

# Effect of insulin dosage on glycemic response in dogs with diabetes mellitus: 221 cases (1993–1998)

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**Objective**—To evaluate glycemic response to insulin treatment in dogs with diabetes mellitus.

**Design**—Retrospective study.

**Animals**—221 dogs with diabetes mellitus.

**Procedure**—Type and dosage of insulin used, minimum and maximum blood glucose concentrations, time of blood glucose concentration nadir, and optimal duration of action of insulin were determined on the basis of data obtained prior to initial examination at the teaching hospital (127 dogs), at the time of initial examination (212 dogs), at the time a second follow-up blood glucose curve was performed (59 dogs), and at the time of clinical control of diabetes mellitus (83 dogs).

**Results**—Prior to examination, 69 of 127 dogs (54%) received 1 SC insulin injection daily. Thirty-one dogs (24%) received a high dose of insulin (ie, > 1.5 U/kg [0.7 U/lb] of body weight); 27 of these dogs (87%) received 1 injection/d. Eleven of 16 dogs (69%) that were hypoglycemic (blood glucose concentration < 80 mg/dl) also received 1 injection/d. However, optimal duration of action of insulin was > 12 hours in only 5 of 83 dogs (6%) evaluated at the time diabetes mellitus was clinically controlled. At that time, only 1 dog (1%) received a high dose of insulin, and the dog received 2 injections/d. Moreover, 8 of 10 dogs (80%) with hypoglycemia received 1 injection/d.

**Conclusions and Clinical Relevance**—Most dogs with diabetes mellitus are clinically regulated with 2 daily insulin injections. Administration of a high dose of insulin or development of hypoglycemia may be more common in diabetic dogs that receive insulin once daily, compared with dogs that receive insulin twice daily. (*J Am Vet Med Assoc* 2000;216:217–221)

Current guidelines for long-term treatment of dogs with diabetes mellitus recommend the use of insulin preparations with an intermediate duration of action (ie, NPH preparations or lente preparations).<sup>1</sup> Duration of action of these insulin preparations is between 4 and 24 hours in dogs<sup>1</sup>; therefore, guidelines advocate administration of 1 or 2 daily injections. Some veterinary endocrinologists recommend that treatment be initiated with 1 daily injection of insulin and increased to 2 daily injections if necessary.<sup>1</sup> Others recommend that dogs receive 2 daily insulin injections from the onset of treatment.<sup>2</sup> Variations in recommendations may be attributable to lack of information regarding the number of dogs for which diabetes mellitus is adequately controlled with 1 or 2 daily insulin

injections. Although veterinary endocrinologists generally agree that most diabetic dogs require 2 daily insulin injections to adequately control blood glucose concentrations, it is not known how many dogs may require only 1 injection. Thus, knowledge of the number of diabetic dogs adequately treated with 1 daily insulin injection may affect treatment decisions.

One reason that 1 daily injection of insulin may have been advocated for treatment of diabetes mellitus in dogs is that results of some pharmacokinetic studies indicate that the duration of action of insulin in dogs is > 12 hours. Authors of 1 such study<sup>3</sup> reported that duration of action of lente preparations was between 14 and 24 hours in 10 dogs with naturally developing diabetes mellitus. However, this result was determined from blood insulin concentrations rather than blood glucose concentrations. In a clinical setting, duration of action of insulin is determined from blood glucose concentrations. Authors of another study<sup>4</sup> that examined 8 dogs with naturally developing diabetes mellitus reported a mean duration of action of 16 hours for lente preparations and a mean duration of action of 24 hours for NPH preparations. Those authors concluded that optimal treatment of diabetic dogs should consist of 2 daily injections of lente preparations of insulin or, less preferably, 1 daily injection of NPH preparations. However, in that study,<sup>4</sup> food was withheld from dogs on days during which duration of action of insulin was determined. Therefore, these results may not accurately reflect duration of action in client-owned dogs. Another reason 1 daily insulin injection may be preferable is that owners of diabetic dogs may find it more convenient to administer insulin only once a day.

