Florida, U.S.A.

" ... the physician's grotesque system – the emptying of miscellaneous and harmful drugs into a person's stomach to remove ailments which in many cases the drugs could not reach at all" Mark Twain, 1900

Pharmakokinetische Konzepte und ihre Bedeutung für die klinische Medizin

Zusammenfassung. In der Geschichte der Medizin findet sich eine große Anzahl von Beispielen für den Kampf von Ärzten mit dem Problem der korrekten Dosierung von Medikamenten. Rezente Studien belegen, dass die mit Arzneimittelgabe-assoziierte Mortalität nach wie vor eine Haupttodesursache darstellt, welche nur durch kardiovaskuläre Krankheiten, Krebs und Schlaganfall übertroffen wird. Zur Rationalisierung der Arzneimitteltherapie wurden in den frühen 70er Jahren pharmakokinetische Prinzipien der Arzneimitteldosierung, hauptsächlich in Form des Therapeutic Drug Monitoring (TDM) in die klinische Praxis eingeführt, eine Maßnahme, die zu einer Reduktion der Arzneimittel-assoziierten Mortalität geführt hat. Inhärente Limitationen der traditionellen Pharmakokinetik (PK) führten jedoch bei vielen Ärzten zur Ansicht, dass klinische PK eine Fleißaufgabe mit beschränkter klinischer Relevanz sei. Trotz dieser Vorstellung kam es in den letzten Jahren zu einigen bemerkenswerten Entwicklungen, die aus dem Gebiet der klinischen PK eine auf physiologischen Mechanismen basierende Disziplin mit wichtigen Implikationen für die klinische Medizin gemacht haben. Insbesondere konnte durch die neuen Konzepte (1) PK-PD (Pharmakokinetik-Pharmakodynamik)-Modeling, (2) Zielgewebs-PK, (3) Populations-PK und (4) Pharmakogenetik eine bessere Integration pharmakokinetischer Prinzipien in die klinisch pharmakologische Therapie ermöglicht werden. Der vorliegende Artikel versucht einen Einblick in diese Entwicklungen und deren Bedeutung für das allgemeine Verständnis der Arzneimitteltherapie zu geben.

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Schlüsselwörter: Klinische Pharmakokinet
sche Pharmakodynamik, Dosierung, Gegenwärti
zepte.

Summary. The history of medicine provides
evidence of the physicians' struggle with the su
appropriate drug dosing. Recent studies indica
drug-related mortality due to inadequate dosing pr
still is a leading cause of death, only surpassed
diovascular diseases, cancer and stroke. In an
rationalize drug therapy, pharmacokinetic (PK) pr
were introduced in medical practice in the early
mainly in the field of therapeutic drug monitoring
This measure was shown to reduce mortality. Sev
itations in traditional PK, however, have led to th
among many physicians that clinical PK is an u
sary assignment of limited clinical relevance. Des
perceived limitations of traditional PK research,
able developments have taken place in recent ye
have made clinical PK a "physiological-mechanism
endeavor" with important implications for clinica
cine. Notably, the introduction of (1) PK-PD (pha
kinetic-pharmacodynamic) modeling (2) target site
population PK and (4) pharmacogenomics has pe
better integration of PK principles into clinical dr
apy. The aim of the present article is to prov
overview of these developments and to discuss t
pact on our understanding of clinical drug therap

Key words: Clinical pharmacokinetics, clinica
macodynamics, drug dosing, current concepts.

Introduction

A brief historical view of clinical pharmacoki

The word "pharmacokinetics" is derived fr
Greek words "pharmacon" (drug) and "kinesis" (m
and was first mentioned in a textbook by the Ger
diatrician Friedrich Hartmut Dost in 1953 [1]. Th
paid credit to recent advances in a newly establishe
which tried to describe the events that govern the
a drug in the human body. One of the first applica

[8–20] – including eminent personalities like Vincent van Gogh [20], Wolfgang Amadeus Mozart [16, 17, 19] and Nicolo Paganini [18]. It was often not clear whether a patient died due to the disease itself or due to the cure that was administered by the physician. This unfortunate situation led Mark Twain in 1900 to decry ".. the physician's grotesque system – the emptying of miscellaneous and harmful drugs into a person's stomach to remove ailments which in many cases the drugs could not reach at all" [21]. In the subsequent decades physicians struggled with the subject of appropriate drug administration. Digitalis was a notoriously "difficult to dose drug" [20] and the narrow effect side effect profile was well known to readers of Agatha Christie thrillers, in which digitalis was used 6 times in a total of 83 cases of lethal poisoning [20]. Similar to digoxin, the synthetic antimalarial agent quinacrine which was developed during World War II as a substitute for the scarce quinine, was either ineffective or produced unacceptable toxicity [22]. Only after its pharmacokinetics (PK) was described and it was realized that large doses had to be given initially, followed by small daily doses, could quinacrine be used successfully [22]. An abundance of similar experiences with different drugs led to the development of an independent research field of clinical PK. From 1950 to 1980 the science of PK became an integral part of drug development and also assumed a significant role in clinical practice [5, 23].

