

Characterization of Reactions to Intravenous Immunoglobulin in Neonatal Calves

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Summary and Implications

Intravenous immunoglobulin (IVIG) products improve passive immunity in neonates. Unfortunately, adverse reactions can occur. This study was designed to determine if physiological changes occurring after IVIG administration were the result of rapid infusion of large molecular weight molecules, or from a more complex mechanism resulting in histamine release. The IVIG was concentrated from bovine abattoir blood and contained approximately 35 g IgG/L. A dextran (75,000 MW) solution was prepared as a high molecular weight control that was similar in osmolarity to the IVIG. Holstein bull calves (n=15) under 1 wk of age were assigned to one of three treatment groups: control calves received 500 ml of 0.9% NaCl; dextran calves received 500 ml of dextran; IgG calves received 500 ml of IVIG. Treatments were rapidly administered (less than 5 min) intravenously via jugular catheter. Heart rate, respiration rate, and blood pressure were measured prior to treatment, and at 1, 3, 5, 10, 15, 20, 25, 30, 45, 60, 75, and 90 min after start of infusion. Blood samples were obtained at the same sampling times, centrifuged, and the plasma immediately placed on ice for determination of histamine concentration using an enzyme immunoassay. Mean respiration rates were higher in calves treated with IVIG compared to calves in the other two groups at all time periods measured. Mean heart rates were lower in calves treated with IVIG compared to calves in the other groups through 45 min. Calves treated with dextran had higher mean heart rates than calves on the control treatment from 10 min through 30 min. Mean blood pressure tended to be higher in calves treated with IVIG compared to calves on the control treatment at 1 min, however, there were no differences between groups at any other time period. Mean histamine concentrations were higher in calves treated with IVIG compared to calves on the control treatment at 1 min, but were not different at any other time period. These data indicate that adverse reactions to IVIG in calves are not mediated by high molecular weight molecules or by histamine release.

Introduction

Calves are essentially agammaglobulinemic at birth, although a small percentage of calves may have negligible amounts of circulating serum IgG₁, IgG₂, IgM, and IgA. In ruminants, passive immunity is provided through ingestion of colostrum by the neonate after birth. Colostrum is vital

to the health and survival of the neonatal calf, and 18% of cows provide colostrum with less than 100 g of IgG, the most commonly recommended amount needed to prevent failure of passive transfer (FPT). Colostrum-deprived calves are 50-75 times more likely to die before 21 d of age than colostrum-fed calves, with most deaths occurring during the first week of life.

Oral colostrum supplements and replacers are available and can be offered when either the dam's or some other fresh or frozen colostrum source is not available; however, the calf small intestine is unable to absorb intact IgG molecules after approximately 26 h of age. Once the period of intestinal permeability to immunoglobulin molecules has passed, passive immunity can be provided by i.v., i.p., or s.c. injection. Intravenous infusions of a bovine plasma product in calves can increase serum IgG approximately 2.9 g/L.

Unfortunately, adverse reactions to intravenous immunoglobulin (IVIG) administration can occur and have been reported to occur in approximately 25-55% of foals, a species where IVIG products are commonly used to treat FPT. The incidence rate for reactions in foals appears to be related to product IgG concentration and method of production, with infusion of lyophilized IgG products resulting in an increased rate of reactions. Intravenous immunoglobulin products are also commonly used in human medicine to treat a variety of disorders, and adverse reactions are reported to be due to anaphylaxis, complement activation, vasoactive properties of the infusion product, or other unknown.

Clinical signs of adverse reactions and the mechanism of action causing these reactions have not been documented in calves receiving IVIG. Therefore, this study was designed to characterize adverse reactions to IVIG in calves, and to determine if physiological changes occurring after IVIG administration were the result of rapid infusion of large molecular weight molecules or were due to a more complex mechanism resulting in histamine release.

Procedures

Fifteen Holstein bull calves under one week of age were assigned to one of three treatment groups. The treatment groups were: (1) Control, calves received 500 ml of 0.9% NaCl; (2) Dextran, calves received 500 ml of a dextran solution; and (3) IgG, calves received 500 ml of an IVIG product. The dextran solution was prepared by adding 10 g of dextran powder (75,000 MW) to 500 ml of a NaCl solution. The dextran solution was prepared so that the osmolarity of the solution (269 mOsm) was similar to that of the concentrated plasma product (277 mOsm). The IVIG product was prepared from plasma obtained after a two-time enrichment process of bovine abattoir blood, with the final product containing approximately 35 g IgG/L. Previous

analysis showed that the product had low endotoxin levels, and low complement activity.