A thorough assessment of response to insulin administration in diabetic dogs may help improve the guidelines for treatment of diabetes mellitus. The purpose of the study reported here was to evaluate the glycemic response to insulin treatment in a large group of client-owned dogs with diabetes mellitus.

## Criteria for Selection of Cases

A computer search of all dogs admitted to the Veterinary Hospital of the University of Pennsylvania (VHUP) between January 1993 and May 1998 identified 295 dogs with diabetes mellitus. Medical records of all 295 dogs were reviewed in detail by 1 board-certified veterinary internist (RSH). Inclusion criteria included clinical signs suggestive of diabetes mellitus and at least 1 of the following: persistent hyperglycemia with glucosuria or persistent hyperglycemia despite insulin treatment. Two hundred twenty-one of the 295 dogs met the criteria for inclusion in the study; 174 (79%) of these dogs had persistent hyperglycemia with glucosuria, and 47

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(21%) had persistent hyperglycemia despite insulin treatment. Seventy-four of 295 dogs were excluded from the study. Exclusion criteria included insufficient data for a diagnosis of diabetes mellitus (ie, 1 measurement of blood glucose concentration above reference range without urinalysis; 43 dogs), unavailability of medical records for review (11), erroneous coding of dogs as diabetic (10), concomitant glucocorticoid treatment (6), treatment for insulinoma (2), and transient diabetes mellitus (2).<sup>5,6</sup>

## Procedures

Insulin treatment was assessed by reviewing blood glucose concentration versus time curves (ie, blood glucose curves) and other data obtained prior to examination at the VHUP, at the time of initial examination at the VHUP, at the time a follow-up blood glucose curve was performed, and at the time of clinical control of diabetes mellitus. A blood glucose curve was defined as determination of blood glucose concentration every 2 hours for 12 to 24 hours while dogs were treated with insulin. Dogs that received insulin once daily had a blood glucose curve performed over at least 24 hours, and dogs that received insulin twice daily had a blood glucose curve performed over at least 12 hours.

Insulin treatment was characterized by determining the type and dosage of insulin used, minimum and maximum blood glucose concentrations during the blood glucose curve, the time of blood glucose concentration nadir, and the optimal duration of action of insulin. We considered the time of blood glucose concentration nadir to be the time of peak insulin action. Optimal duration of action of insulin was defined as the number of hours after insulin administration in which blood glucose concentration remained < 200 mg/dl.<sup>1</sup> When blood glucose concentration remained < 200 mg/dl or > 200 mg/dl during the entire blood glucose curve, optimal duration of action was not determined.

A second blood glucose curve was reviewed only for those dogs in which a blood glucose curve was performed after the time of initial examination and before clinical control of diabetes mellitus. Clinical control was defined as the time at which the owner perceived the dog to be normal, and all clinical signs of diabetes mellitus (eg, polydipsia, polyuria) had resolved. A blood glucose curve was performed at the time of clinical control; however, the curve was not used to determine clinical control. Clinical control was determined from owner-reported resolution of clinical signs alone.

Blood glucose measurements were performed on a chemistry analyzer<sup>a</sup> or a glucometer.<sup>b</sup> Blood glucose concentrations > 600 mg/dl are presented as "Hi" readings on the glucometer and were recorded as 600 mg/dl for the purpose of this study. In clinically normal, nondiabetic, noninsulin-treated dogs, hypoglycemia is defined as a blood glucose concentration < 60 mg/dl. However, for the purpose of this study, hypoglycemia was defined as blood glucose concentration < 80 mg/dl, because well-regulated diabetic dogs should have a blood glucose concentration > 80 to 100 mg/dl.<sup>1</sup>

## Results

Mean ( $\pm$  SD) age of dogs at the time diabetes mellitus was diagnosed was  $8.9 \pm 2.9$  years (median, 7 years; range, 3 months to 16 years). Eighty-nine of the 221 dogs (40.3%) were spayed females, 78 (35.3%) were castrated males, 38 (17.2%) were sexually intact males, and 16 (7.2%) were sexually intact females. Fifty-eight dogs (26%) were mixed-breeds, 27 (12%) were Miniature Schnauzers, 18 (8%) were Labrador Retrievers, 16 (7%) were Miniature Poodles, 11 (5%) were Samoyeds, 9 (4%) were Toy Poodles, 7 (3%) were Yorkshire Terriers, 7 (3%) were Rottweilers, 6 (3%) were Lhasa Apsos, 5 (2%) were Pugs, and the rest (57; 26%) represented other breeds.

