Stochastic Approach to Pharmacokinetics *vs* Principles of Quantum Mechanics

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Introduction

A stochastic modelling in pharmacokinetics [1,2] is an important method of tracking the fate of endo- as well as exogenous substances in the organism. These mechanistic models provide a statistical description of the behaviour of single molecules of the investigated compound. Their mechanistic character is of great advantage. A systematic description of stochastic modelling in pharmacokinetics was given by Rescigno [1]. Nanocarriers, which can be viewed as nanocompartments, constitute a very attractive field of application of these models. However, to ensure true mechanistic character of the model being created, one should be very cautious not to come into conflict with the fundamental laws of nature. In certain textbooks as well as in scientific papers one can read: *The net effect of … entero-hepatic recirculation is that each bile salt molecule is reused about 20 times, often two or three times during a single digestive phase* [3]. Zhao, Li and Yang claim: *… little research has been done to systematically determine the probability for a drug molecule to follow a specific traveling route* [4]. Their paper (and some others [5]) is based on the concept of *the probability P_{ij} for a drug molecule in compartment i at time 0 to end in compartment j after an elapsed time t.*

Objectives

The purpose of the present study is:

1. to indicate that the abovementioned concept of travelling route becomes meaningless in the presence of many identical molecules.
2. To suggest a direction in which to search for a solution.

Theoretical

As far as one considers a single molecule, it is possible, at least in principle, to watch its trace. However, the number of molecules is of order in range $10^{17} - 10^{20}$ and then their tracking is excluded by the principles of quantum mechanics, namely the indistinguishability of identical particles [6]. Each particle can be localized with a limited precision, corresponding to the dispersion of its wave function. Consider two identical molecules, A and B, initially well separated in space. If later their wave functions get in contact, then one can no longer say which of them is A and which is B, and even posing such a question makes no sense. That particles as large as many drugs or some nanocarriers still demonstrate their quantum properties has been demonstrated with C_{60} fullerenes [7].

For illustration, consider a one-dimensional example, which one can view as a simple model of pharmacokinetic compartment. A particle (e.g. drug molecule) is initially placed in a compartment. Walls of that compartment prevent the particle from leaving. The interaction between particle and walls may be modelled by a square potential (Fig. 1). If a kinetic energy of the particle is less than V_0, then in classical physics the particle cannot pass through the barrier.

But it is possible in quantum mechanics and that phenomenon is called a tunneling effect. The probability that a molecule stays in the compartment decreases exponentially in time, as in classical pharmacokinetic model. The difficulty arises, when many molecules are present. Even if one can neglect interaction between them, they are not independent, because of indistinguishability of identical molecules. This requires reasoning other than in classical stochastic models, where independence of particles is assumed. Though under certain assumptions the final course of the drug concentration in time may be the same as in a classical modeling, one can expect moderate discrepancies, if the number of molecules is small, what can be important in the nano-world.

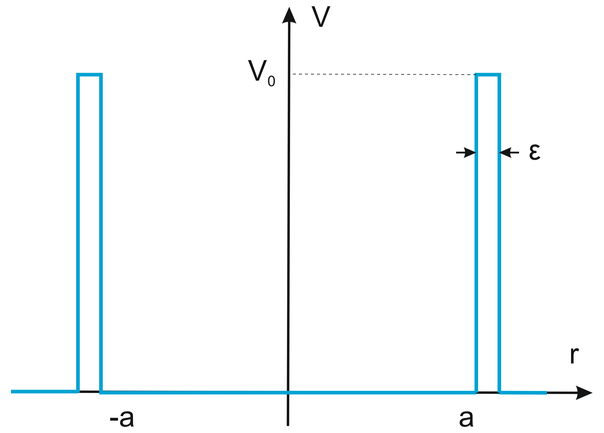

Fig. 1 Simple potential describing PK compartment.

Conclusions

One cannot say about the route of the molecules or count their visits in particular compartments. This is not necessary, though. An effectiveness of drug action or physiological process can be expressed in other manner, not violating laws of nature. Stochastic modelling can and should be done by means of correctly described quantum states. It is especially important in nanopharmacokinetics [8] which should also appear a quantum pharmacokinetics.

References

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