The First Approved “Deuterated” Drug: A Short Review of the Concept

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Abstract
The first “deuterated” drug has recently been approved by the U.S. FDA (Food & Drug Administration). A “deuterated” drug is a drug in which the hydrogen atom in one or more of the carbon-hydrogen bonds in its chemical structure is replaced by deuterium (“heavy hydrogen”, a hydrogen isotope that has a neutron, i.e., one neutron instead of the usual no neutrons). A carbon-deuterium (C-D) bond is more stable in the body than a carbon-hydrogen (C-H) bond. If the deuterium is strategically located in a drug’s chemical structure, the extra stability of the bond will be more resistant to metabolic breakdown, and the duration of drug action will be prolonged. We review the general concept of deuterated drugs, historical examples of the classes of application, and the new approval.

Keywords
Deuterium, Drug Structure, Chemical Bonds, Drug Metabolism, Duration of Action

1. Introduction
Although there are notable exceptions, the majority of drugs are administered over the course of several days, or even much longer. In such cases, the dose and dosage regimen needs to be designed such that the blood level (concentration) of the drug falls within the therapeutic “window”, i.e., between too low (below the required threshold) and too high (into toxicity). Keeping the level constant over time is almost impossible, unless the drug is infused at a constant rate directly into a vein. Alternatively, a drug could be administered so frequently that the
process mimics continuous infusion. Neither of these is very practical for most drugs or for most patients.

A good design of a dosing regimen keeps the drug’s blood level (surrogate for target organ drug concentration) within the therapeutic window as much as possible throughout the course of therapy. A key factor in this design is the drug’s half-life \( (t_{0.5}) \), which is the time that it takes for a drug level (usually the blood level) to drop to 1/2 its initial value. Several factors contribute to a drug’s half-life, but one of the most important for most drugs is the rate of its metabolism [1]. Anything that slows a drug’s rate of metabolism will increase its half-life. Drug metabolism involves the breaking of chemical bonds, so something that inhibits or delays the breaking of chemical bonds will increase the half-life, which usually translates into favorable features. We present the conceptual framework for this approach, and we discuss a few drugs as representative examples.

2. Drug Metabolism, Duration of Action, and Compliance

The typical profile of plasma level of a drug demonstrating 2nd-order pharmacokinetics, the more common type [2], is shown in the upper panel of Figure 1. The ascending limb of each tracing follows administration of the drug (indicated by the arrows). The descending limb of each tracing occurs because of elimination of drug. For most current drugs, the major contributor to drug elimination is metabolism. Thus, if metabolism is prolonged, so is elimination. The resulting pharmacokinetic curves then look like the bottom panel in the figure. Note that the requirement for frequency of dosing is reduced. If the dotted line in the figure represents one day, then prolongation of metabolism translates to a dosing regimen of once-per-day instead of twice-per-day. Patient compliance is better when only once-per-day dosing is required [3] [4].

2.1. Chemical Reactions in Drug Metabolism

Drugs are metabolized in two major ways: modification of their chemical structure (termed Phase 1), and linking to an endogenous substance (termed Phase 2). Both ways involve chemical reactions and both tend to decrease efficacy (e.g., by decreasing the goodness of “fit” to a receptor) and to increase elimination rate (e.g., by making the molecule more hydrophilic). All of these reactions involve the breaking of bonds and the making of new bonds. Most of these reactions are catalyzed by enzymes. The effectiveness of catalysis is determined by the specific atoms and the 3-dimensional shape of the drug molecule, and the complementary fit with the enzyme. An alteration in any one of these components will alter the efficiency of catalysis, and hence the rate of drug metabolism (Figure 2). Common chemical reactions involved in the metabolism of drugs include one or more “non-synthetic” types (e.g., involving oxidation, reduction, hydrolysis, cyclization, decyclization, or the addition of oxygen or removal of hydrogen) and “synthetic” types, which involve joining (conjugation) the drug molecule with an endogenous substance (such as glucuronic acid to form
Figure 1. The effect of prolonged metabolism on pharmacokinetic curves. The upswing of each curve is a function of drug de-formulation, absorption and distribution. The downswing results from metabolism and elimination. If metabolism is prolonged, dosing (arrows) can be less frequent, e.g., once/d instead of twice/d if dotted line = 24 h. Modified from Wikimedia Commons.