Catheters were aseptically placed in each jugular vein so that the treatment could be administered through one, while blood samples were obtained from the other. A catheter was also placed in an ear artery and connected to a manometer for arterial blood pressure monitoring.

Calf heart rate, respiration rate, and mean arterial blood pressure were measured prior to the start of treatment infusion, and then at 1, 3, 5, 10, 15, 20, 25, 30, 45, 60, 75, and 90 min after the start of the infusion. Blood samples were collected into tubes containing EDTA at the same sampling times, centrifuged, and the plasma immediately placed on ice for determination of histamine concentration.

The amount of histamine present in plasma was determined using a commercially available ELISA (Immunotech, Marseille, Cedex 9, France).

Experimental data were analyzed using the general linear models procedure of SAS (SAS Inst. Inc., Cary, NC). Multiple measurements recorded over time were analyzed using the mixed procedure with calf within treatment interaction used as the random statement. Significance was declared at $P < 0.05$ and trends towards significance at $P > 0.05$ to $P < 0.10$.

Results and Discussion

Two calves died within 30 minutes after the infusion of IVIG, therefore, they were excluded from the results, and least squares means are reported. There was an overall treatment effect ($P < 0.001$), an overall time effect ($P < 0.001$), and a time by treatment effect ($P < 0.001$) for respiration rate (Figure 1). Mean respiration rates were not different among treatments prior to the start of infusions, but were higher in IgG calves compared to calves in the other two groups at all other time periods measured. Respiration rate also showed a large increase after the start of the infusion in calves receiving IVIG, whereas respiration rate remained more or less constant in calves on the other two treatments.

There was no overall treatment effect for heart rate (Figure 2), however, there was a time effect ($P < 0.001$) and a time by treatment effect ($P < 0.001$). Mean heart rates were not different among treatments prior to the start of the infusions, however, heart rates decreased in calves receiving IVIG, and were lower compared to calves in the other two groups through 45 min. post infusion. Heart rates increased in both control and dextran calves, and dextran calves had higher mean heart rates compared to control calves from 10 min. through 30 min. post infusion.

There was no overall treatment effect for mean arterial blood pressure (Figure 3), however there was a time effect ($P < 0.001$) and there tended to be a time by treatment effect ($P < 0.07$). Mean arterial blood pressure was not different among treatments prior to the start of the infusions, nor was it significant between treatment groups at any other time period measured. After the start of the infusion, blood pressure increased initially and then decreased rapidly in IgG calves. In contrast, calves receiving the other two treatments

had a more gradual increase and then decrease in arterial blood pressure.

Mean histamine concentrations (Figure 4) were not different among treatments prior to the start of the infusions, nor were they significant between treatment groups at any other time period measured.

The IVIG product utilized in this trial consistently caused clinical signs of infusion reactions in all calves. Within seconds after the start of the infusion, calves showed increases in respiration rate and became increasingly dull and lethargic. In contrast, calves receiving the dextran and saline solutions showed no visible clinical signs of discomfort, although they did show increases in heart rate. The increase in heart rate is likely due to expansion in fluid volume, and could be attributed to the rapid infusion of large molecular weight molecules in the dextran group.

There are three ways by which exposure to a substance can cause anaphylaxis: 1. exposure to a foreign protein that results in IgE antibody formation. Reexposure results in IgE mediated degranulation of mast cells and basophils; 2. formation of immune complexes that activate the complement cascade; and 3. administration of certain agents (hyperosmolar solutions, radiocontrast agents, etc.) that directly stimulate the release of mediators by unknown mechanisms. Classic anaphylactic reactions are defined as resulting from a Type I immune response, also called immediate hypersensitivity. This type of reaction requires three components: 1. an antigen; 2. IgE antibody; and 3. effector cells such as mast cells and basophils that synthesize and release pharmacologic mediators. Reactions that appear clinically similar to anaphylactic reactions, but are not mediated by IgE are referred to as anaphylactoid reactions. Because the calves on this trial did not have previous exposure to IVIG, it is unlikely that the observed reactions were mediated by IgE. Therefore, the observed reactions will be classified as anaphylactoid reactions for the remainder of this discussion.

