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TITLE: DEXMEDETOMIDINE ALTERS THIOPENTAL DOSE REQUIREMENT AND DISTRIBUTION PHARMACOKINETICS

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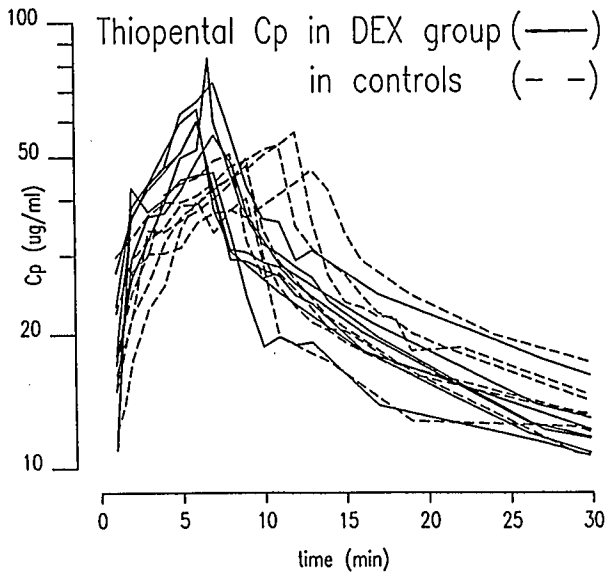
Dexmedetomidine (DEX) is a potent α_2 agonist that is an anesthetic adjuvant[1]. This study quantitates the pharmacokinetic and pharmacodynamic interactions between thiopental (TP) and DEX using the EEG as a measure of CNS drug effect.

Methods: 14 ASA I, unpremedicated patients (20-46 yr) were randomly assigned to receive IV infusion of either saline (control) or DEX that achieved a constant DEX plasma concentration (Cp) of 0.5 ng/ml. At 35 min TP was infused at 100 mg/min until EEG burst suppression (dose requirement endpoint). Arterial blood was sampled for TP kinetic analysis using a 3 cmpt model. The TP Cp vs EEG effect (waves/sec from aperiodic waveform analysis) was examined with a semi-parametric pharmacodynamic analysis[2] that determined blood:brain equilibration half-time (T1/2 keo) for thiopental. The two groups were compared with the Mann-Whitney U test.

Results: TP dose-requirement to obtain EEG burst suppression was significantly reduced 30% by DEX (median: 575 mg; range: 458-650 mg) vs control (833 mg; 733-1325 mg). During TP infusion, the Cp increased more rapidly in the DEX group (figure). DEX significantly reduced TP distribution clearance and steady state volume of distribution (Vd_{ss}) by 37%. Other kinetic parameters were not altered. DEX did not alter TP dynamics (T1/2 keo, TP Cp vs EEG effect).

Discussion: DEX decreased TP dose requirement by decreasing the rate (distribution clearance) and extend (Vd_{ss}) of TP distribution to body tissues. DEX did not alter TP pharmacodynamics as measured with the EEG. The decrease of TP distribution kinetics can be explained by a DEX induced decrease of cardiac output and regional blood flow. These findings contrast to potent inhalational anesthetics where DEX alters pharmacodynamics (MAC)[3]. DEX effects on other IV drugs dependant upon redistribution mechanism to terminate anesthetic effect must be established.

References:
1. Anesthesiology 73: 230, 1990
2. Biomed Meas Infor Contr 2: 161, 1988
3. Anesthesiology 69: 818, 1988



A307

Title: ANESTHETIC AND HEMODYNAMIC INTERACTIONS OF DEXMEDETOMIDINE AND FENTANYL IN DOGS

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Introduction. Opioids are incomplete anesthetics.[1] The α_2-agonist, dexmedetomidine (Dx), reduces MAC for inhalational anesthetics in dogs by more than 90%.[2] Hemodynamic changes may limit the clinical utility of Dx as an anesthetic.[2] Since different receptors mediate the effects of Dx and fentanyl (Fe), lower doses of each may be combined to produce anesthesia and decrease adverse hemodynamic consequences of Dx.

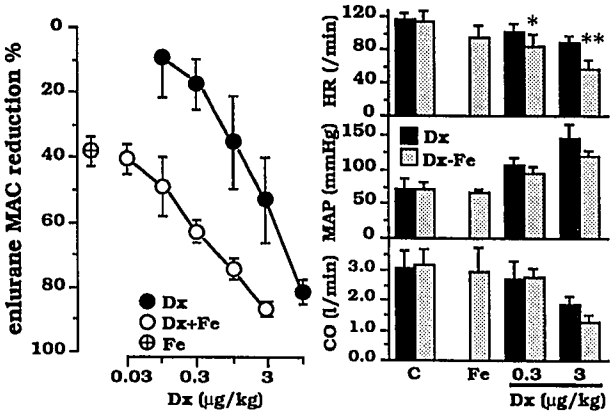
Methods. After at least 1 hr of stable enflurane anesthesia in 10 mongrel dogs, heart rate (HR), mean arterial pressure (MAP), cardiac output (CO) and enflurane MAC (EMAC tail-clamp method) were determined. Then the dogs were divided into two groups of 5. Dx dogs received successive 10 min iv infusions of Dx 0.1, 0.3, 1, 3 and 10 µg/kg. After each dose, EMAC and hemodynamics at MAC were measured. Dx+Fe dogs received Fe 45 µg/kg in 20 min followed by an infusion of 0.2 µg/kg/min. After 1 hour of Fe-infusion, EMAC and hemodynamics were measured. Dx was administered in doses from 0.03 to 3 µg/kg and the measurements repeated as described above. Plasma Fe was determined by RIA every 30 min during the study. EMAC data were fitted to the Emax model using nonlinear regression and the slopes of log Dx dose vs EMAC were dermined by linear regression. Fe levels and hemodynamics were analyzed with ANOVA or ANCOVA followed by Sheffe's test. Values are mean±SD.

Results. Dx produced a dose dependent reduction of EMAC (ED50 2.04±0.53 µg/kg). A stable plasma level of Fe 4.3±0.7 ng/ml shifted the Dx log dose-response curve to the left without changing its slope. Fe did not modify dose-dependent increase in MAP or decrease in CO but it did augment significantly the decrease in HR.

Discussion. The parallel leftward shift of the Dx log dose-response curve by Fe suggests at least an additive anesthetic interaction between the two. Coadministration of the agents could allow smaller doses to reach the same anesthetic end-point and thus, mitigate undesirable hemodynamic effects of Dx. However, Fe potentiation of the HR decrease by Dx suggests that bradycardia, an inherent property of opioid anesthesia, may be a disturbing occurence after Dx and Fe combination.

References. 1. Anesthesiology 57: 485-488, 1982
2. Anesth Analg 67: 611-615, 1988

Figure. EMAC reduction and hemodynamic effects of dexmedetomidine (Dx) alone, fentanyl (Fe) alone and in combination (Dx+Fe). C=control, *P<0.05 **P < 0.01, Dx vs Dx+Fe. Values are mean±SD.



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