Current status of PK in clinical drug use

Clinical PK emerged as a clinical discipline in the early 1970s. Initially it was largely concerned with therapeutic drug monitoring (TDM), i.e. the measurement of plasma drug concentrations to guide drug dosing. Drugs usually are suitable candidates for TDM, provided they have substantial pharmacokinetic variability, a narrow therapeutic index, and provided a concentration-effect relationship is established. Commonly monitored drugs are aminoglycosides, vancomycin, teicoplanin, theophylline, methotrexate, digitalis glycosides, cyclosporin, and several antiepileptic agents. TDM was advocated for optimizing the use of other selected drugs as well [24]. The widespread acceptance of clinical PK in the pharmaceutical care process was triggered by reports on reduced mortality, shorter duration of treatment and hospital stay, decreased morbidity, and less adverse effects from drug therapy due to TDM [25].

current principles of drug therapy might be suboptimal, adverse drug reactions are a leading cause of death in ho pitals [29–32]. It was shown that 0.32% of hospitaliz patients became victims of fatal ADRs. Consequently t authors estimated that, in the USA, 106,000 patients p year had fatal ADRs, making these reactions the four leading cause of death, only surpassed by cardiovascul disease, cancer and stroke [29]. This rather alarming fin ing, which is not very much unlike the situation in t times of Mozart and Paganini, was attributed in part to i sufficient knowledge of PK principles and individual do ing principles in many clinical specialties [29]. Intere ingly, programs that survey drug therapy according clearly stated principles were shown to reduce the nu ber of drugs per patient, the number of drugs in hospita and also the number of ADRs [20, 25, 31, 33–35].

Current status of PK in drug development and drug use

Whereas PK principles were rather hesitantly e braced in routine care, they are of paramount importan in drug development [36, 37]. Clinical drug developme programs are faced with the challenge of identifying ea on those drug candidates that will successfully make through the costly and time-consuming phase III and eve tually enter the market. Experience shows that reasons candidate attrition are varied and include problems relat to tolerability, pharmacokinetics and lack of adequate fectiveness [37]. While in some instances tolerabil problems cannot be spotted until large numbers of patie have been exposed, discontinuation of a development pr gram due to poor pharmacokinetic (PK) properties usua occurs early during phase I/II studies. The fact that ev today candidate development is sometimes discontinu merely for (predictable) PK-related reasons during or ter phase III [38] testifies to the importance of PK ch acterization by clinical management.

Traditional concepts in clinical PK – descriptiv pharmacokinetics

The old dream of an optimal dose

Dose individualization, i.e. giving the right dose the right patient, has long been a preoccupation of cli cal pharmacologists who justly railed against the comm practice of administering a standard dose to all patien

ance of antileukemic agents, which usually differs by a factor of 3 to 10, is an important predictor of outcome [26]. Outcome could be improved when doses were individualized to prevent low systemic exposure to the drugs in patients with fast drug clearance. Children who received individualized therapy had a significantly better outcome than did those given conventional therapy, and the time-dependent systemic exposure to methotrexate was significantly related to the risk of early relapse [26].

The traditional LADME system and its limitations

PK studies are usually tailored to the characteristics of the individual drugs in order to obtain as much information as possible on so-called LADME events, i.e. liberation (L), absorption (A), distribution (D), metabolism (M) and elimination (E). Traditional PK approaches have provided a large body of information on LADME events, which have had a major influence on the drug armamentarium that is available to combat various diseases.

One limitation of traditional LADME studies was fact that they were focused on plasma concentration measurements and paid little attention to the distribution of the substance into the anatomically defined target site. Whereas L, A, M, and E events were described directly for many years, D events could not be measured directly and were usually indirectly modeled from plasma concentration curves. This approach implied a seldom communicated consensus on the fact that concentrations in so-called "deep" or "shallow" compartments have no actual anatomical correlate and do merely represent virtual values in hypothetical spaces. Although plasma-based modeling procedures help us to understand certain principles of drug distribution, their value is clearly limited if plasma and tissues are not in full equilibrium, as is the case in blood-tissue barriers e.g. in the brain. However, it should be remembered that a number of other barriers besides the blood brain barrier exist in the body, e.g. blood-prostate, blood–eye, blood-ear, blood–placenta or blood-tumor barriers [40–43], which either develop physiologically during organogenesis or might develop during pathological processes. Other limitations of traditional PK approaches were the need for rich data sets in individual patients, the lack of predictability for the variability encountered in the population, and a paucity of models that would allow for correlating concentration values to drug effects.

