Pharmacokinetic reasoning

Per Hartvig Honoré

Dosing of drugs is an art and a science. Scientific-based dosing is based on pharmacokinetics and knowledge of the positive and negative effects of the drug. Evaluation of dose strength, dose interval and eventually dosing length is based on measurement of drug concentration over time in the blood, the body or the urine. The relation of drug concentration to effect over time is expressed by simple mathematical expressions. The different relations are expressed in a series of technical terms such as bioavailability, volume of distribution, elimination rate, ED_{50} (effective dose for 50% given it) and clearance, assuming that the processes of pharmacokinetics and pharmacodynamics are linear and non-saturated.

The technical terms form a language for expert pharmacokineticists to talk and understand pharmacokinetics and to use for dose suggestions. For others, in the beginning they have a high degree of abstraction. The relation to normal physiology, pathophysiology and drug-induced changes is difficult to see and to use. Therefore, it is essential to point out that pharmacokinetics has its base in physiology and quantitative drug characteristics. This is a knowledge base that has been termed pharmacokinetic reasoning.[1]

Pharmacokinetic reasoning is the concept of: *From pharmacokinetic parameters and the relation to the pharmacodynamics understand the physiology for drug disposition in other terms and to get understanding on its mechanism of action and an integration of PK-PD into biological meaning giving basis for execution of trials and for safety sciences*.

Pharmacokinetic reasoning opens up a mechanism-based pharmacokinetic–pharmacodynamic domain enabling the elucidation of normal physiology or pathophysiology; understanding the site of action of the drug; understanding the mechanism of action of the drug; and separating physiological changes from the effect of the drug.

There are many problems to be solved by pharmacokinetic reasoning. What is the mechanism of action of acetaminophen and where is its target? Acetaminophen has been acclaimed to be a weak cyclooxygenase inhibitor, a monoamine oxidase blocker and a free radical scavenger, among other things. The fraction bound to plasma proteins is relatively low, the volume is large, and clearance and bioavailability are high. Recent evidence points to acetaminophen acting as a cyclooxygenase inhibitor, although weak and by use of pharmacokinetic reasoning it is evident that the site of action is in the brain. The brain distribution of acetaminophen is high due to high volume and the free fraction being large. This results in a rapid and high brain concentration but with limited effect duration. The tentative pharmacodynamics also fits in with the clinical properties of acetaminophen with a rapid onset of action within an hour. How do these acetaminophen characteristics compare with non-steroidal inflammatory drugs (NSAIDs)? NSAIDs have a very low free plasma drug concentration, hence giving rise to a low volume of distribution. The clearance is highly different, giving a variable dosing interval. Looking at effect properties, they also have a rapid onset of action and are not compatible with the very slow distribution and low perfusion into, for example, the joint. Indeed, NSAIDs are also agreed to have a target on the prostaglandin system in the brain. Brain distribution is rapid but low and the high potency as cyclooxygenase inhibitors will give a good central nervous effect on analgesia. Early pharmacokinetic reasoning could address the long unresolved question of mechanism of action of acetaminophen.

Changes in normal physiology can also be deduced from pharmacokinetic reasoning. Running changes the blood flow to a more central localisation, resulting in higher digoxin blood concentration.

Why is the dose higher per kilogram of aminoglycoside in the neonate compared with older children and adults? (for answer see page 144).

In daily life we need pharmacokinetic reasoning to understand and give relevant dose recommendations, but also to understand unexpected changes in drug effects or in deterioration of symptoms induced by the pharmacokinetics and pharmacodynamics of the substance. Pharmacokinetic reasoning should be included in all dose discussions. This would require extensive training but would benefit patients and give healthcare personnel a sound view of drug influences on physiology, not necessarily resorting to the technical terms or mathematical calculations not absolutely relevant to the clinical situation.

There are many more examples. Please report them as a contribution to this journal.

Correspondence to Professor Per Hartvig Honoré, Department of Drug Design and Pharmacology, Faculty of Health Sciences and Medicine, University of Copenhagen, Universitetsparken 2, Copenhagen 2100, Denmark; peh@farma.ku.dk

Competing interests None.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Hartvig Honoré P. *Eur J Hosp Pharm* 2013;**20**:68.

Eur J Hosp Pharm 2013;**20**:68.
doi:10.1136/ejhpharm-2012-000271

REFERENCE

1 Gabrielsson J, Dolgos H, Gillberg PG. Early integration of pharmacokinetic and dynamic reasoning is essential for optimal development of lead compounds: strategic considerations. *Drug Discov Today* 2009;14:358–72.

Eur J Hosp Pharm: first published as 10.1136/ejhpharm-2012-000271 on 20 February 2013. Downloaded from http://ejhp.bmj.com/ on April 9, 2024 by guest. Protected by copyright.