One hundred and twenty seven dogs were treated with insulin prior to examination at the VHUP. Types of insulin used were NPH preparations (79 dogs; 62%), lente preparations (31; 24%), ultralente preparations (7; 5.5%), regular insulin (2; 2%), and PZI preparations (1; 1%). Seven (5.5%) dogs were treated with recombinant human insulin, but the type of preparation used was not known. Sixty-nine (54%) dogs were treated once daily with SC injections of insulin, 57 (45%) dogs were treated twice daily with SC injections of insulin, and 1 (1%) dog received IM insulin injections every 2 hours. Mean insulin dose administered prior to examination at the VHUP was  $1.2 \pm 0.8$  U/kg ( $0.6 \pm 0.4$  U/lb) of body weight (median, 1 U/kg [0.5 U/lb]; range, 0.1 to 5.3 U/kg [0.05 to 2.4 U/lb]). Thirty-nine (31%) dogs had a blood glucose curve performed prior to examination at the VHUP. Mean minimum blood glucose concentration was  $153 \pm 152$  mg/dl (95 mg/dl; 20 to 604 mg/dl). Sixteen of these 39 (41%) dogs had at least 1 blood glucose concentration that was < 80 mg/dl, and most of these dogs (11/16) received 1 insulin injection/d. Mean maximum blood glucose concentration was  $297 \pm 187$  mg/dl (245 mg/dl; 47 to 798 mg/dl).

Thirty-one of the 127 (24%) dogs that had been treated with insulin prior to examination at the VHUP received an insulin dose > 1.5 U/kg (0.7 U/lb). Mean dose of insulin for these dogs was  $2.3 \pm 0.8$  U/kg ( $1.1 \pm 0.4$  U/lb; median, 2.0 U/kg [0.9 U/lb]; range, 1.6 to 5.3 U/kg [0.7 to 2.4 U/lb]). Most of these dogs (27; 87%) were treated with 1 daily SC injection of insulin, and most (22; 71%) did not have a blood glucose curve available for review. However, blood glucose curves were recorded for 9 (29%) of these dogs; 8 were hypoglycemic (mean minimum blood glucose concentration,  $43 \pm 19$  mg/dl; median, 38 mg/dl; range, 22 to 71 mg/dl), and 1 was not (minimum blood glucose concentration, 382 mg/dl). This dog was believed to have insulin resistance attributable to liver and splenic masses and a lytic lesion on the right fourth rib.

Two hundred and twelve dogs received insulin treatment at the time of initial examination at the VHUP. This group included 118 of the 127 dogs that were treated with insulin prior to examination at the VHUP and 94 dogs that were treated with insulin for the first time at the VHUP. At the time of initial examination, most dogs (155; 73%) were given an NPH preparation of insulin. Other dogs received lente preparations (28; 13%), regular insulin administered

by continuous rate IV infusion (18; 8.5%) or IM injection (3; 1.5%), ultralente preparations (4, 2%), human recombinant insulin of unknown preparation (3, 1.5%), or PZI preparations (1, 0.5%). One hundred and ninety-five of the 212 (92%) dogs had a blood glucose curve performed at the time of initial examination. Of these dogs, 107 (55%) had been treated with SC injections of insulin prior to examination at VHUP. At the time that initial blood glucose curves were performed at the VHUP, 141 (72.3%) dogs received 2 daily SC insulin injections, 34 (17.4%) received 1 daily SC insulin injection, and 20 (10.3%) dogs received regular insulin administered by continuous rate IV infusion or IM injection every 2 hours. Mean insulin dose administered by SC injection was  $0.7 \pm 0.6$  U/kg ( $0.3 \pm 0.3$  U/lb; median, 0.6 U/kg [ $0.3$  U/lb]; range, 0.1 to 6.9 U/kg [ $0.05$  to  $3.1$  U/lb]). Mean minimum blood glucose concentration for these 195 dogs was  $168 \pm 103$  mg/dl (median, 144 mg/dl; range, 23 to 600 mg/dl), and mean maximum blood glucose concentration was  $389 \pm 141$  mg/dl (382 mg/dl; 106 to 1,278 mg/dl). Blood glucose concentration nadir was observed at a mean of  $6.0 \pm 4.1$  hours after insulin administration (5 hours; 2 to 24 hours).

