COMFA MODELING AND PHARMACOKINETICS OF IV. ANESTHETIC AGENTS

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Introduction: Previous publications have described pharmacophores for immobilizing activity, induction dose potency and cardiovascular effects of iv. anesthetics [1,2,3,4]. The present study examines for a molecular basis for the pharmacokinetics of 14 intravenous anesthetic agents.

Methods: A group of fourteen structurally-diverse iv. anesthetics were included in the modeling with data for their pharmacokinetics in man obtained from the literature and unpublished studies. Separate models were derived for two disposition parameters - systemic clearance (Cls), and apparent volume of distribution at steady state (Vdss). Low energy conformers of each anesthetic were constructed and geometry-optimized using semi-empirical quantum mechanics. The conformers were aligned by field-fit minimization to provide the best correlations between steric and electrostatic fields (ESF) of the molecules and those of a single lead structure, the same conformer of eltanolone as used in previous studies [1,2,3,4]. CoMFA models for each disposition parameter were formulated using SYBYL v7.3 (Tripos Inc, MO). Orientations yielding models with the greatest predictive capability when assessed by leave-one-out cross-validation (q2) were retained.

The disposition CoMFA models were then compared with the corresponding models for immobilizing activity (based on EC50: free drug concentration abolishing movement in response to noxious stimuli in 50% subjects)[2] and cardiovascular depression (free drug concentration associated with a 20% decrease in mean arterial pressure)[4].

Results: Both CoMFA models for the two disposition parameters were based on 2 latent variables. For Cls, the model explained 95.2% of the variance in observed values, and showed good intrinsic predictive ability (q2=0.663), absolute log residual (ALR) 0.076(SD 0.067); for Vdss, r2=0.986; q2 =0.718, ALR 0.025 (0.020). The contributions of ESF to the overall CoMFA models were 65.9% and 73.7% for Cls and Vdss respectively, with ratios for the relative contributions of electrostatic and steric interactions differing between clearance and apparent volume of distribution (Cls 1.9:1; Vdss 2.8:1).

All four pharmacophoric maps showed distinct areas of positive and negative charge, and bulk favoured and dysfavoured areas. However there were poor isocontour correlations between the two disposition parameters - electrostatic r=-0.220; steric r=0.018 [based on 9025 lattice points]. When the disposition pharmacophore maps were compared with the pharmacophores for immobilization, there were some areas of commonality in both the ESF and steric maps (pLog EC50 and Cls: ESP r=0.512 and r=-0.159, and Vdss: steric r=0.424 and r=-0.483). When compared with the corresponding maps for cardiovascular depression, the correlations for ESF were r=0.551 for Cls and r=-0.255 for Vdss; and for the steric features, Cls r=0.407 and Vdss r=-0.448.

Conventional physico-chemical models based on logP (octanol-water partition coefficient) showed associations for Cls (r=0.507), and free drug fraction (r=0.753), but no correlation between Log P and Vdss (r=-0.153). There were improved correlations between Log P and unbound drug parameters (Clsu and Vdssu r=0.769 and r=-0.700 respectively); as well as between drug molecular weight and free (unbound) drug fraction and Vdss (r=0.462 and r=-0.669 respectively).

Conclusions: Four CoMFA activity models have been derived describing the disposition of a series of 14 intravenous anesthetic agents in terms of the spatial distribution of key steric and electrostatic features of the molecules. These models show only weak similarities with corresponding maps for anesthetic immobilizing potency and cardiovascular depression [2,4]; implying different molecular bases of these properties of intravenous anesthetic agents.

References:

1. Sewell JC, Sear JW (2002) Br J Anaesth 88; 166-174
2. Sewell JC, Sear JW (2004) Br J Anaesth 92; 45-53
3. Sear JW (2011) Br J Anaesth 106; 312-318
4. Sear JW (2010) Br J Anaesth 104: 684-690

Summary: Two pharmacophoric activity models have been developed using CoMFA analysis which describe the systemic clearance and apparent volume of distribution of 14 intravenous anesthetic agents in terms of the spatial distribution of electrostatic and steric features. The disposition models show little similarity to the pharmacophores for immobilizing potency and cardiovascular depression.