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Antiretroviral-Drug Concentrations in Semen

In a recent minireview (2), Kashuba et al. provide physicochemical and pharmacokinetic data to rationalize how anti-HIV agents are distributed in human seminal compartments. Unfortunately, the acid-base characteristics of 9 of the 12 drugs in their Table 2 are categorized incorrectly.

The strength of an acid depends on its ability to lose a proton, as measured by its acid dissociation constant (K_{acid} or K_a). K_a is usually expressed as its negative logarithm (base 10), or pK_a. However, the designation pK_a does not differentiate between proton loss from an acid and that from the conjugate acid of a base (conjugate acids are protonated salt forms of the corresponding bases). The term pK_a becomes more confusing when compounds contain functional groups that are both acidic and basic (i.e., amphoteric). Thus, pK_a values alone do not specify if a neutral organic compound is an acid or a base. To avoid confusion, the terms pK_{BH} and pK_{BH+} are sometimes used to refer to removal of a proton from a neutral organic acid and a protonated organic base, respectively. However, these terms rarely appear in the pharmacological literature.

Lamivudine, zalcitibine, and ritonavir are weak bases and not weak acids. There is no ionizable hydrogen that confers acidity consistent with a pK_{BH} of 2 to 5 in these molecules. The pK_a of 2.8 for ritonavir refers to loss of a hydrogen from a protonated thiazole group because thiazole itself is a weak base (pK_{BH+}, 2.4 [3]). Delavirdine is amphoteric, with a weakly acidic sulfonamide hydrogen and a number of basic nitrogen atoms. The pK_{BH} of sulfonamides like sulfabenz is generally about 11 (1). The reported pK_a of 4.6 is probably the pK_{BH+} for deprotonation from one of the nitrogen atoms, consistent with delavirdine's ability to form a mesylate salt. Likewise, nevirapine is amphoteric. A pK_a of 2.8 suggests a moderately strong acid, but nevirapine has only a weakly acidic amide hydrogen. There are three weakly basic nitrogen atoms available for protonation, and the pK_a likely reflects deprotonation at one of these sites, consistent with nevirapine's higher aqueous solubility at a pH of <3 (1). The pK_a values of 9 to 11 for zidovudine, didanosine, efavirenz, and nelfinavir indicate that these compounds are weak acids and not weak bases. Zidovudine contains an acidic hydrogen on the thymine moiety (thymine pK_{BH}, 9.9 [1]). Didanosine is amphoteric and contains an acidic hydrogen on the hypoxanthine ring. Nelfinavir is amphoteric, and the pK_a of 11.1 reflects the acidic phenolic group (*o*-cresol pK_{BH}, 10.2 [3]).

Reclassifying these drugs changes their predicted distribution characteristics in seminal fluid such that their semen-to-plasma concentration ratio is now expected to be about 1. Therefore, the predicted distributions of zidovudine, didanosine, efavirenz, and nelfinavir are not possible exceptions as stated. The high and variable semen-to-plasma concentration ratios observed by the authors for zidovudine may result from its slower elimination from semen than from plasma as observed in cerebrospinal fluid (4).

The authors should revise Table 2 to complete the otherwise excellent review.

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Author's Reply

We thank Dr. Gallicano for his interest in our minireview and for his vigilance in reviewing the acid-base properties of the antiretrovirals listed in our Table 2 (1). We agree that pK_a values alone do not allow determination of whether a compound behaves as an acid or a base. In fact, in order to avoid any misclassification of these compounds during development of this table, pK_a information and acid/base classification were solicited directly from the drug manufacturers themselves (generally, from the medical information divisions, which often, we were told, consulted with their respective pharmacology divisions). In reviewing the structures of these compounds, it appears that, surprisingly, we were in fact given incorrect information regarding their acidic or basic properties. Lamivudine, zalcitabine, and ritonavir do indeed appear to be weak bases. We would classify delavirdine and nevirapine as bases—a result of the aniline-like structures in delavirdine and the multiple aromatic amines in nevirapine. We would agree with Dr. Gallicano in the classification of zidovudine, didanosine, efavirenz, and nelfinavir as a weak acids. We have revised the table (2). It is indeed difficult to predict the acid/base characteristics of certain compounds, and this example speaks to the need for careful review of chemical structures before making final determinations. In comparing data from this table to currently available seminal plasma antiretroviral concentration data (3, 4; S. Taylor, R. van Heeswijk, R. Hoetelmans, J. Workman, S. Drake, and D. Pillay, Abstr. 39th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 335, 1999), it is evident that genital tract penetration is complex and relies on multiple mechanisms yet to be fully elucidated. Whether these are similar to the mechanisms of concentration and elimination from cerebrospinal fluid is unknown.

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