

The Development of Deuterium-Containing Drugs

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Deuterium offers a subtle, but sometimes powerful, medicinal chemistry tool that has received little attention to date – but when applied to compounds with well-understood therapeutic utility, selective deuteration can be used to create new drugs that address significant unmet medical needs.

Selective incorporation of deuterium in place of hydrogen (deuteration) has the unique effect of retaining the biochemical potency and selectivity of physiologically active compounds while, in select instances, modifying metabolic fate to substantially alter their overall therapeutic profile. In favourable cases, this modification has the potential to have a positive impact effect on safety, efficacy and/or tolerability. By starting from compounds with well-defined human pharmacological effects – such as approved drugs – deuteration potentially provides a unique, streamlined approach to creating significantly differentiated, patentable new medicines that can address important unmet medical needs. Deuterated compounds have been widely studied in non-clinical settings and used in humans as metabolic or pharmacokinetic probes. Although no deuterated compound has been approved as a human medicine, there do not appear to be any economic or regulatory reasons preventing the registration of deuterium-containing drugs. The early clinical evaluation of several candidate compounds has been encouraging, supporting the potential for important new deuterated drugs to reach the market.

WHAT IS DEUTERIUM?

Deuterium is a naturally-occurring, stable, non-radioactive isotope of hydrogen. Hydrogen consists of one electron surrounding a nucleus composed of one proton and has an atomic mass of approximately 1.0 atomic mass unit (AMU). Deuterium also has a single electron but its nucleus contains one neutron and one proton, resulting in an atomic mass of approximately 2.0 AMU.

Deuterium can be sourced through a multi-step distillation process that concentrates naturally occurring deuterium from bulk water to produce highly enriched D₂O (heavy water). D₂O has the property of modulating the reactivity of fissile ²³⁵U and is used in multi-ton

quantities in heavy water nuclear reactors (1). Depending on the desired sites of deuteration, deuterium from D₂O can be exchanged directly into finished drug compounds or into reagents that are used to synthesise drug molecules.

When deuterium is incorporated into molecules in place of hydrogen, the deuterated compound is – in most respects – exceedingly similar to the all-hydrogen compound. Since the electron clouds of its component atoms define the shape of a molecule, deuterated compounds have shapes and sizes that are essentially indistinguishable from their all-hydrogen analogues (2).

Minor physical changes can be detected in the properties of partially or fully deuterated compounds versus their all-hydrogen analogues including reduced hydrophobicity and altered pKa when adjacent to ionisable groups. These differences are small enough that we are not aware of any case in which deuteration of a non-covalent drug has been demonstrated to change its biochemical potency or selectivity to relevant pharmacological targets.

Deuterium-carbon bonds are generally about six to 10 times more stable than the corresponding hydrogen-carbon bond. These stronger bonds are more difficult to break, which can slow the rate of bond cleavage. This effect upon rate is called the kinetic isotope effect (KIE) (3). In principle, the deuterium KIE has the potential to affect the biological fate of many drugs that are metabolised by pathways involving hydrogen-carbon bond scission.

In practice in biological systems, numerous competing effects mask the deuterium KIE (4). Such competing effects include, for instance, alternate metabolic routes, different rate-limiting steps in enzyme mechanisms and biological sequestration. As a result, deuteration can result in compound metabolism effects ranging from



undetectable to quite substantial. The observed magnitude and even direction of the KIEs are unpredictable, and depend on a compound's substituents and the specific substitution pattern.

DEUTERIUM SAFETY AND PHARMACOLOGY

The effects of deuterium have been widely explored since sufficient quantities of deuterium-containing compounds became available. In general, deuterium has remarkably low systemic toxicity. Single-celled organisms can often be grown in conditions of full deuteration. Lower organisms including fish and tadpoles reportedly survive in at least 30 per cent D_2O . Mice and dogs do not display visible effects from long-term replacement of at least 10-15 per cent of body fluid hydrogen with deuterium, although concentrations above 25 per cent are broadly toxic to those species.

Humans can tolerate high levels of deuterium in body fluids. Acute exposure levels of 15-23 per cent deuterium replacement in whole body plasma have been reported with no evident adverse effects (5). Deuterated water is renally excreted by humans with a half-life of about 10 days.

As a result of the KIE, deuteration can result in altered metabolism patterns. We are not aware of cases of deuteration resulting in the formation of unique metabolites in animals that were not produced by the all-hydrogen analogue. However, reduced rates of metabolism and metabolic shunting, where the ratio of metabolites is changed, have been reported (6,7). Although rarely reported in the literature, we have also observed several cases where selective deuteration increases the rate of metabolic clearance *in vitro*.

We have found it convenient to conceptualise the pharmacological effects of deuteration in three major categories, as illustrated in Figure 1. Panel 1 illustrates cases where the major effect of deuteration is to reduce the rate of systemic clearance. As a result, the biological half-life of the compound is increased. Potential drug benefits could include a reduction in dosage and the ability to maintain similar systemic exposure with decreased peak levels and increased trough levels. This could result in a lower incidence of side effects and enhanced efficacy, depending on the particular drug's pharmacokinetic/pharmacodynamic relationship.