Increased histamine concentrations are often observed in anaphylactic and anaphylactoid reactions. However, some studies do report increased histamine levels after challenge in control mice, while others report no change in histamine levels before or after anaphylaxis in both control and mast cell deficient mice. Hypotension and death due to anaphylactic reactions in mice also do not appear to require mast cell-derived mediators. Adverse reactions to IVIG in humans have also been shown to be associated with increases in IL-6 and thromboxane B₂, but not change in blood pressure, kininogen, histamine, or tryptase.

Concentrations reported for histamine in this study were well within the normal range. Plasma histamine concentrations were never greater than 3 nM histamine. Mean whole blood values for histamine in 1-week old calves are 173 nM. Whole blood histamine concentrations are generally 20 – 200 times greater than plasma histamine concentrations.

Administration of contrast media and hyperosmolar solutions to humans can also cause reactions similar to those observed from infusion of IVIG. However, the osmolarity of the dextran and the IVIG solution were both

similar to the osmotic pressure in calves. The osmotic pressure in newborn calves is 293 mOsm/L and decreases to 286 mOsm/L after feeding. Thus, hyperosmolarity is not the cause of the anaphylactoid reactions observed in these calves.

These data indicate that the adverse reactions to IVIG observed in this trial are not mediated by high molecular weight molecules or by the release of histamine. Further research is needed to determine the role of platelet activating factor in anaphylactoid reactions in calves.

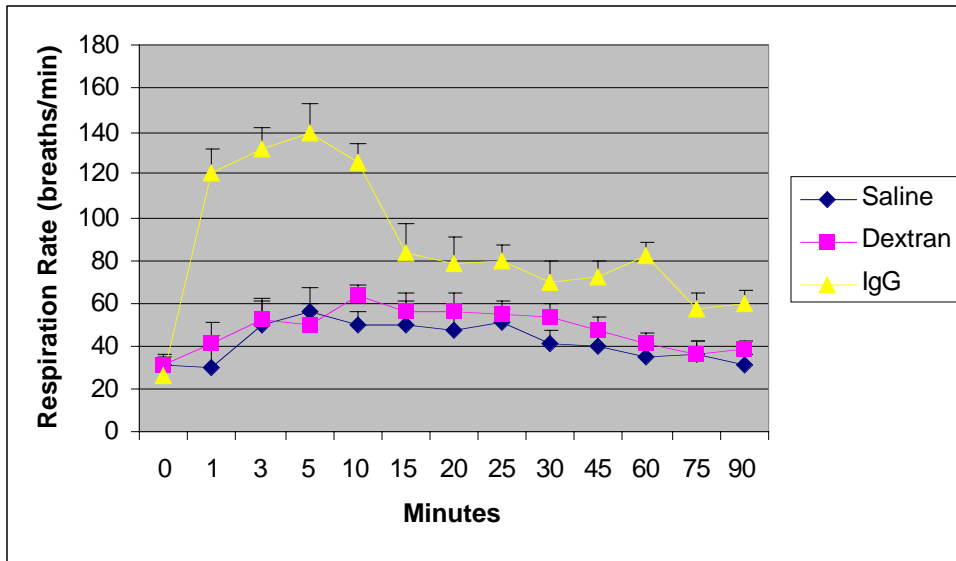


Figure 1. Mean respiration rates for calves receiving saline, dextran, or intravenous immunoglobulin.

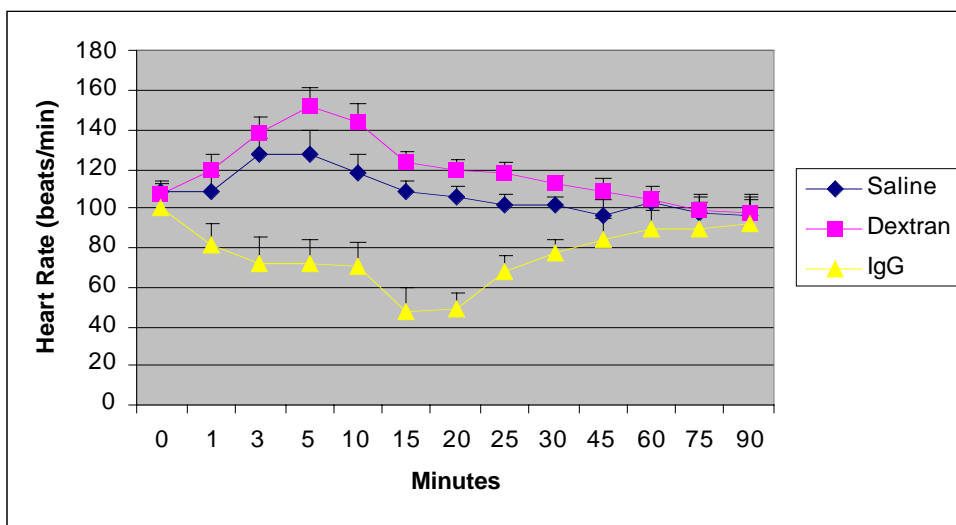


Figure 2. Mean heart rates for calves receiving saline, dextran, or intravenous immunoglobulin.

