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CARDIOVASCULAR

Development of pharmacophoric maps for cardiovascular depression by intravenous anaesthetic agents: comparison with maps for immobilizing activity

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Background. The molecular basis of the cardiovascular effects of i.v. anaesthetics was investigated using comparative molecular field analysis (CoMFA).

Methods. The cardiovascular effects, measured as changes in mean arterial pressure (MAP), compared with awake values of continuous infusions of 13 structurally diverse i.v. anaesthetics were compared at EC_{50} plasma concentrations, and by determination of plasma-free drug concentrations associated with a 20% decrease in MAP ($dMAP_{20}$). Data were obtained both from the literature and from unpublished data of the author. The results were fitted to a CoMFA activity model using field-fit minimization techniques to maximize similarities in molecular bulk and electrostatic potential to the lead compound, eltanolone.

Results. The final model for cardiovascular depression based on free drug concentrations associated with $dMAP_{20}$ explained 95.8% of the variance in observed activities, with a cross-validated q^2 of 0.824 (n=12). A second model based on change in MAP at EC_{50} plasma concentrations explained 98.3% of the variance in arterial pressure, but performed poorly at cross-validation (q^2 0.526). The comparative model for immobilizing potency had an r^2 value of 0.987 and q^2 0.823. Comparison of pharmacophoric maps showed several key electrostatic and steric regions common to both models when isocontours were constructed linking lattice grid points, making the greatest 40% contributions (87.57% for electrostatic fields and 86.16% for steric fields).

Conclusions. Comparison of activity models for cardiovascular depression and immobilizing potency for i.v. anaesthetics shows significant commonality, suggesting that it may not be possible to separate those molecular features associated with each of these effects.

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We have previously reported studies identifying the molecular bases of inhalation and i.v. anaesthetic immobilizing activity using the ligand-based molecular modelling technique, comparative molecular field analysis (CoMFA).[1–4] In CoMFA, the steric and electrostatic interaction energies between the anaesthetic molecules and a charged probe atom are calculated and correlated with potency to formulate an activity model. Pharmacophoric maps can be derived to highlight the spatial distribution of key regions where the steric and electrostatic interactions are making the greatest contribution to the activity model.

Cardiovascular depression is an important side-effect of most anaesthetics, but the molecular properties that determine this activity are unknown. The present study aimed to identify the molecular basis for *in vivo* cardiovascular depression seen during i.v. continuous infusion anaesthesia and to compare the resulting pharmacophore maps with the equivalent models for *in vivo* immobilizing activity.

Methods

Thirteen structurally diverse i.v. general anaesthetic agents were considered [eltanolone (5β-pregnanolone), alphaxalone,

minaxolone, ORG 21465 (a water-soluble dimethylmorpholin-4-yl, 5α-pregnane steroid), thiamylal, thiopental, methohexital, pentobarbital, *rac*-ketamine, *R*-etomidate, ORG 25435 (an α-amino acid phenolic ester derivative), clomethiazole, and propofol].

Cardiovascular activity

Haemodynamic data during continuous infusion anaesthesia, measured as the mean arterial pressure (MAP), were taken from the literature[5–33] together with additional unpublished data from the author. All measurements were made under conditions of steady-state anaesthesia, with the arterial pressure calculated as the per cent change from arterial pressure during the pre-anaesthetic awake state and the associated plasma-free drug concentrations. In all studies, the arterial pressure changes were noted at times of no surgical or other noxious stimulation.

Two different measures of cardiovascular activity were determined. The first model compared the plasma-free anaesthetic concentration that resulted in a 20% decrease in MAP ($dMAP_{20}$). Since infusions of ketamine are associated with an increase in arterial pressure, haemodynamic data for ketamine were excluded from this analysis, with the final model being derived for the other 12 agents.

Data used for this cardiovascular model were the results of individual plots of free drug concentration *vs* change in MAP (%) compared with the pressure recorded in the awake state for each of the studies referenced. The mean $dMAP_{20}$ (as shown in Fig. 1) was calculated from the linear regression equation of log drug concentration and per cent change in MAP for each anaesthetic. As such, values in Figure 1 represent point estimates. Data were obtained from both human and non-human (dog, pig, or both) studies for alphaxalone, etomidate, thiopental, methohexital, and propofol. Cardiovascular data for pentobarbital and thiamylal were obtained from studies in the dog. Where data from different species were available, comparison was made of the separate estimates for $dMAP_{20}$ for each species.

