

The advantages for an H₁ antihistamine of a low volume of distribution

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With a few exceptions, antihistamines are rapidly and completely absorbed after oral administration, peak plasma concentrations being reached after 1–4 h. However, the plasma concentration of antihistamines after recommended doses is highly variable as a result of differences in metabolism and tissue distribution. The method used to define the basis for a new classification of a well-known pharmacologic class requires the selection of drugs according to their respective potencies. However, in the case of the H₁ antagonists, many drugs in current use, particularly those belonging to the second generation of antihistamines, are already well recognized as very effective treatments in allergy-based diseases. Since these drugs are often used to treat non-life-threatening conditions such as allergic rhinitis, consideration of their benefit/risk ratio is of great importance (1, 2). Therefore, progress with this class of drugs might involve not only an increase in efficacy but also improvements in their safety and specificity.

In pharmacokinetic terms, it is desirable for any drug to have the lowest volume of distribution (V_D) compatible with the therapeutic goal of interacting with the target receptors at effective concentrations, while avoiding organs where the drug is ineffective or toxic. Many drugs available today are extensively distributed throughout all the organs of the body. This is because they are liposoluble, a feature which, together with nonionization, is a prerequisite for tissue transfer by passive diffusion after oral administration. Liposolubility does not result in any selectivity of organ transfer and in fact permits passive diffusion across almost all cell membranes. Consequently, the distribution of a drug is often greater than necessary for its therapeutic effect, with the potential to lose a significant part of its activity. This is especially true of those H₁

antagonists which are metabolized by the liver. It can be seen that the optimal distribution of a drug should be the lowest which provides the amount of the drug necessary to reach the selected receptor effectively while avoiding organs where the drug is useless or toxic.

A low V_D can be defined as that smaller than the volume of exchangeable water in the body which is freely and quickly exchanged between extracellular fluids and cytosol; this concept is illustrated in Fig. 1. Evaluation with antipyrine has shown the volume of exchangeable water to be 0.6 l/kg (3). Exchangeable water in the body includes the plasma volume, interstitial fluids, and the water in equilibrium with extracellular fluids and cytosol. A lower V_D than that of exchangeable water in the body means that the drug may not be uniformly distributed in the body fluids and consequently will be retained in one of its components. The intermixture of free and bound forms will result in partial restrictive distribution with an overall V_D of 0.6–0.1 l/kg. When a drug is almost completely bound to human serum albumin (HSA), its V_D is superimposable on that of its binding protein; 0.1 l/kg for HSA. Conversely, a higher V_D than 0.6 l/kg indicates that the drug can not only diffuse throughout the exchangeable water but also bind to cellular structures. A low V_D may represent a distinct advantage for a H₁ antagonist, as it would optimize the body distribution to the lone targeted receptors and minimize the potential to cross the blood–brain barrier.

H₁ receptors have a wide cellular distribution, being found on smooth-muscle cells, endothelial cells, and eosinophils; antihistamines exert their effects by competing with histamine for occupancy of these receptors (4). In man, the H₁ receptors of the brain are numerous, constituting about 40% of the total amount of H₁

receptors (5). Ideally, H_1 antagonists would not reach these receptors; that is, they would be unable to cross the blood-brain barrier. Drugs which have a relatively high liposolubility are thought to cross the blood-brain barrier by a process of passive transport. It is obviously desirable to prevent antihistamines from interacting with the H_1 receptors of the brain. However, it is impossible to prevent these receptors from having any contact with the drugs, especially those in direct contact with endothelial cells, but brain transfer can be drastically limited (6). The same considerations apply to heart receptors, since, while it is impossible to prevent their having contact with blood, it is possible to inhibit drug penetration at appropriate dosages. The H_1 receptors represent the best targets for H_1 antihistamines, and these either are located on the outside of cell membranes which are in direct contact with the blood, such as those of endothelial cells and eosinophils, or are located on cells which are in direct contact with the extracellular fluid, such as bronchial muscle cells. Some H_1 receptors present in other tissues are not suitable targets for H_1 antagonists, such as those in the heart. Fortunately, they are not very numerous.

