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Letter to the Editor

Distribution coefficients of atenolol and sotalol: a critique

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We refer to the recent paper by Taylor & Cruickshank (1984) which contains two sections open to criticism. The paper initially sets out to clarify the relationship between *distribution* and *partition* coefficients in view of the 'common confusion' which often surrounds these terms. It is therefore unfortunate that this paper does not truly clarify the situation. The Definitive Rules (IUPAC 1977), to which the authors make no reference, clearly set down the nomenclature that should be used to describe distribution of a substance between organic and aqueous phases at equilibrium. The Distribution Constant, K_D, is the ratio of the concentration of a substance in a single definite form in the organic solvent phase to its concentration in the same form in the aqueous phase at equilibrium. This is frequently termed a partition coefficient (e.g. Taylor & Cruickshank 1984). However the use of this latter term by Taylor & Cruickshank does not fit the IUPAC symbol K_D even though partition coefficient is not disallowed by IUPAC. The (Concentration) Distribution Ratio, D_C, is the ratio of the total analytical concentration of a substance in the organic phase to its total analytical concentration in the aqueous phase, usually measured at equilibrium. The term distribution coefficient (e.g. Taylor & Cruickshank 1984) or extraction coefficient can be used in place of the term distribution ratio (IUPAC 1977).

It may be considered pedantic to criticize this use of terminology, but if the particular intention of the paper was to clarify the terminology situation, a strict adherence to the IUPAC Definitive Rules should have been made. For example the phrase '...effective partition coefficient, i.e. distribution coefficient...' confuses both terms, and falls foul of the IUPAC (1977) warning not to use partition coefficient to describe a (concentration) distribution ratio because of the confusion that has arisen in the past. In addition, the assertion that distribution coefficient (sic) is the relevant quantity under physiological conditions is too general a statement. In membrane transport studies for example, the distribution constant K_D (non-ionised species) might be a more relevant quantity to consider.

The second point concerns the pK_a value assigned to sotalol. There is a pK_a at about 8·37 (pK_a = 8·30 by spectrophotometry; Garrett & Schnelle 1971: pK_a = 8·15 by spectrophotometry at 35 °C; Schoenwald & Huang 1983). This is however the pK_a of the acidic sulphanilo group. The pK_a of the basic amine group has been established at 9·80 (Garrett & Schnelle 1971) and 9·72 (Schoenwald & Huang 1983).

Taylor & Cruickshank have ignored the upper pK_a, and have incorrectly treated the lower pK_a as basic in character, which when applied to the correction equation (which is for bases) produces a log partition coefficient (sic) value of −0·79. If the Garrett & Schnelle values for pK_a are used, then we can calculate the proportion of ionized basic and acidic groups in sotalol at pH 7·40. The basic pK_a 9·80 group will be 99·6% ionised at pH 7·40, whilst the acidic pK_a 8·30 group will be 11·2% ionized at pH 7·40. The proportion of molecules present as zwitterions (as opposed to being unionized) cannot be calculated without knowledge of the microdissociation constant for the zwitterion/uncharged species pair. However a reasonable approximation can be made from knowledge of the percentage present as anionic and cationic forms at pH 7·40 from the two pK_a values. The proportion of zwitterionic form will fall between 10·8 and 11·2% and effectively the percentage with an overall neutral charge will be around 11%. Garrett & Schnelle (1971) indicate that the zwitterionic form is capable of partitioning into n-octanol and thus behaves as a neutral form. Therefore at pH 7·40 approximately 89% of the drug is present in the cationic form the rest being effectively neutral. This is equivalent to the compound having a basic pK_a of around 8·30 and therefore by calculation a log K_D value of −1·741 (K_D = 0·018).

It is interesting to note that the result which Taylor & Cruickshank (1984) quote is of the same order but is obtained incorrectly, by only taking into account the acidic pK_a and mistakenly treating it as a base.

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