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Anticoagulant Effects of *N*-Chlorotaurine and the Analogs *N*-Monochloro-2,2-dimethyltaurine and *N,N*-Dichloro-2,2-dimethyltaurine

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Introduction

Intravascular catheter-related bacteremia is an important source of morbidity and mortality in hemodialysis patients. The current standard of care in many institutions is the use of heparin as a catheter lock solution to prevent thrombosis. However, heparin has limited intrinsic antimicrobial activity. The use of therapeutic catheter lock solutions containing antimicrobial agents, either alone or in combination with anticoagulants may be an important addition to the arsenal for the prevention of intravascular catheter-related bacteremia. *N*-chlorotaurine (NCT) is an endogenous chloramine compound produced by human phagocytes as part of the innate immune system response to pathogens (1). This study aimed to evaluate the activity of NCT and the analogs *N*-monochloro-2-2-dimethyltaurine (NVC-612) and *N,N*-dichloro-2,2-dimethyltaurine (NVC-422) on blood coagulation pathways. All agents have broad-spectrum antimicrobial activity and the additional selective effect on coagulation cascade would allow for their possible application as catheter lock solutions in human medicine.

Materials & Methods

Test Substance preparation: NCT was produced at the Division of Hygiene and Medical Microbiology (Innsbruck, Austria) and NVC-612 and 422 were prepared at NovaBay Pharmaceuticals, Inc. (Emeryville, CA.) All test substances or controls were dissolved in sodium chloride, and serially diluted in fresh human blood to evaluate effects on prothrombin time, activated partial thromboplastin time, thrombin time, fibrinogen (Dade Behring GmbH, Marburg, Germany), and direct Thrombin inhibition (AnaSpec, Inc., Fremont, CA USA). Human venous blood was drawn from the cubital vein from healthy volunteers.

Results

Final concentrations of 1.38 mM NCT (0.025%), 1.38 mM NVC-612, and 1.02 mM NVC-422 prolonged prothrombin time (Quick value 17 – 30%), activated partial thromboplastin time 3- to 4-fold to 76-125 sec, and thrombin time 2- to 4-fold to 34 to 68 sec (range each) (Figure 1). Fibrinogen decreased from 258 to 283 mg/dl (range of controls) to < 40 mg/dL in samples containing chloramines (Figure 1).The effects were significant compared to controls without oxidative power ($p < 0.01$ for all). No direct thrombin inhibition was observed by NVC-422, NVC-612 or dimethyltaurine at concentrations tested (0.4, 4 and 40mM) (Figure 2).

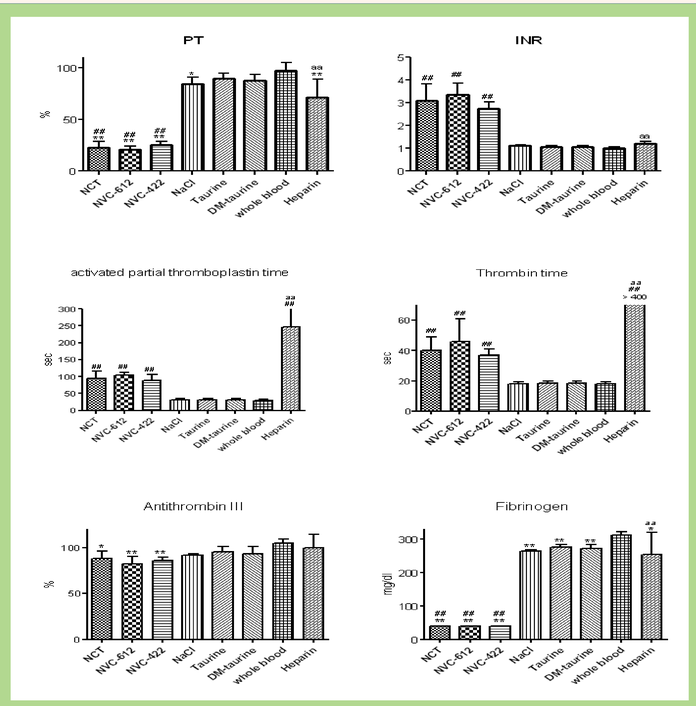

Figure 1. Influence of NCT and Aganocides dissolved in saline on coagulation parameters after ten-fold dilution in whole human blood (0.2 mL plus 1.8 mL) to a final concentration of 1.38 mM.
Mean values ± SD of 3-4 independent experiments.
* P < 0.05 versus whole blood
** P < 0.01 versus whole blood
P < 0.01 against all controls taurine, DM-taurine
aa P < 0.01 versus NCT and aganocides
One-way ANOVA and Dunnett's Comparison Test

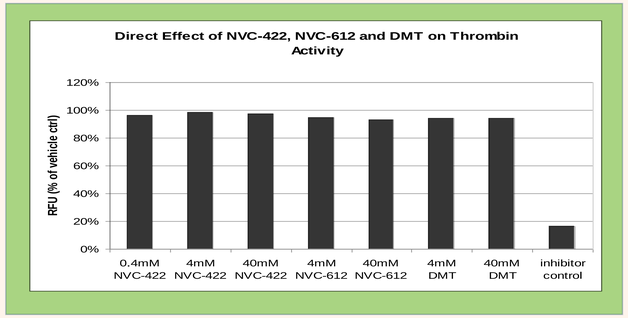

Figure 2. NVC-422, NVC-612, and dimethyltaurine have no inhibitory effect on thrombin activity at any concentration tested. A known inhibitor (N-α-NAPAP synthetic inhibitor) does show direct thrombin inhibition.

Conclusion

- There is a specific anticoagulant effect of NCT, NVC-612 and NVC-422 on the blood coagulation system consistent with previous literature reports on chloramines.
- This added effect is beneficial for evaluating NCT, NVC-612 and NVC-422 as potential broad spectrum antimicrobials for central venous catheter lock solutions.

References

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