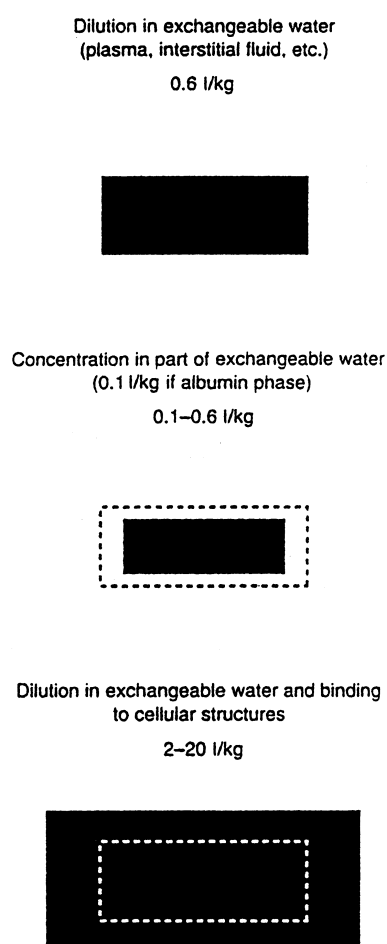


Figure 1. Schematic representation of possible volumes of distribution of drug.

When non- H_1 receptors and other targets are considered, they can be divided into three main categories. Firstly, there are receptors located on cell membranes, such as 5 HT receptors. Secondly, there are cholinergic receptors and those targets located inside the cell; for example, CYP 450 which is found within the microsomes, cytoplasmic PLA_2 , and the store-operated calcium channel. Thirdly, there are targets located on both the inner and outer surfaces of the membrane; for instance, the K^+ and Ca^{++} channels. A very low V_D for a given drug will result in a low concentration within the tissues; therefore, some intracellular targets will not be affected by the drug. An important point to keep in mind is that the concentration of most drugs is very low in the extracellular fluid. In this case, their toxicity to several non- H_1 targets, such as ion channels, is probably due to their accumulation in the cells. H_1 receptors are more easily accessible from blood than the nontarget receptors; thus, there is no need for antihistamines to enter the cell. It is interesting to note that all these receptors are easily reached from the blood, as they are either in direct contact with it (as are endothelial cells), or very close to it and thus readily accessible (as are the vascular smooth-muscle cells). Therefore, a H_1 antagonist does not need an extensive tissue distribution as part of its mode of action. The relationship between the potential distribution of a H_1 antagonist in tissues and its V_D is illustrated in Fig. 2.

Table 1 shows the pharmacokinetic parameters in man of a number of currently available second-generation antihistamines. Among these, cetirizine has the lowest V_D followed by acrivastine, suggesting that their distribution is poor in tissues and organs. In contrast, the majority of H_1 -receptor antagonists have a large apparent V_D and total body clearance (7, 8). The exceptionally low V_D of cetirizine may partially explain the safety of this drug. At therapeutic concentrations, cetirizine exhibits poor penetration of the heart, liver, or brain, a fact which explains the absence of any dose-dependent effects in these organs. Because cetirizine exhibits poor liver penetration, biotransformation of about 10% of the administered dose results. This fact precludes any risk of dose-dependent toxicity and leads to minimal interindividual variability in the intensity of the therapeutic effect. Among the currently available second-generation antihistamines, only acrivastine, cetirizine, and fexofenadine are excreted with negligible liver metabolism (9-11). It is unlikely that an extensive tissue distribution would be required for the mode of action of H_1 antagonists, and it may be of interest to look for a correlation between the frequency of side-effects and corresponding V_D , as these factors might be linked to the relative accumulation of this class of drugs.

These findings raise the question of how cetirizine comes to have a remarkably small V_D . The association constant of the binding of an antihistamine (Table 1) to

