QSAR correlation of clinical gastric irritancy of non-steroidal anti-inflammatory drugs

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One of the main side-effects of non-steroidal anti-inflammatory drugs (NSAIDs) is gastrointestinal irritancy, leading to bleeding and ulceration, and resulting sometimes in the need for hospital treatment. Assessment of gastrointestinal irritancy can be made in animals (Dearden & Nicholson 1984), but there is no guarantee that this will reflect the clinical situation. The ability to model and predict human gastrointestinal irritancy from NSAIDs would be of value to the clinician and the drug designer.

Recently MacDonald et al (1997) published relative gastrointestinal risk values (RGR) of a range of commercially available NSAIDs, and we have carried out a quantitative structure–activity relationship (QSAR) study of their results. Physico-chemical parameters were generated using the ClogP for Windows (Biobyte Inc., Claremont CA) and MOPAC6 (QCPE, Bloomington IN) software; for the latter, molecules were first constructed and energy-minimised in NEMESIS (Oxford Molecular Ltd.). Topological parameters were generated using MOLCONN-X2 (Hall Associates, Quincy MA). A total of 49 parameters was generated with these packages. Statistical analysis was carried out using MINITAB ver. 10.1.

MacDonald et al (1997) used two categories of diagnoses of irritancy—complicated upper gastrointestinal events (CU) and any upper gastrointestinal event (AU). Their study involved 12 NSAIDs, namely azapropazone, diclofenac, fenbufen, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, nabumetone, naproxen and piroxicam. We used step-wise regression to select the best parameters, and obtained the following correlations:

$$RGR_{CU} = -1 \cdot 27 \, DPM + 0 \cdot 131 \, Sum\text{-}I - 0 \cdot 50 \quad (1)$$

$$n = 11, r^2 = 0 \cdot 870, Q^2 = 0 \cdot 655, s = 0 \cdot 558, F = 26 \cdot 9$$

$$RGR_{AU} = -0 \cdot 737 \, DPM + 0 \cdot 029 \, \tau_4 + 0 \cdot 335 \quad (2)$$

$$n = 11, r^2 = 0 \cdot 912, Q^2 = 0 \cdot 792, s = 0 \cdot 379, F = 41 \cdot 5$$

where DPM = calculated dipole moment, Sum-I = sum of intrinsic topological state values (Hall 1991), τ_4 = a total topological index (Hall & Kier 1990), n = number of compounds, r = correlation coefficient, Q = cross-validated correlation coefficient (by leave-one-out procedure) and is a measure of the predictivity of the correlation, s = standard error of estimate, F = Fisher statistic. In each case, indomethacin was a pronounced outlier, being predicted to be much more irritant than reported, and was therefore omitted from the correlations.

It is significant that dipole moment appears as a consistently important parameter; its negative coefficient indicates that a high dipole moment is conducive to low gastro-intestinal irritancy. The other terms in eqs. 1 and 2 are topological in nature, and are difficult to interpret; they probably reflect aspect of molecular size and/or shape. The good predictivity of the correlations means that they can be used with confidence to predict the gastro-intestinal irritancy of other NSAIDs.

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