be seen in the context of several different conditions. This is true not only for physical signs but also for cognitive disorders and biochemical data. Memory impairment, for instance is frequently observed in the context of depressive or anxious reactions and should not be uncritically ascribed to senility (39).

Similarly an important decrease in renal function (with marked decrease in creatinine clearance) may occur in absence of any significant increase in serum creatinine levels because of parallel diminution of endogenous creatinine muscular production (44).

The sensitivity of symptoms is also decreased. Pain threshold is frequently altered so that severe events like myocardial infarction, gastric perforation or even hip fractures may occur nearly unnoticed (15).

The preferential distribution of blood flow to vital organs associated to reduced plasma protein binding may lead to an higher drug up take by brain and/or heart. This may partially explain the higher incidence of CNS side effects noticed in elderly with highly liposoluble drugs (25).

Finally a modified receptor sensitivity may be the basis for increased or decreased drug responses observed with various therapeutic agents such as opiates, antidepressants, warfarin, benzodiazepines and ß adrenoceptor agonists and antagonists (Fig. 2.).

These aspects of the pharmacology of ageing have been somehow neglected and surely a more systematic approach would help in better understanding the "increased drug sensitivity in the elderly".

DRUG	EFFECT IN OLD AGE
Warfarin	↑anticoagulation
Nitrazepam	↑impairement of performance
Diazepam	↓dose for CNS Depression
Diazepam	↓dose for intubation
Diazepam	↑body sway
Temazepam	↑body sway and reaction time ↓CNS arousal
Chlormethiazole	↑body sway and reaction time ↓CNS arousal
Dichloralphenazone	↑body sway
Isoprenaline	↑dose for tachycardia
Propranolol	↑dose for block of isoprenaline-induced tachycardia
Propranolol	↑dose for block of exercise-induced tachycardia

Figure 2.:Alteration in drug response in old age occuring in the absence of significant pharmacokinetic changes

It is clear from the above that specific studies for dose/response curve have to be carried out in the elderly, and that when doing such studies different sub-groups should be considered. However before trying to indentify the various sub-groups, there is still a general issue which is worthwhile to discuss: the assessment criteria.

The correct assessment of the clinical efficacy and safety profile of any drug in the elderly is not an easy task. One principle reason is an astonishing lack of normative data for most of the physiological and cognitive functions as well as for clinical chemistry data for people over 70 years. As already mentioned symptoms are frequently attenuated (15) and the usual assessment criteria may fail in evidentiating a difference between pretreatment and during treatment conditions.

Furthermore the very frequent presence of polytherapy and concomitant diseases makes very difficult the attribution of any signs to the tested drug.

Because of all this a meaningfull evaluation of drug/response curve should be constructed applying more strict criteria than in adults and utilizing:

- multiple measures over time;
- placebo in order to define possible confounding factors;
- group oriented normative data.

It is also evident that multivariate statistical analysis should be applied whenever possible.

Which elderly ?

As mentioned earlier the word "elderly" defines a rather abstract non-existing population or better, encompasses a series of sub-population widely different with respect to both physical status and response to drug treatment (40-41). We feel that dose/response curves should be defined in most representative groups of possible users in various age sub-group (i.e: 65-75; 75-85; F 85 years).

For each of these age groups, we could define as users:

- active home-living subjects;
- diseased home-living polymedicated subjects ;
- diseased institutionalized polymedicated subjects.

For each of these sub-groups, we should also carefully define several parameters such as cardiac, hepatic, renal functions, arterial blood pressure, together with cognitive and psychomotor capabilities.

This type of evaluation should permit to estimate the "differential risk" in the various pathological situations, and avoid the constructing of a hypothetical dose/response curve in a "theoretical" elderly.

CONCLUSIONS

As described above various factors conditions different dose/response curves in various ages. Data obtained in young or middle aged patients cannot be extrapolated to pediatric or geriatric patients, furthermore different subgroups should be considered both in pediatrics and in geriatrics.