Mean optimal duration of action of insulin at the time of initial examination at the VHUP was  $11.1 \pm 4.3$  hours (12 hours; 4 to 26 hours). Optimal duration of action in 141 dogs treated with insulin administered twice daily was  $\leq 12$  hours in 49 (34.7%) dogs,  $> 12$  hours in 8 (5.7%) dogs, and undetermined in 84 (59.6%) dogs. Optimal duration of action in 34 dogs treated with insulin administered once daily was  $\leq 12$  hours in 17 (50%) dogs,  $> 12$  hours in 8 (23.5%) dogs, and undetermined in 9 (26.5%) dogs. Optimal duration of action in 155 dogs treated with NPH preparations of insulin was  $\leq 12$  hours in 63 (40.6%) dogs,  $> 12$  hours in 15 (9.7%) dogs, and undetermined in 77 (49.7%) dogs. Optimal duration of action in 28 dogs treated with lente preparations of insulin was  $\leq 12$  hours in 12 (43%) dogs,  $> 12$  hours in 4 (14%) dogs, and undetermined in 12 (43%) dogs. Optimal duration of action in 4 dogs treated with ultralente preparations of insulin was  $\leq 12$  hours in 1 dog,  $> 12$  hours in 2 dogs, and undetermined in 1 dog.

At the time of initial examination at the VHUP, most dogs (193/212; 91%) were evaluated because of diabetes mellitus. However, 19 (9%) dogs were considered by their owners to be clinically controlled diabetics and were examined because of other conditions. These other conditions included orthopedic disorders (4 dogs), masses or neoplastic disease (3), vomiting (3), cataract surgery (2), and other problems that affected only 1 dog each. Most of these 19 dogs (13) were treated with 2 insulin injections/d; however, 6 were treated with 1 insulin injection/d.

A second blood glucose curve was performed for 59 of the 221 (27%) dogs prior to clinical control of diabetes mellitus. At this time, 51 (86%) dogs were receiving NPH preparations of insulin, and 8 (14%) were receiving lente preparations. Most of these dogs (49; 83%) were treated with 2 SC insulin injections/d; however, 10 (17%) dogs were treated with 1 injection/d. Mean dose of insulin administered by SC injection

was  $0.7 \pm 0.3$  U/kg ( $0.3 \pm 0.1$  U/lb; median, 0.7 U/kg [ $0.3$  U/lb]; range, 0.2 to 1.6 U/kg [ $0.1$  to  $0.7$  U/lb]). Mean minimum blood glucose concentration was  $204 \pm 135$  mg/dl (median, 192 mg/dl; range, 31 to 600 mg/dl), and mean maximum blood glucose concentration was  $368 \pm 146$  mg/dl (388 mg/dl; 70 to 600 mg/dl). Mean optimal duration of action of insulin was  $10.2 \pm 4.6$  hours (11 hours; 4 to 24 hours).

At the time of clinical control of diabetes mellitus, 83 of 221 (38%) dogs had a blood glucose curve performed. Of these 83 dogs, 42 (51%) had a second blood glucose curve performed prior to clinical control. At the time of clinical control, 74 of these 83 (89%) dogs were receiving NPH preparations of insulin and 9 (11%) were receiving lente preparations. Most of these dogs (73; 88%) were treated with 2 SC insulin injections/d; however, 10 (12%) were treated with 1 injection/d. Mean insulin dose administered by SC injection was  $0.7 \pm 0.3$  U/kg (median, 0.7 U/kg; range, 0.2 to 1.6 U/kg). Mean minimum blood glucose concentration was  $158 \pm 94$  mg/dl (median, 127 mg/dl; range, 35 to 560 mg/dl). Ten (12%) dogs had a blood glucose concentration  $< 80$  mg/dl, and most of these dogs (8/10) received 1 insulin injection/d. Duration of action of insulin was determined for 5 hypoglycemic dogs and was 10 hours in 2 dogs, 12 hours in 2 dogs, and 21 hours in 1 dog. Mean maximum blood glucose concentration was  $308 \pm 119$  mg/dl (314 mg/dl; 101 to 600 mg/dl). Blood glucose concentration nadir was observed at a mean of  $5.3 \pm 3.7$  hours after insulin administration (4 hours; 1 to 24 hours). Mean optimal duration of action of insulin was  $10.2 \pm 4.6$  hours (10 hours; 4 to 24 hours). Once clinical control was achieved, only 5 of 83 (6%) dogs had an optimal duration of action of insulin  $> 12$  hours. Three of these 5 dogs received NPH preparations of insulin, and 2 received lente preparations.

