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 ($K_a$ or $K_w$). $K_a$ is usually expressed as its negative logarithm (base 10), or p$K_a$. However, the designation p$K_w$ 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 p$K_w$ becomes more confusing when compounds contain functional groups that are both acidic and basic (i.e., amphoteric). Thus, p$K_w$ values alone do not specify if a neutral organic compound is an acid or a base. To avoid confusion, the terms p$K_{HN}$ and p$K_{NH+}$ 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, zalcitabine, and ritonavir are weak bases and not weak acids. There is no ionizable hydrogen that confers acidity consistent with a p$K_{HN}$ of 2 to 5 in these molecules. The p$K_w$ of 2.8 for ritonavir refers to loss of a hydrogen from a protonated thiazole group because thiazole itself is a weak base (p$K_{NH+}$, 2.4 [3]). Delavirdine is amphoteric, with a weakly acidic sulfonamide hydrogen and a number of basic nitrogen atoms. The p$K_{NH}$ of sulfonamides like sulfabenz is generally about 11 (1). The reported p$K_w$ of 4.6 is probably the acidity consistent with delavirdine’s ability to form a mesylate salt. Likewise, nevirapine is amphoteric. A p$K_w$ 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 p$K_w$ likely reflects deprotonation at one of these sites, consistent with nevirapine’s higher aqueous solubility at a pH of <3 (1). The p$K_{NH+}$ 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 p$K_{NH+}$, 9.9 [1]). Didanosine is amphoteric and contains an acidic hydrogen on the hypoxanthine ring. Nelfinavir is amphoteric, and the p$K_w$ of 11.1 reflects the acidic phenolic group (o-cresol p$K_{NH+}$, 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.

REFERENCES


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