In general (excluding newborns, a group which has to be considered separately) we may expect a steeper curve with less interindividual variability and reduced dose ranges in children, while in the elderly, because of the increased interindividual variability in drug response, the dose/response curve is more flat and, shifted to the left of the adult one.

The definition of the optimal dosage is more aleatory unless various sub-groups are specifically identified.

More data are needed on this issue, more specific studies are needed, but in order to be meaningfull, validated assessment criteria and procedures should be made available through a collaborative effort among Universities, Governamental Agencies and Pharmaceutical Industries.

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Discussion - Effects of age on the dose-response curve

B.P. du Souich

I think that every time the volume of distribution of a drug is altered, we don't know what to do with dosage since, in fact, changes in distribution may modify the concentrations at the effector site.

P.L. Morselli

I agree. I think the volume of distribution is much more meaningful than it is often realized.

L.F. Prescott

One of the things that bothers me in the elderly and which causes a great deal of trouble in clinical practice, is the increased variation. Textbooks may say that the mean half life of a drug is twice as long in the elderly, but that doesn't tell you that the spread is much greater than in younger people, and those at the extreme upper end of the range are the ones that can get into very serious trouble. I wonder if there is any way of predicting which of these elderly individuals is in that very vulnerable state. On the other hand, it would be very interesting to know whether they are also more susceptible on a pharmacodynamic basis.

P.L. Morselli

As far as receptor sensitivity is concerned, there are indications that in elderly people a number of receptors may be reduced, but homeostatic mechanisms may also fail. I think that the elderly exhibits a reduced sensitivity or, better, a modified sensitivity which modifies the response to drugs. Unfortunately there is no systematic information about this and I think this is an area where a collaborative effort between the pharmaceutical industry, regulatory bodies and universities is needed.

E. Perucca

Do you have any explanation for the increase of the hepatotoxicity of valproic acid in the age below 2?

P.L. Morselli : No. I have no explanation.

D. Lalka

Have we any substantial information as of this date regarding the changes in the distribution of the P450 isozymes as a function of the age and, if that data is not available, say from autopsy material, have we good information in animals?

P.L. Morselli

I can't answer your question, maybe Dr. Davies has some information.

D.S. Davies

Not in the elderly. In the newborn, as you probably know, there is a relative absence of certain forms of cytochrome P450, which then develop, but I am not aware of any information on liver samples from elderly patients.

J. Lahuerta

You have mentioned that the perception of pain is diminished in the elderly. Do you have any ideas why this should occurr?

P.L. Morselli

I do not remember of any specific study that could answer your question, but I think that many sensory inputs, among them pain, arrive at a lower intensity in the elderly.

R.J. Temple

I don't know about iso-enzymes, but there are a number of instances that suggest that there is a decline in oxidase functions with age, that may even be sex-related. That has been shown for lidocaine and a number of other drugs.

E.A. Carr

I agree that it is good to have data on "normal" aged individuals but what will the criteria of normal be? When we take normal volunteers from a population, we get their blood chemistry, ECG etc. As we know the normal values for younger people, we can use such data as proof of their normality. If we want to find

out what the values are in the normal individual who is aged, what criteria of normality will we use, functional criteria? How will one decide that certain aged individuals are normal, in order to say their bood chemistries, ECG, etc. can be used as standards in other aged people?

P.L. Morselli

As I said, I think this is something which should be addressed and solved by different groups working together. Three different categories should be considered: a) functionally active individuals, b) individuals with limitation in mobility, and c) individuals with impaired social life.

L. Lasagna

I think that it is worth remembering that the National Institute on Aging in the USA has shown, from longitudinal studies on originally healthy people, that a significant number of quite elderly people have renal function that is indistinguishable from that of healthy young adults, which means that with something like an aminoglycoside antibiotic if one uses the same lower dosage in all the elderly patients one is going to undertreat a great number of them.