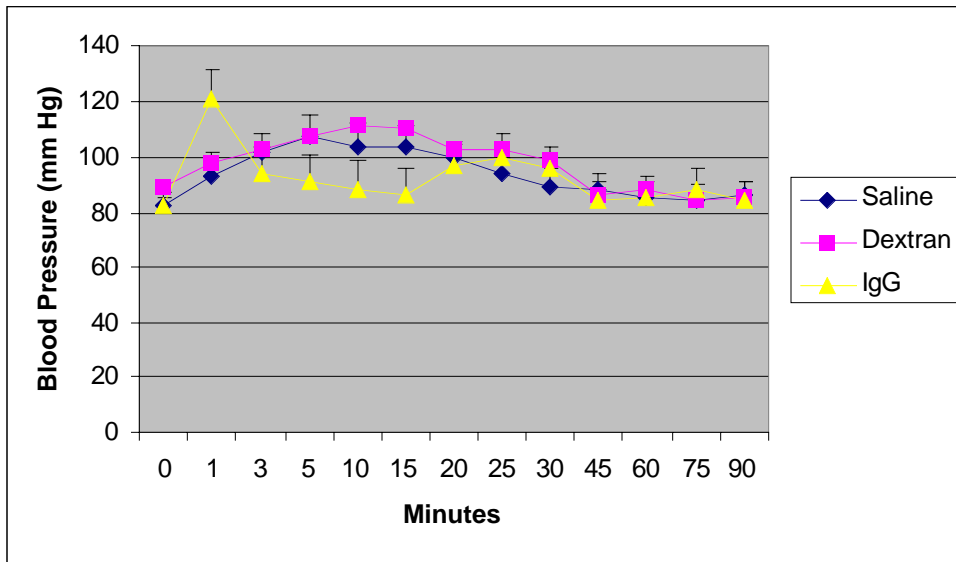


Figure 3. Mean arterial blood pressure for calves receiving saline, dextran, or intravenous immunoglobulin.

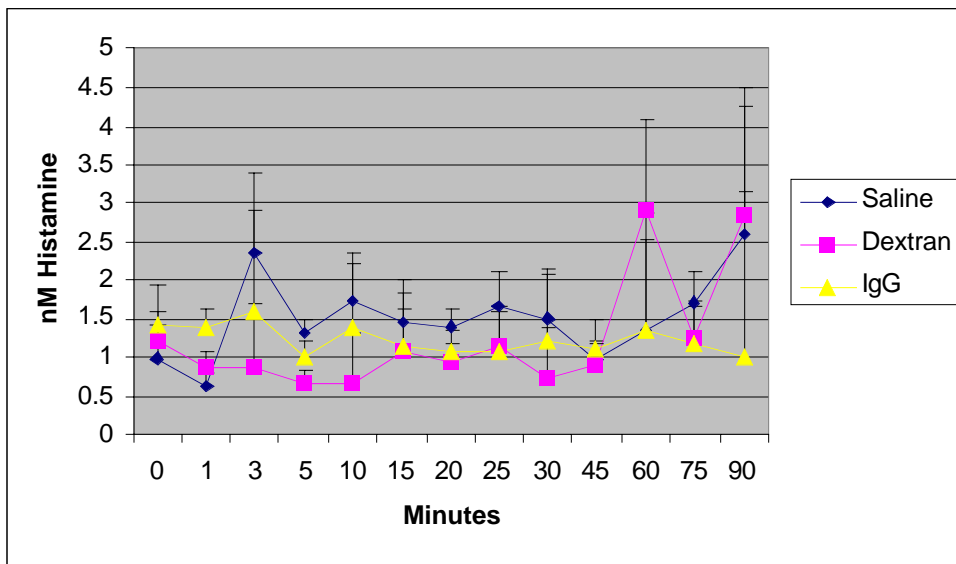


Figure 4. Mean histamine concentration for calves receiving saline, dextran, or intravenous immunoglobulin.