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A fresh Look at Teaching Pharmacokinetics

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It is commonly believed that the passive diffusion of weak electrolytes through cell membranes is heavily dependent on the pH of the microenvironments, since only lipid-soluble unionized molecules can freely permeate through the lipid bilayer of membranes. Therefore, supposedly acidic drugs are absorbed better from the stomach and weak bases from the intestine. This principle can be found in many textbooks on pharmacology and toxicology. We have tried to assess the validity of these arguments.

The percentage of uncharged molecules and ions in any solution for each compound is determined by calculation according to the Henderson - Hasselbach equation. It is believed that these data may be used to quantitatively measure weak electrolytes absorption from different parts of the gastrointestinal tract (GI Tract) into the blood. We compared the results of the calculation with the data of clinical trials.

As a rule, at the pharmacokinetics classes students must be able to solve problems using the Henderson - Hasselbach equation, for example, «determine the amount of acetylsalicylic acid (ASA) absorbed from the stomach when the pH of gastric juice is about 4,5». According to these calculations the number of charged forms for ASA (pKa 3.5) has to be 10 times greater than the number of the unionized forms. As such, students must answer, that in this case only 10% of this drug will pass from the stomach into the blood and that alkalization of the gastric content will decrease ASA absorption. In addition, in the alkaline environment of intestines, ASA will not be absorbed at all because of the vanishingly small number of uncharged molecules. However, it is not the case. Clinical trials demonstrate that many acidic drugs have a good absorption in the intestine and therefore are administrated as the enteric-coated tablets. In addition, coadministration of wake acids with commonly administered antacids or food intake do not decrease the bioavailability of such compounds.

Theoretical arguments are not consistent with the data on the absorption of weak bases.

For example, according to the calculations, propranolol (pKa 9,4), metoprolol (pKa 9,8), atropine (pKa 9.7) do not have to be absorbed in the in the GI tract at all, as not only in the stomach, but in the alkaline environment of the intestines they will be practically completely ionized. Therefore, the greater portion of molecules there will be in water-soluble form and will not be able to leave the gut.

This contradiction is explained by the inapplicability of the Henderson-Hasselbach equation for calculations of biological systems. Such calculations do not account for the possibility of transition of participants of the chemical equilibrium with each other and the shift of balance in the direction of the uncharged form, as its absorbs into the blood.

Thus, mathematical calculations of numbers of unionized molecules of drugs do not permit an assessment of their capacity to be absorbed into different parts of the GI Tract and should not be used in the pharmacokinetics tests. The formula fails to take into account the dynamic nature of the chemical equilibrium, as well as the possible availability of specific transporters.