Most of these limitations have also led to the belief

the above mentioned limitations of the traditional L
system have been resolved by the introduction o
methodologies. Thus we have entered a phase in
clinical PK has indeed become a "physiological-
nism based endeavor" [5] with important implicat
clinical medicine.

Novel concepts in clinical PK – predict
pharmacokinetics

In recent years 4 new developments in PK h
to major advances in understanding and defining dr
apy, i.e. (1) PK-PD (pharmacokinetics-pharmaco
ics) modeling by the integration of drug effects, (
ulation PK by the integration of population variabi
target site PK by integrating anatomically defin
distribution, and (4) pharmacogenomics by truly i
ing individual PK parameters.

1. Integrating drug effects – PK-PD model

It was realized that the usefulness of mere P
ies is quite limited if PK is viewed isolated from p
codynamics. The science of PK/PD creates a bri
tween these 2 classical disciplines of clinical pha

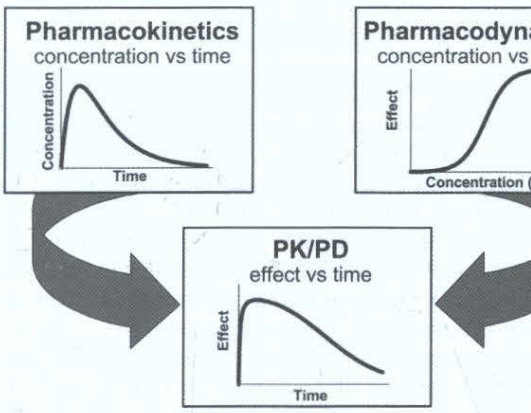

Fig. 1. Basic concept of the PK-PD (pharmacokinetic-p
codynamic) approach. Based on time versus concentrati
surements (top, left panel) and known relationships
drug receptor effects and drug concentrations (top, righ
an integrated model is constructed that allows for
variant description of the effect profile (bottom pa

ical routine, as it became clinical practice to administer gentamicin as a high dosed i.v. bolus – rather than as an i.v. infusion with plasma concentrations above a static threshold value – the MIC. Long times above MIC threshold values do not contribute to increased efficacy and lead to severe side effects. Aminoglycosides are a good example to demonstrate that the effect and side effect profiles of drugs may be determined by different PK profiles, and that it makes good sense to elucidate such mechanisms in order to fully exploit the therapeutic options of a given drug. β-lactams, in contrast, should be administered in a way as to keep target site concentrations above MIC values without sub-MIC windows [46]. A further example of the usefulness of PK-PD in clinical practice was the realization that the infusion rate of nifedipine is an important determinant of its antihypertensive effect. Due to reflex mechanisms, the same dose given as a fast release formulation is much less effective than when it is administered as a slow release formulation [47]. Similar relationships which could help to dissociate therapeutic effect and side effects were described for 5-fluorouracil; continuous infusion led to a better effect / side-effect profile than bolus administration [48].

2. Integrating population variability – Population PK

Population pharmacokinetics (Pop PK) is the study of the sources and correlates of variability in drug concentrations among patients. Certain demographic or pathophysiologic features such as body weight, excretory and metabolic function and disease characteristics are liable to alter dose-concentration relationships. However, PK data were frequently obtained from healthy volunteers and it is questionable whether these data reflect those in a given patient population. In fact, it was realized that the variability that occurs in the "real life" clinical situation is critical for drug therapy and the occurrence of adverse events [49, 50].

Pop. PK aims at collecting PK data from patients who are representative of the target population to be treated, tries to identify and explain causes for variability and gives a quantitative estimate of unexplained variability. This approach is currently gaining importance in drug development and the FDA reported that, in the fiscal years 1995 and 1996, one quarter of new drug submissions contained pop. PK data sets [50]. The mathematical background of

ments from several individuals (top panels) an integrated mod
is constructed. The model allows for a time variant descriptio
of the concentration profile and enables the investigator to re
late pharmacokinetic variability to individual parameters suc
as clearance, weight or disease status (bottom panel)

pop. PK is relatively complex. The principle is to compar
individual concentration data sets with the collective dat
set and to regard individual parameters such as weight a
individual specific covariates. The probability of distrib
ution of the concentration data is then modeled as a func
tion of these covariates. One major advantage of pop. P
is that the approach is also feasible for sparse data set
i.e. when only few data points are available per patien
(Fig. 2). The pop. PK approach is particularly useful fo
defining the influence of physiological as well as patho
logical conditions on PK in a target collective of patient