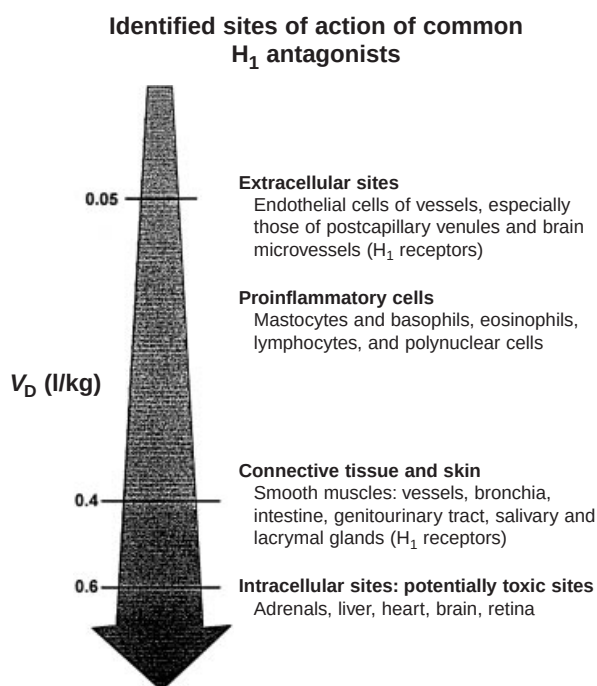


Figure 2. Relationship between potential sites of action and V_D of common H₁ antagonists.

HSA is insufficient in itself to explain fully its low V_D . A small V_D may be related to other mechanisms including the ionization of the molecule, its low lipophilicity, and its H₁-receptor affinity (12). Classical H₁-receptor antagonists are lipophilic drugs with a single, strongly basic center which, at physiologic pH, exist mostly as lipophilic cations. However, a number of antihistamines exist as zwitterionic forms, and these include acrivastine, cetirizine, levocabastine, and fexofenadine (Table 1). The modulating effect that this chemical state may exert on the pharmacokinetic behavior of an antihistamine has been investigated for cetirizine (13). This recent study examined the ionization and lipophilicity behavior of cetirizine, and it demonstrated that cetirizine exists almost exclusively as a zwitterion in the pH region of 3.5–7.5, where its octanol/water lipophilicity was found

Table 1. Pharmacokinetic parameters of some second-generation antihistamines in man (*zwitterionic drugs)

Drug	Terminal half-life (hours)	% Bound in plasma	Volume of distribution (V_D)
Astemizole	26	96	48
Azelastine	25	—	14.5
Ebastine	10–12	—	—
Loratadine	12 ± 4	97	120
Mequitazine	18	90	67
Mizolastine	12.9 ± 4.5	98	1.4 ± 0.4
Terfenadine	16–23	98	2.2–2.9
Acrivastine*	1.7 ± 0.2	50	0.64 ± 0.13
Carebastine*	13–16	98	2.1–2.4
Cetirizine*	10	88–90	0.4
Fexofenadine*	18.3 ± 2.0	65	5.6 ± 0.7

to be constant and low as compared to other cationic antihistamines ($\log D = \log P^z = 1.5$), whereas its hydrogen-bonding capacity was found to be relatively large ($\Delta \log P^z \geq 3.1$). Conformational, electronic, and lipophilicity potential calculations revealed that zwitterionic cetirizine exhibits partial intramolecular charge neutralization in folded conformers of lower polarity factors. These observations may contribute further to our understanding of the pharmacokinetic behavior of cetirizine.

In conclusion, it is apparent that cetirizine exhibits several unique structural characteristics when compared with other second-generation H₁ antagonists. The advantages resulting from a small V_D include minimal risk of dose-dependent toxicity in cells and organs, minimal interindividual variation in the therapeutic effect, reduction in unwanted drug–drug interactions, and no accumulation in the heart or liver.

Discussion

Nicolas: I am a little surprised by the distribution volume of fexofenadine since that compound is also reported to be a zwitterionic antihistamine, like cetirizine.

Tillement: Yes, but it's not sufficient for an antihistamine to exist as a zwitterionic form to have a low distribution volume.

Timmerman: So, in your opinion, fexofenadine is predicted to bind extensively in the different tissues?

Tillement: Yes, but take acrivastine, for example, which is also a zwitterionic antihistamine, and look at its distribution volume. It is not significantly different from that of cetirizine. Thus, I feel that all new drugs should not exhibit extensive distribution in the tissues. This is one of the keys to future drug discovery. My opinion is that in the future drugs will be less and less metabolized by the liver and more and more excreted by the kidneys, but this is a question open for discussion.

Nicolas: I was thinking about the possibility that these compounds might be interfering with the P-glycoprotein transporter, which is also present in the blood vessels. So, if you block that, you keep all the compounds in the blood.

Tillement: We have not looked at the binding of cetirizine to the P-glycoprotein but have investigated its binding to alpha-1 glycoprotein, because, when you have a compound which binds well to P-glycoprotein, you will also see binding to alpha-1 [acid] glycoprotein, which we do not see with cetirizine.

