What Is the Efficacy of Iminosugars in Inhibiting Glucosylceramide Synthase in Canine Macrophages?

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Canine Gaucher's disease is an inherited Lysosomal Storage Disorder characterized by a near complete deficiency in the catabolic activity of the enzyme glucocerebrosidase. As a result, the macromolecule glucosylceramide accumulates within the cells preventing proper function. Herein is reported an evaluation of the efficacy of iminosugar based Substrate reduction therapy in inhibiting the excess production of glucosylceramide, allowing the body to break down residual substrates through other chemical pathways. Peripheral blood mononuclear cells were isolated from whole blood using Ficoll density gradient separation and subjected to treatment with the iminosugar, N –Butyldeoxynojirimycin, commonly known as Miglustat. Levels of glucosylceramide were then evaluated through HPLC analysis of O-Phthalaldehyde derivatives deacetylated with sodium hydroxide. The HPLC analysis showed a 55.63% decrease in height and 54.01% decrease in the area of the primary peak from the control to the treated samples. Both the control and experimental group showed similar patterns with peaks at approximately 0.86, 1.04, and 1.32 min. The control group showed an additional peak at 2.21 min while the experimental group's fourth peak appeared at 7.75 min. The significant decrease in the amount of glucosylceramide in the experimental group shows promise for the future of iminosugar based SRT. The treatment applied in this study proved successful in reducing glucosylceramide concentrates within mononuclear cells. However, further studies showing sufficient reproducibility must be performed before any definite conclusion may be drawn from the treatment as a whole.