Control of diabetes mellitus in cats with porcine insulin zinc suspension

G. J. MARTIN, J. S. RAND

The required dose rate of porcine insulin zinc suspension to control the signs of diabetes mellitus in 25 cats was assessed, and their response to insulin treatment was investigated over 12 months. The cats required a median dose of 0·5 iu/kg bodyweight twice a day, and only two of the cats required doses higher than 1·0 iu/kg twice a day. Their lowest blood glucose concentration was on average significantly higher during the night than during the day. Seven of the cats went into diabetic remission during the study, and the control of the clinical signs in the others was either excellent or good by the end of the study.

ALTHOUGH cats appear to have a type of diabetes analogous to type 2 diabetes in human beings, the majority of diabetic cats are insulin-dependent (Rand 1999). There have been several studies of the use of various insulins for the treatment of diabetes mellitus in cats, including protamine zinc insulin, ultralente and lente, and neutral Hagedorn (NPH) insulins (Moise and Riemers 1983, McMillan and Feldman 1986, Nelson and others 1992, Bertoy and others 1995). The proprietary veterinary formulation of porcine insulin zinc suspension (40 iu/ml) (Caninsulin; Intervet) is approved for use in dogs and/or cats in more than 20 countries in Europe, North America and Australasia, and has recently been approved for use in dogs in the USA (Vetsulin; Intervet). Pharmacokinetic and pharmacodynamic data for this insulin indicate that twice-daily administration would be necessary in diabetic cats (Martin and Rand 2000), but its efficacy has not been reported.

It has proved difficult to determine how best to evaluate diabetic control in cats. Subjective criteria, for example, the owner's opinion of the general health of the cat, have failed to match quantifiable measures of glycaemic control, such as the mean blood concentrations of glucose or serum fructosamine, particularly in cats in which diabetes is not well controlled (Goossens and others 1998, Martin and Rand 1999a). One study found that the choice of insulin was unrelated to the success of glycaemic control, and improved glycaemic control did not correlate with the improved survival of diabetic cats (Goossens and others 1998).

This study evaluated the clinical response of 25 diabetic cats to treatment with porcine insulin zinc suspension over a period of up to a year.

MATERIALS AND METHODS

Animals and treatment regimen

The 25 cats were all cared for according to the guidelines specified by the University of Queensland Animal Experimental Ethics Committee.

The 17 male and eight female cats had been referred to the University of Queensland Veterinary Teaching Hospital for treatment. Their median age at admission was 12 years (range six to 15 years); there were 12 domestic shorthair cats, six Burmese, two Burmese cross, three domestic longhair, one Abyssinian and one Tonkinese. Seven of the cats had a history of the recent use of diabetogenic drugs (corticosteroids or progestogens), although none of them had received these drugs during the six weeks preceding their inclusion in the study. All the cats had normal total thyroxine concentrations. The cats that had persistent polydipsia and polyuria, despite insulin doses of more than 1·0 iu/kg twice a day, were tested for hyperadrenocorticism with a low-dose dexamethasone suppression test (Feldman and Nelson 2004).

Of the 25 cats, 15 had been newly diagnosed with diabetes and had not received any treatment. Two of the cats had been diagnosed within the previous four weeks and had been treated unsuccessfully with a sulphonylurea drug. Eight of the cats had been treated previously with insulin (human lente, human NPH, human ultralente or porcine insulin zinc suspension) for up to eight months, but the diabetic control in all of them was regarded as poor.

The clinical signs shown by the cats included polydipsia and polyuria in 23, polyphagia in 12 and marked weight loss in 14. The body condition of the cats was scored subjectively on the scale described by Donaghue and Kronfeld (1993) (Table 1). The results of haematological, biochemical and urinary analyses were similar to previous studies (Crenshaw and Peterson 1996, Kirsch 1998). The activities of the liver enzymes aspartate aminotransferase or alanine aminotransferase were slightly raised in 15 of the cats, seven had a leucocytosis (white blood cell count >19·5 x 10^9/l) and seven had bacteriuria. The cats with leucocytosis or bacteriuria were treated with broad-spectrum antibiotics. Twenty-three of the cats were hypercholesterolaemic (cholesterol >5·5 mmol/l, laboratory reference range 2·5 to 3·4 mmol/l) and 15 were hypertriglyceridaemic (total triglycerides >3·4 mmol/l, laboratory reference range 0·3 to 1·1 mmol/l). All the cats had glycosuria and one had ketonuria by urine dipstick analysis.