The second panel illustrates a predominantly pre-systemic effect of deuteration, which we have observed in a number of instances. In these cases, reduced rates of (usually oxidative) metabolism in the gut wall and/or liver result in a larger percentage of unmetabolised drug reaching systemic circulation. In many cases, the rate of systemic clearance is unchanged. Deuterated drugs showing this effect may have reduced dosing requirements and produce lower metabolite loads. Since gastrointestinal irritation has been related to the amount of dosed compound rather than blood concentration for certain drugs, this effect could allow enhanced tolerability and/or the ability to achieve a higher maximum tolerated dose.

The third panel illustrates metabolic shunting. Many drugs are metabolised in complex patterns, sometimes forming both active and innocuous metabolites. We and others have demonstrated that the deuterium KIE can result in reduced formation of toxic or reactive metabolites, as well as increased formation of desirable active metabolites (7). Clear potential benefits in terms of human medicines are apparent.

Figure 1: Pharmacological expressions of drug deuteration effects

A: Reduced systemic clearance resulting in increased half-life. B: Decreased pre-systemic metabolism resulting in higher bioavailability of unmetabolised drug. C: Metabolic shunting resulting in reduced exposure to undesirable metabolites or increased exposure to desired active metabolites.

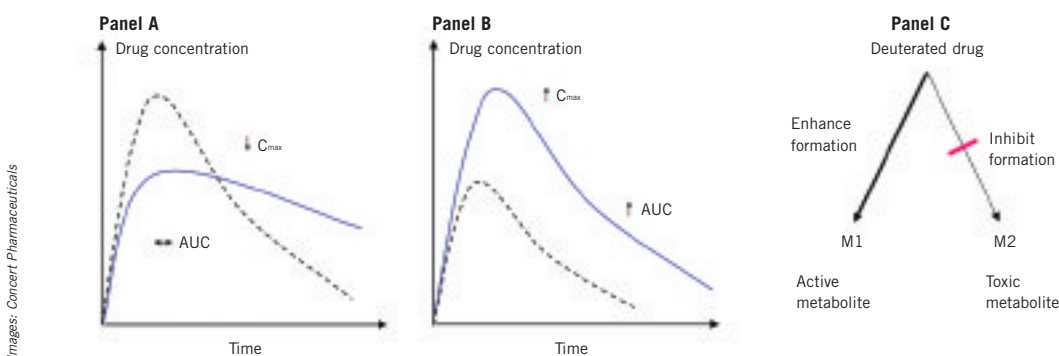
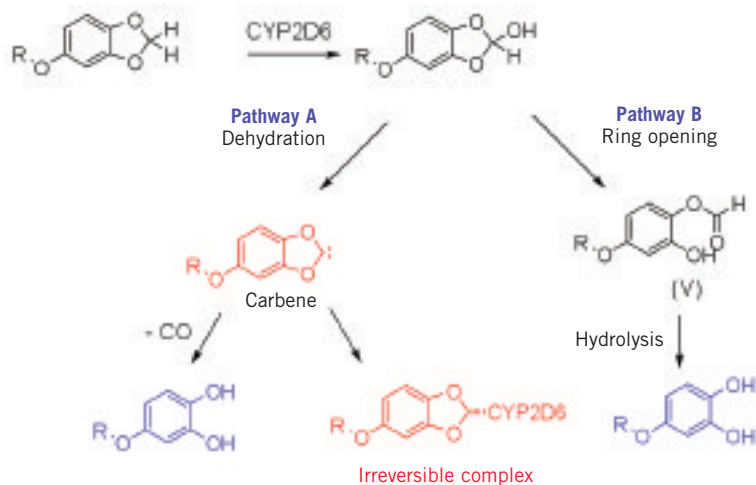


Figure 2: Proposed pathway for inactivation of CYP2D6 by paroxetine metabolite. Structures in red show the putative reactive metabolite and resultant inactivated enzyme



CLINICAL EVALUATION

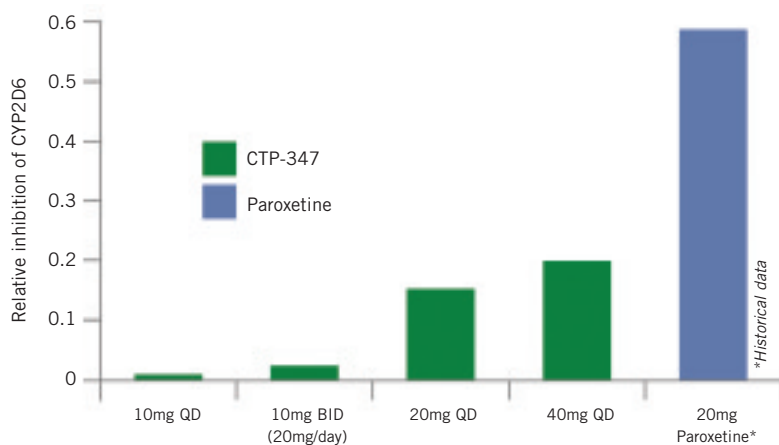
Deuterated compounds have a long history of use in humans as metabolic and pharmacokinetic probes. In contrast, there have been few reports of deuterated compounds being studied as potential new drugs. Fludalanine (2-deutero-3-fluoro-D-alanine), developed by Merck, appears to be the most extensively studied deuterated drug candidate. Fludalanine, combined with cycloserine, displays broad and potent antibacterial