Nicolas: A couple of years ago, a paper was published on a study in which terfenadine and cetirizine were tested for their ability to inhibit P-glycoprotein, and terfenadine was found to be a very potent inhibitor, but cetirizine was not.

Tharp: Can I ask a somewhat more clinically relevant question? I'm intrigued by this volume of distribution, and it makes great sense to me, especially in terms of toxicity, which I think we'll hear about in a minute. But one thing which doesn't make a whole lot of sense in this explanation is that astemizole has a volume of distribution of 48 and terfenadine has a volume of distribution of 2.2–2.9; both of these drugs have been shown to be extremely cardiotoxic. So there appears to be no correlation between toxicity and volume of distribution.

Tillement: As we discussed this morning, if you want to avoid organ toxicity, one way is obviously to try to have a drug which is ineffective in this organ, but the other way is to try to avoid distribution in this organ. I wanted to emphasize that decreasing the drug distribution is a good way of reducing organ toxicity. If you decrease the distribution volume, you decrease the concentration of the drug inside selected organs. In this case, you may minimize the dose-dependent toxicity. That is why it is interesting because when you look at the evolution of drugs, I think that we had a period where in order to get good efficacy, we used highly liposoluble drugs which had a large distribution volume to be sure of reaching active targets. Today, improvement of drugs will come about by keeping the same activity with smaller and smaller distribution volumes.

Taglilatela: I don't agree in every sense with you; the digitalis-like compounds target the heart and have a large distribution volume, but they only remain in the blood for a very short time. So your general statement is not correct; I think it is correct to say that you should try to target the compounds to the organs, but I don't think you can generally say that there should always be a low distribution volume.

Tillement: No, I generalized in the case of H_1 antagonists because some members of this family have particularly toxic effects if localized in all the organs. This is not the case for digitalis because the toxicity of digitalis is the result of an overdose at the same place as the targets. A small V_D is only correct when the drug targets are outside cells, which is not the case with digitalis.

Timmerman: I have a question for UCB. What have your animal experiments shown about distribution of the compounds in the organs?

Rihoux: Animal experiments were performed with cetirizine, but we found nothing special, in that cetirizine has no particular affinity for any tissue. In the literature, you can find some studies showing that, for example, terfenadine accumulates to some extent in the tissues, including the heart with a

concentration ratio of heart to plasma of about 4 or 5 to 1. In the case of cetirizine, the concentrations within the tissues were always lower than the plasma concentrations.

Timmerman: One observation that I would make is that pharmacology is not only about pharmacokinetics; there is a selective toxicity which we should be looking at which is not necessarily only related to the distribution of these drugs. And that's probably also what's happening when cardiotoxicity is considered.

Tillement: I fully agree with you. I am a professor of pharmacology, not a professor of pharmacokinetics, and my topic today is the importance of the distribution volume. I told you that if the distribution volume is small, you may avoid much toxicity in organs when the toxicity is dose-dependent.

Rihoux: Do you yourself think that the low volume of distribution is a kind of quality criterion for a drug of this kind?

Tillement: No, I think it is a way to improve safety if we can dissociate targets and toxic receptors.

Rihoux: Do you think that if a new family of antihistamines were to arrive, all with a low distribution value, we might classify according to that?

Tillement: I feel that today we do not have any major problem with efficacy; we have drugs which are effective in terms of H_1 antagonism, and we can improve these drugs only in terms of safety. One way to improve safety is to avoid distribution of the drug in tissues where it is not going to be useful. But I agree with you that there are other ways of defining a third generation of antihistamines.

Annunziato: Is anything known about the volume of distribution of hydroxyzine?

De Vos: The volume of distribution of hydroxyzine is almost 12 l/kg.

Annunziato: I think that you were trying to say before that in the future we can decrease the volume of distribution for those drugs which act on the periphery, because you try to get a higher volume of distribution if you want to develop a drug which reaches the brain and interacts with receptors which are located in the cell membranes.

Timmerman: I feel that greater specificity in recognizing receptors may allow us to have a lower volume of distribution. Prof. Tillement says that the affinity for the receptor determines the volume of distribution outside the cell, etc. If you were to take D and L cetirizine and you found that one isomer has a high affinity relatively and the other low affinity for the receptor, then such a clear difference could provide an explanation for the two volumes of distribution.

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