Figure 2. The rate of a drug-metabolism reaction depends on the rate of catalysis by an enzyme. The rate of catalysis is, in turn, a function of the complementarity of the 3-dimensional shape of the drug and the enzyme (protein). From Wikimedia commons.
glucuronides). Many of these reactions involve the making or breaking of hydrogen bonds either directly or in the transition state (e.g., conversion of C-H to C-OH) [5].

2.2. Breaking/Making Chemical Bonds during Drug Metabolism

As a drug molecule is metabolized to one or more metabolite molecules, it proceeds to a lower-energy state. But it must pass through the transition state, which is at higher energy than is the parent drug molecule (Figure 3) [5]. Enzymes facilitate the reaction by lowering the activation energy needed to get to the transition state. Carbon bonds are almost always involved, e.g., C-H, O-H, N-H, etc.

3. “Deuterated” Bonds

3.1. Deuterium

Deuterium is a stable isotope of hydrogen. In contrast to the more common hydrogen isotope on Earth (one proton and no neutron in the nucleus), the nucleus of deuterium consists of one proton and one neutron (Figure 4). It is not radioactive, as is tritium (one proton and two neutrons).

3.2. Carbon-Deuterium Bonds

The effect of deuterium is summarized by Blake et al. (1975): [6]

The difference in mass between deuterium and hydrogen causes the vibrational frequencies of carbon, oxygen, and nitrogen bonds to deuterium to have lower frequencies than corresponding bonds to hydrogen. As a result, the chemical bonds involving [deuterium] will generally be more stable than those of [hydrogen].

...The more stable deuterium bond requires a greater energy of activation to achieve the transition state; as a consequence, the rate of reaction involving a bond to deuterium is generally slower than that involving a bond to hydrogen. Thus, substitution of deuterium for hydrogen in a chemical bond can affect significantly the rate of bond cleavage and exert marked effects on the relative rates of chemical reactions.

Large isotope effects on reaction rates are apparent where cleavage involves a bond to deuterium at the reaction site.

An observable isotope effect will only be apparent, of course, where the breaking of a C-H or C-D bond is involved in the rate-determining step.

4. Deuterated Drug Molecules

4.1. Early Examples

Efforts to modify the pharmacology of drugs by using deuterium date back at least several decades. As reviewed by Blake et al. (1975) [6], the effect of deuterium on the duration (metabolism) of a variety of classes of drugs have been investigated, including barbiturates, anesthetics, antibiotics, and others.
Figure 3. A drug metabolism reaction proceeds through several steps before reaching the final product(s). The rate at which the reactants overcome the activation energy influences the rate of reaction. Therefore, if the chemical bonds in one molecule are stronger than corresponding bonds in another, the rate of metabolism of the first drug will be slower. Modified from Wikimedia Commons.

Figure 4. Comparison of “deuterium” to “hydrogen”. From Wikimedia Commons: [https://upload.wikimedia.org/wikipedia/commons/1/1c/Blausen_0530_HydrogenIsotopes.png](https://upload.wikimedia.org/wikipedia/commons/1/1c/Blausen_0530_HydrogenIsotopes.png)

4.2. Recent Approval

The first U.S. FDA-approved deuterated drug is deutetetrabenazine (AUSTEDO®; by Teva Pharmaceutical Industries) to treat the involuntary movements (chorea) of Huntington’s disease. Tetrabenazine has been used clinically for many years as treatment for movement disorders. The molecule has two methoxy groups, which are targets of rapid metabolism to demethylated metabolites that subsequently undergo Phase 2 conjugation reactions. Deutetetrabenazine (Figure 5) [7] is metabolized at a slower rate than is non-deuterated tetrabenazine, which imparts less patient-to-patient variability and a dosing advantage to the deuterated drug.

5. Perspective and Conclusions

One or more well-placed deuterium isotope in place of hydrogen in a drug molecule can delay metabolism and extend a drug’s half-life. The hoped-for result is
a drug that can be administered less frequently, thereby enhancing patient compliance. Because the strategy is so attractive for new drugs and for revamping older ones, at least a dozen companies are pursuing the idea.

However, the strategy does not always work, and the path to regulatory approval is not always shortened. In addition, there is question about patentability and other issues of IP (intellectual property) protection. Nevertheless, the approach promises to provide a new tool for drug development.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References


https://doi.org/10.2147/DDDT.S138828