Perhexiline is concentrated in both human atria and ventricles: perioperative analysis

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Introduction: Therapeutic monitoring of drugs is predicated on the idea that plasma drug concentrations are predictive of their concentrations at the sites of efficacy and/or toxicity. However, in the case of cardioactive agents, this hypothesis has rarely been tested in man.

Aims: As a component of an evaluation of the efficacy of the cardioprotective agent perhexiline, an inhibitor of carnitine palmitoyl transferase-1 (CPT-1), in high risk patients undergoing cardiac surgery, we evaluated plasma: myocardial drug concentration relationships.

Methods: Patients were treated with perhexiline maleate (200mg twice daily for three days, then 200mg daily thereafter) for a mean ± S.D. of 10 ± 5 days preoperatively. Plasma (n = 88), atrial (n = 88) and ventricular (n = 26) perhexiline concentration determination was performed *via* high performance liquid chromatography with simultaneous sampling.

Results: The median (range) of plasma, atrial and ventricular perhexiline concentration were 0.25 (0.03, 1.82) mg/L, 6.54 (0.74, 31.52) mg/L and 10.48 (3.06, 35.71) mg/L, respectively. Of the 88 plasma samples, 59 (67%) fell within the established therapeutic range of 0.15 to 0.6 mg/L, 22 (25%) were subtherapeutic, and 7 (8%) were over-therapeutic. There was substantial and similar accumulation of perhexiline in both atria and ventricles relative to plasma. There was also a significant linear correlation between plasma and myocardial perhexiline concentrations ($r2 = 0.83$, $P < 0.0001$ and $r2 = 0.70$, $P < 0.0001$ for atrial and ventricular concentrations, respectively). The median (range) of the ventricular: atrial concentration ratio was 1.65 (0.90, 3.90).

Discussion: Whilst at this stage the underlying mechanism of perhexiline uptake into the myocardium is unknown, (whether it be simple diffusion, high tissue binding or active transport), the above results suggest that perhexiline is highly concentrated in human atria and ventricles. Plasma perhexiline concentrations are strongly predictive of those within its major site of action.