activity. Its all-hydrogen analogue is also a highly effective anti-infective agent, but preclinical studies reportedly demonstrated that it was metabolised to form 3-fluorolactate, a toxin that caused brain vacuolisation (8). Kahan reported in a recent letter that the deuterium KIE reduced 3-fluorolactate production to what were deemed acceptable levels in healthy volunteers. However, higher 3-fluorolactate levels were observed in patients, potentially resulting from metabolic derangements. Studies on fludalanine were discontinued at Phase IIb.

Several other potential novel deuterated drugs have entered clinical evaluation. Concert Pharmaceuticals recently presented Phase I results on CTP-347, a selectively deuterated analogue of paroxetine for the treatment of hot flashes (9). Low dose paroxetine reportedly has good efficacy in treating hot flashes. However, in patients potentially benefiting from such therapy, such as post-menopausal women and cancer patients receiving endocrine disrupting agents, paroxetine use can be complicated or contraindicated as it causes extensive drug-drug interactions (DDIs) with other drugs.

The cause of these DDIs is believed to be predominantly irreversible inactivation of the hepatic enzyme CYP2D6. This inactivation is believed to be due to a highly reactive metabolite that covalently binds the active site of CYP2D6. *In vitro* metabolism experiments with CTP-347 demonstrated little to no CYP2D6 inactivation, apparently due to metabolic shunting preventing the formation of the reactive metabolite (see Figure 2) (10). CTP-347 demonstrated equivalent serotonin reuptake inhibition and selectivity to paroxetine, and was indistinguishable from paroxetine in a battery of over a hundred receptor and enzyme assays.

Figure 3: Drug-drug interaction between CTP-347 and dextromethorphan from Phase Ib study. Y-axis shows the ratio of intact excreted dextromethorphan versus dextromethorphan metabolite (9)



CTP-347 was subsequently studied in a 96-patient single- and multiple-ascending dose clinical trial. The multiple-dose subjects initially received a single dose of dextromethorphan, followed by 14 days of treatment with CTP-347, then another single dose of dextromethorphan. Dextromethorphan acts as a selective probe for CYP2D6 activity. Subjects receiving CTP-347 retained substantially greater ability to metabolise dextromethorphan than occurs with paroxetine, correlating well with *in vitro* data (see Figure 3) (9). Minor CYP2D6 inhibition was observed at higher CTP-347 doses, consistent with reversible, competitive inhibition seen *in vitro*. The study is also the first clinical demonstration that deuteration

can be utilised to ameliorate drug-drug interactions in humans.

Concert recently announced initiation of multiple ascending dose studies with its development candidate CTP-518, an HIV protease inhibitor (PI) based on the atazanavir scaffold. Due to its favourable antiviral potency and pharmacokinetic profile, CTP-518 is being developed to be optimally administered without the need for ritonavir, a pharmacokinetic booster. The current standard of care is to co-administer all marketed HIV PIs with ritonavir. However, ritonavir co-dosing complicates dosing regimens and is associated with nausea and increased blood lipids, including LDL cholesterol and triglycerides. Eliminating the need for this agent would therefore be clinically advantageous.

Auspex Pharmaceuticals is developing SD-254, a selectively deuterated analogue of the antidepressant venlafaxine. In October 2008, Auspex issued a press release on their SD-254 Phase I healthy volunteer study in which the compound reportedly “exhibited a pharmacokinetic profile that appears to be superior to that of venlafaxine”.

Berolina innovative Research and Development Services Pharma (BiRDS Pharma) is developing BDD-10103, a deuterated analog of the muscle relaxant tolperisone. Specific data have not been publicly released, but BiRDS reported “enhanced overall bioavailability of BDD-10103 compared to tolperisone”.

CONCLUSION

Deuterium offers a subtle, but sometimes powerful, medicinal chemistry tool that has received little attention to date in the context of new drugs. Selective deuteration retains biochemical potency and selectivity, but can sometimes enable substantial benefits to the overall pharmacological profile of the resulting compounds.

When applied to compounds with well-understood therapeutic utility, selective deuteration can be a unique risk-reduced approach to creating new chemical entity drugs that address significant unmet medical needs. Several companies are focused on deuteration as a business model and have received substantial funding to pursue the approach. With more deuterium-containing compounds entering clinical evaluation, it appears increasingly likely that the approach will succeed in producing important new medicines.

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