Eighty-four of 221 (38%) dogs received insulin once daily as their first mode of treatment, either prior to or at the time of initial examination at the VHUP. Optimal duration of action of insulin was determined at the time of clinical control for only 16 of these 84 (19%) dogs. Optimal duration of action was  $\leq 12$  hours in 11 of the 16 dogs and  $> 12$  hours in 5 dogs (24, 22, 21, 20, and 14 hours, respectively). For 11 of 16 (69%) dogs, 1 daily insulin injection failed to control diabetes mellitus, and in these dogs, initial dosage was increased to 2 daily injections.

At the time of clinical control of diabetes mellitus, only 1 of 83 dogs received an insulin dose  $> 1.5$  U/kg; that dog received 1.6 U of insulin/kg (0.7 U/lb) twice a day. Blood glucose concentration in this dog at the time of clinical control was between 164 and 246 mg/dl.

## Discussion

Dogs with diabetes mellitus can be treated with 1 or 2 daily SC insulin injections, although most dogs require 2 injections/d. However, the number of dogs that require 1 or 2 insulin injections/d for adequate control of diabetes mellitus has not been established. The results of this study suggest that only 5 of 83 (6%) dogs with diabetes mellitus were adequately treated with 1 daily insulin injection. Nevertheless,  $> 50\%$  of

the 127 dogs treated with insulin before they were initially examined at the VHUP received 1 insulin injection/d. It is possible that these dogs were treated once daily, because owners of diabetic dogs find it easier to provide insulin once a day rather than twice a day. However, results of the present study suggest that in most cases, 1 daily insulin injection is not adequate. Follow-up blood glucose curves and determination of optimal duration of action of insulin are needed to determine the optimal dosage of insulin required for individual dogs.

Sixteen of 84 dogs that received insulin once daily as their first mode of treatment had optimal duration of action of insulin determined at the time of clinical control of diabetes mellitus. Diabetes mellitus was not controlled in 11 of these 16 (69%) dogs that received 1 daily insulin injection; these dogs required 2 daily injections for clinical control. However, this finding must be interpreted cautiously because of the small sample size. Further studies that compare glycemic control in dogs that receive insulin once and twice daily are needed to determine the true rate of failure of 1 daily insulin injection in dogs with naturally developing diabetes mellitus.

Another finding of this study was that prior to examination at the VHUP, 27 of 31 dogs that required doses of insulin  $> 1.5$  U/kg received 1 injection/d. A dose of insulin  $> 1.5$  U/kg in a dog that is hyperglycemic is consistent with a diagnosis of insulin resistance.<sup>7</sup> However, in all but 1 of the 9 dogs that received this high dose of insulin and for which blood glucose curves were available for review, at least 1 blood glucose concentration was abnormally low (ie,  $< 80$  mg/dl). Additionally, at the time of clinical control, only 1 of 83 dogs required an insulin dose  $> 1.5$  U/kg. Therefore, most of the dogs that received  $> 1.5$  U of insulin/kg did not have insulin resistance and were inappropriately treated with a high dose of insulin. High insulin doses may have been inappropriately prescribed because of the Somogyi effect, which results in compensatory hyperglycemia caused by insulin-induced hypoglycemia. If blood glucose concentration is measured only when it is high, then insulin dose prescribed may be erroneously high, causing profound hypoglycemia. Treatment of diabetic dogs with 2 daily insulin injections may decrease inappropriate administration of insulin at doses  $> 1.5$  U/kg.

