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Research Article

Glucono-Delta-Lactone Inhibits E. Coli Induced-Upregulated Blood Coagulation

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Abstract:
Endotoxin, when added to human blood produces many deleterious agents which can upregulate the clotting system. In previous studies it has been shown that these hypercoagulable effects can, in part, be bioassayed by the reduction in this endotoxin-associated clotting time when compared to control (saline) values. The cellular generation of tissue factor, the initiator of the clotting cascade is more pronounced in diseases and conditions causing the greatest mortality and morbidity. Glucono-delta-lactone, when added to the endotoxin treated aliquots mitigates this clotting state whether it is added to the blood samples before incubation or after incubation, just prior to the addition of calcium ions to initiate the clotting process. The reduction in clotting reveals anticoagulant properties which enhances the need to develop the biomedical applications of glucono-delta-lactone.

Key words: Glucono-delta-lactone (GDL), tissue factor (TF), endotoxin (ET), hypercoagulable.

INTRODUCTION:

Bacterial endotoxin, also known as lipopolysaccharide (LPS) is a potent initiator of upregulated blood clotting. This medical condition has a high morbidity and mortality. When endotoxin is added to anticoagulated human blood in a test tube, dramatic changes result. The time necessary for the blood to clot (go from liquid to a gel) is called the clotting time. Endotoxin-treated bloods clot more quickly than the same blood without its addition due to the biochemicals generated.

Tissue factor (TF), the initiator of the blood clotting cascade, is among those generated. Unfortunately, there are few, if any, low toxicity anticoagulants to prevent this danger.

In humans, this TF generation produces a multiple of thrombotic conditions finally resulting in tissue and organ failure. This process may end with uncontrolled bleeding (hemorrhage) and death.

Glucono-delta-lactone (GDL) is a substance that is found in many foods and cosmetic products and is on the FDA's GRAS

(Generally Recognized as Safe) list. In recent studies, GDL has also been shown to have anticoagulant effects in blood (1,2).

METHODS:

Human citrated whole blood (CWB) samples were obtained from the University Hospital's clinical labs (A: n=25; B: n=16)

Five samples were made by adding the following reagents to 990 µl of CWB:

1. 20 µl of E. coli endotoxin, 1.0 microgram/ml final
2. 20 µl of GDL, 2.5 mg/ml final
3. 20 µl of E. coli endotoxin + 20 µl GDL
4. 20 µl of E. coli endotoxin + 20 µl GDL after incubation (Rescue)
5. 20 µl of H_2O (Control)

Samples were then incubated for 2 hours at 37º C. 300 µl of each sample was then added to cuvettes containg 32 µl of $CaCl_2$ and analyzed using the Sonoclot Coagulation Analyzer.

RESULTS:

Experiment A

Clotting Times (sec)

	ET	GDL	ET + GDL	CONTROL
Mean	176	233	215	203
SD	26	24	27	24

Table 1. The mean and standard deviation (seconds) for E. coli endotoxin (ET) incubated with GDL in human citrated whole blood. When compared to control value ET significantly reduces the clotting time (hypercoagulable state). GDL prolongs the clotting time and when ET and GDL are incubated together, the clotting time is prolonged compared to ET alone. GDL mitigates hypercoagulable state.

Experiment B

Clotting Times (sec)

	ET	GDL	ET + GDL	RESCUE	CONTROL
Mean	206	253	240	229	229
SD	21	22	24	21	17

Table 2. The mean and standard deviation (seconds) for *E. coli* endotoxin (ET) incubated with GDL in human citrated whole blood. When compared to control value ET significantly reduces the clotting time (hypercoagulable state). GDL prolongs this time and when ET and GDL are incubated together, the clotting time is prolonged compared to ET alone. GDL mitigates hypercoagulable state.

In Rescue column ET is incubated with blood alone and then GDL is added just prior to performing the clotting time. The rescue value was significantly prolonged compared to ET.

DISCUSSION:

While *E. coli* endotoxin exposure results in a significant decrease in clotting time, adding GDL restores clotting times toward normal values. Additionally, this effect is seen after acute (Rescue Data) administration of GDL, restoring values within minutes. This suggests that GDL may have pharmaceutical use in opposing the effects to endotoxin or diseases presenting with upregulation of clotting.

GDL is a small molecule with a low toxicity profile in animal models (3).

GDL has the potential to markedly reduce the complications of a hypercoagulable state associated with sepsis-like conditions and other prothrombotic states. These diseases could include heart disease, diabetes, cancer and stroke (4).

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