A second cardiovascular model was formulated based on the absolute change (increase or decrease) in MAP when the i.v. anaesthetic was infused at the EC_{50} drug concentration (the free drug plasma concentration of anaesthetic that abolishes movement in response to noxious stimuli in 50% of patients). Data for 13 i.v. agents (the 12 in the previous model plus *rac*-ketamine) were included.

Immobilizing activity

Potency data (expressed as the EC_{50} plasma-free drug concentration that abolishes movement in response to noxious stimuli) together with data for protein binding were obtained from the literature and have been reported previously.[2] Wherever possible, data were taken from studies in which no other adjuvant drugs were administered up to the time of the stimulus (either the initial surgical incision for human studies or the response to comparable noxious stimulus in animal studies). Where 67% nitrous oxide was given as part of the anaesthetic, this was assumed to equate to 0.6 MAC.

For the comparison of changes in MAP at the EC_{50} drug concentration, data from individual studies were collated, and again mean values are shown as point estimates in Table 1.

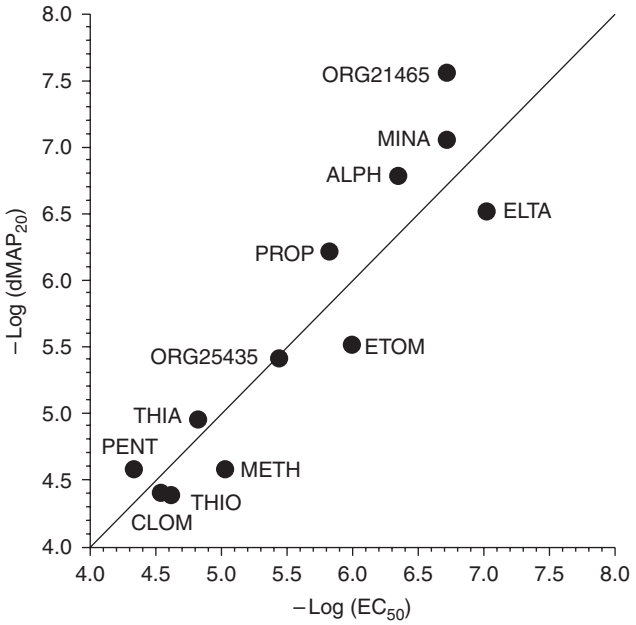

Fig 1 Plasma free drug concentrations associated with cardiovascular depression (as a 20% decrease in MAP, $dMAP_{20}$) and immobilization (EC_{50}, failure in 50% subjects or animals to respond to noxious stimulation). Where appropriate, corrections have been made for patients receiving 67% nitrous oxide. MINA, minaxolone; ALPH, alphaxalone; ELTA, eltanolone; PROP, propofol (di-isopropyl phenol); ETOM, *R*-etomidate; THIA, thiamylal*; PENT, pentobarbital*; METH, methohexital*; THIO, thiopental*; CLOM, clomethiazole. *Drug administered as racemate.

Table 1 Data for cardiovascular depression as absolute change in MAP during continuous infusions at the EC_{50} plasma drug concentration; the concentration associated with the infusion rate of the anaesthetic needed to maintain anaesthesia in 50% patients (rac, racemate)

	Observed change in MAP (%)	**Predicted change in MAP (%)**	**EC_{50} (μM)[2]**
Alphaxalone	−29	−26.7	0.46
Minaxolone	−25	−24.0	0.197
Eltanolone	−14	−16.5	0.094
ORG 21465	−20	−19.3	0.202
ORG 25435	−22	−22.7	3.79
Pentobarbital (rac)	−17	−17.8	48.26
Thiopental (rac)	−10	−9.5	24.76
Thiamylal (rac)	−18	−17.8	15.33
Methohexital (rac)	−12	−10.2	9.53
Propofol	−15	−13.4	1.57
R-etomidate	−35	−38.0	1.02
Clomethiazole	−10	−9.1	29.75
Ketamine (rac)	+19	+17.1	4.30