Low blood glucose concentration is a reported complication of insulin treatment and can be fatal.<sup>8</sup> Low blood glucose concentration was detected in a number of dogs prior to examination at the VHUP and at the time of clinical control of diabetes mellitus. In both instances, hypoglycemia was observed more commonly in dogs treated with 1 daily insulin injection; prior to examination at the VHUP, 11 of 16 hypoglycemic dogs received 1 daily insulin injection, and at the time of clinical control, 8 of 10 hypoglycemic dogs received 1 daily insulin injection. Treatment of dogs with 2 daily insulin injections may prevent some cases of insulin-induced hypoglycemia.

Low blood glucose concentration following administration of insulin may also result in rapid compensatory hyperglycemia, which may be erroneously

interpreted as a short duration of action of insulin. However, we found that duration of action in 5 dogs with low blood glucose concentration at the time of clinical control was between 10 and 21 hours. Therefore, the Somogyi effect was not observed in these dogs.

One of the limitations of this study is that information regarding the type of insulin used was incomplete. The species from which insulin was produced was often not known, and in some dogs it was not known what preparation of recombinant human insulin was used. Therefore, we could not compare the effects of different types of insulin with an intermediate duration of action in dogs with diabetes mellitus. Additional studies focusing on the use of human recombinant insulin in dogs may be needed, because the availability of bovine and porcine insulin has decreased.

The study is further limited because it is retrospective in nature and not all dogs were treated with 1 and 2 insulin injections/d. Ideally, each dog would have received identical types of insulin administered once a day for a certain time period, and treatment would have been switched to 2 daily insulin injections. This type of prospective study design would facilitate a more accurate comparison of the 2 modes of treatment. However, ethical constraints may not allow for such a study in a clinical setting. If a dog responds favorably to 1 of the treatment regimens, it may be difficult to justify a switch to the other regimen just for the purpose of comparison. Therefore, some of the dogs in this study treated successfully with 2 daily insulin injections from the onset of treatment may have also done well with 1 daily injection.

Another limitation of this study is that clinical control of diabetes mellitus does not necessarily reflect optimal blood glucose concentration or optimal insulin treatment. For example, at the time of clinical control, 1 dog had blood glucose concentrations between 361 and 485 mg/dl during a 24-hour blood glucose curve. This dog had several follow-up blood glucose curves determined for 50 months after initial examination, and a blood glucose curve that indicated better glycemic control could have been reviewed for this study. Similarly, although 10 dogs that received 1 insulin injection/d were reported by their owners to be clinically controlled diabetics, optimal duration of action of insulin was  $< 12$  hours in 5 of these dogs; these dogs should have been treated with 2 daily insulin injections. Therefore, clinical control of diabetes mellitus does not always correlate with maintenance of blood glucose concentrations within acceptable limits or optimal duration of action of insulin that is at least equivalent to dosing frequency. However, to maintain consistency throughout the study, only blood glucose curves at the time that owners perceived their dogs to be clinically controlled were reviewed. Clinical control of diabetes mellitus in dogs has an important role in monitoring the response of dogs to treatment, because blood glucose concentrations may be affected by stress of hospitalization and may not reflect the true state of glycemic control.

Results of this study suggest that most dogs

(73/83; 88%) with diabetes mellitus were clinically controlled with 2 daily insulin injections. Additionally, most dogs (27/31) that required doses of insulin > 1.5 U/kg received 1 injection/d, and most cases of hypoglycemia were observed in dogs treated with 1 daily insulin injection (11/16 dogs prior to examination at the VHUP and 8/10 dogs at the time of clinical control). We recommend that diabetic dogs initially receive 2 doses of insulin/d. Frequency of dosing can be decreased if results of follow-up blood glucose curves suggest that duration of action of insulin is > 12 hours.

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<sup>a</sup>Chemistry analyzer, Kodak Ektachem 700, Eastman Kodak Co, Rochester, NY.

<sup>b</sup>Encore glucometer, Bayer Corp, Elkhart, Ind.

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