A Novel Adsorbent System Rapidly Clears Amlodipine from Human Blood

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Background

- Calcium channel blockers are not effectively removed by current extracorporeal removal techniques, such as hemodialysis or charcoal hemoperfusion
- Amlodipine is highly (>95%) protein bound
- CytoSorb® is a perfusion cartridge containing porous, divinylbenzene co-polymer beads, approved in Europe to reduce excess cytokines in critically-ill patients

Research Question

- Can a cartridge containing porous, divinylbenzene co-polymer beads efficiently clear amlodipine from human blood?

Methods

- Ex vivo GLP pharmacokinetic study
- 20 mg amlodipine was added to 4 liters of citrate-anticoagulated whole human blood and stirred to equilibrate, with a target initial whole blood amlodipine concentration of 5.0 mg/L
- This blood was then recirculated through a Cole-Parmer Masterflex L/S Digital Drive blood circuit at a rate of 300 mL/min
- In the experimental arm, a saline-primed 300-mL CytoSorb cartridge was installed in-line with the circuit
- Whole blood samples were obtained prior to amlodipine instillation, following equilibration, and after 0, 15, 30, 60, 120, and 180 minutes of blood recirculation
- Whole blood amlodipine concentrations were determined using previously-validated ultra-performance liquid chromatography (UPLC) methods

Results

- Whole blood amlodipine concentrations were 0.55 – 0.64 of whole blood levels, with slightly more rapid elimination from plasma
- Plasma amlodipine concentrations were 0.55 – 0.64 of whole blood levels, with slightly more rapid elimination from plasma
- All quality control checks were within 15% of their respective nominal values.
- At the start of recirculation, whole blood amlodipine concentrations were 5.44 (+/- 0.63) mg/L in the experimental and 4.70 (+/- 0.16) mg/L in the control arms.
- No measureable degradation of amlodipine was observed in the control arm.
- Amlodipine extraction followed first-order kinetics, best fit to with a two-compartment model ($r^2 > 0.98$)
- First hour: $k_e = 0.028$ min$^{-1}$; $t_{1/2} = 25$ minutes
- Subsequent: $k_e = 0.009$ min$^{-1}$; $t_{1/2} = 77$ minutes
- Approximately 65% of amlodipine was removed in the first 30 minutes of perfusion and 89% in the first 120 minutes
- The two-compartment kinetics observed likely correspond with very rapid clearance of amlodipine from the plasma, followed by continued clearance of amlodipine from the cellular compartment

Discussion

- Amlodipine is not considered traditionally dialyzable due to high protein binding and large volume of distribution.
- CytoSorb adsorption appears to overcome protein and cellular binding issues and rapidly reduces whole blood amlodipine concentrations to near zero
- The whole blood volume and circuit flow rates used in this experiment were chosen to approximate clinical use
- The two-compartment kinetics observed likely correspond with very rapid clearance of amlodipine from the plasma, followed by continued clearance of amlodipine from the cellular compartment
- The ability to remove amlodipine from the cellular compartment may represent a significant advantage over other extracorporeal removal techniques, such as hemodialysis.
- In vivo, the device should rapidly establish and maintain a diffusion gradient that favors movement of amlodipine out of tissues
  - The pharmacokinetics of diffusion of amlodipine out of tissues has not been studied
  - The relationship of serum : whole blood amlodipine concentrations in vivo is not well-characterized
- A head-to-head comparison with hemodialysis has not been performed
- The CytoSorb cartridge has been successfully deployed as a side-limb off a venoarterial extracorporeal membrane oxygenation (VA-ECMO) circuit
- Clinical experience in patients with septic shock, another example of mixed cardiogenic and distributive shock, and in other critically ill patients with hemodynamic instability, has shown no major safety issues
- No significant hemolysis or immune system activation
- Mild thrombocytopenia with prolonged use (> 6 hrs)

Conclusion

- Hemoperfusion over divinylbenzene co-polymer beads rapidly removes amlodipine from whole human blood

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This device is not currently approved by the FDA

The CytoSorb® device is approved in Europe as an extracorporeal cytokine adsorber, for use in any situation in which cytokines are elevated.