3. Integrating drug distribution – target site PK

Most drugs, with few notable exceptions such as he
parin, exert their effects not within the plasma compar
ment but in defined target tissues into which drugs wi
have to distribute from the central compartment. Unfortu
nately a complete and lasting equilibration between bloo
and tissue can by no means be taken for granted [40–4
51] and several studies have shown that tissue concentra
tions are more predictive of outcome than plasma con
centrations [52, 53]. This fact, which is best establishe
for CNS diseases, is also taken into account in locoregion
strategies for drug application e.g. intraarterial or in
trathecal chemotherapy [54].

Despite the perceived inability to directly measu
drug concentrations in tissues, several clinical metho
have become available, which enable us to trace the pa
of a drug within the human body [37, 52–58]. Autorad
iography, post mortem organ sampling and homogeniz
tion have been available for many decades and yield son
information on drug distribution into individual organ
but, for obvious ethical reasons, were frequently off lim
its for clinical drug studies. The last few years have wi
nessed the development of novel techniques that are sui
able to study tissue PK in humans, i.e. magnetic resonan
spectroscopy (MRS, [52]), single photon emission com
puted tomography (SPECT, [55]), positron emission to
mography (PET [56], Fig. 3) and in vivo microdialysis [4
58]. By applying these techniques to clinical studies it b

Fig. 3. Representative PET images of human subjects following administration of [18F]trovafloxacin. The area of maxi sue trovafloxacin concentration on each image is represented as 100% on the color scale. Reprinted from Fischman et a macokinetics of [18F]Trovafloxacin in Healthy Human Subjects Studied with Positron Emission Tomography", Anti Agents and Chemotherapy, August 1998, pp 2048-2054, Vol. 42, No. 8; with permission from the American So Microbiology

came obvious that the previously neglected drug distribution process to the target site might be an important determinant of clinical outcome and contributes more to variability in the dose-effect relationship than variability in plasma PK.

4. Integrating individual parameters-pharmacogenomics

Physicians have long recognized a familial clustering of unusual responses to drugs. In 1957 Motulsky published an article on a number of genetic conditions as the cause for a toxic reaction to a drug or an environmental chemical [59]. Vessel and Page showed that the large interindividual variability in PK vanished within sets of monozygotic twins [60, 61]. Genetic polymorphisms may occur at different levels in the drug-effect cascade, i.e. at the level of drug targets like receptors, at the level of disease pathways or at the level of drug metabolism [62]. Genetic polymorphisms of metabolic enzymes are important determinants of PK profiles and, thereby, also of toxicity and drug response [62].

The first pharmacogenetic discovery that became a routine aspect of medical practice was the observation that hemolysis was more common among African-American soldiers in the United States Army who were taking the antimalarial primaquine during World War I. Subsequent studies revealed a genetic deficiency of glucose-6-phosphate dehydrogenase as the reason for this serious side effect and it became good medical practice to screen patients for this enzyme defect prior to initiating primaquine therapy [63]. One example for genetic determination of a clinically relevant PK profile is intolerance to 6-mercaptopurine, a standard anti-ALL drug. Extreme intolerance was shown among patients with deficiencies in thiopurine S-methyltransferase (TPMT) enzyme activity. R doses of 6-mercaptopurine in TPMT heterozygot deficient patients permitted the administration of tocol doses of other kinds of chemotherapy whi taining high thioguanine nucleotide concentratio Genotyping, or functional enzyme analysis, has standard practice in major cancer treatment cent as the Mayo Clinic in Rochester and St. Jude's Research Hospital in Memphis [64]. Pharmacog has also provided a number of useful surrogate ters for disease–drug interactions such as polymo for the ACE gene and responsiveness to ACE in mutations in potassium channel genes and their tion with drug induced long-QT syndromes, expre HER2/neu and benefit of adjuvant chemotherapy cancer or polymorphisms in 5-HT2A receptors, a tance to antipsychotic drugs [62].

The opportunities created by recent concep methodological advances in molecular biology w a great impact on drug therapy [65]. Most importa will help to select optimal drug candidates for in patients and avoid unnecessary adverse events by ing a fingerprint of the patient's individual genetic

Conclusions and outlook on the role of principles for patient care

Clinical PK is and will be increasingly regu the above developments and by a further refineme alytical and computational facilities. Thus, by ext ing the last 10 years of PK research it is very likel different trends will emerge in the future.

(1) The revolution in genetics will allow for a tr vidualization of drug therapy. This developm

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