During the study, the cats were fed ad libitum with foods selected on the basis of the preference of each cat (Martin and Rand 1999b); the diets included fresh meat, as well as proprietary canned and dried cat foods.

Criteria for selecting and adjusting insulin dose

Injections of porcine insulin zinc suspension (Caninsulin/Vetsulin; Intervet) were administered to the cats every 12 hours, the dosage for each cat being determined on the basis of 12- and 24-hour serial blood glucose measurements. The starting dose of insulin was determined by the blood glucose concentration. The cats that had a blood glucose concentration above 19 mmol/l were given insulin at a dose rate of 0·5 iu/kg bodyweight twice a day, and the cats with a blood glucose of up to 19 mmol/l were given insulin at a dose rate of 0·25 iu/kg bodyweight twice a day.

Increases in the dose were made on the basis of the cats' blood glucose nadir, with a target of 5 to 9 mmol/l. The increases were made 1 iu at a time, no more frequently than once every two weeks and only after serial blood glucose measurements. The dose of insulin was decreased by 50 to 75 per cent if there was clinical or biochemical (minimum blood glucose <3 mmol/l) evidence of hypoglycaemia (Rand 1997). If the minimum blood glucose was 3 to 5 mmol/l, the insulin dose was reduced by 1 iu if the cat's clinical signs were poorly controlled, but it was not changed if its clinical signs were well controlled.

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G. J. Martin, BVSc, PhD, MACVSc,
J. S. Rand, BVSc, DVSc, DACVIM,
Companion Animal Sciences, University of Queensland, St Lucia, QLD 4072, Australia

Dr Martin's present address is Intervet International, Wim de Körverstraat 35, 5831 AN Boxmeer, The Netherlands

Correspondence to Professor Rand

TABLE 1: Subjective scores for the body condition of the cats*

Score	Severity of clinical signs
1	Cachectic, no obvious body fat
2	Thin, limited body fat evident
3	Optimal, ribs palpated easily but not observed readily
4	Overweight, ribs difficult to palpate
5	Obese, large amounts of subcutaneous fat, obvious incapacity

* Donaghue and Kronfeld (1993)

TABLE 2: Subjective clinical scoring system for diabetic control based on the cats' history and clinical signs

Score	Severity of clinical signs
0	Ideal control: as for normal cat
1	Good control: mild polydipsia or other mild signs
2	Adequate control: maintaining weight, polydipsic and/or other signs
3	Poor control: marked polydipsia, weight loss and/or poor appearance
4	Uncontrolled: pronounced polydipsia, emaciated and/or very poor condition and appearance

Analytical methods

Sample collection Blood samples were collected via a catheter placed in a jugular (Martin and Rand 1999c) or peripheral vein or by venepuncture. Samples for biochemical assay were collected into potassium EDTA tubes kept on ice. Plasma was separated by centrifugation at 4°C, and stored frozen at –70°C until assayed.

Urine samples were collected from samples voided in litter trays, or by antepubic cystocentesis when it was necessary to examine the urine sediment.

Measurements and methods At each visit, each cat was assigned a clinical diabetic score on the basis of its owner's assessment and an assessment of its clinical signs (Table 2) (Goossens and others 1998, Martin and Rand 2007). The cats were weighed and assigned a body condition score (Table 1). Water intake was measured by weighing the cat's water bowl at two-hour intervals during a 24-hour period and recording the changes in weight. The blood glucose concentration was measured every two hours for 24 hours (13 measurements), using a pocket reflectance photometer validated for use in cats (Glucometer II; Boehringer-Mannheim) (Link and others 1997), and used to construct a blood glucose curve. These results were used to calculate the mean, maximum and minimum blood glucose concentrations. The J index, a mathematical index combining the mean and standard deviation of the blood glucose concentration in a single value, was calculated using the following formula (Wojcicki 1995):

$$\text{J index} = 0{\cdot}324 \times (\text{mean blood glucose} + \text{standard deviation of blood glucose})^2$$

The area under the blood glucose curve (AUC) was calculated by using the linear trapezoidal method (Rowland and Tozer 1989). The samples of plasma were analysed with an automated chemical analyser (AU400; Olympus). Analysis kits were used for fructosamine (Unimate 5 Fruc; Roche), beta-hydroxybutyrate (Ranbut; Randox), cholesterol (IS cholesterol kit; Integrated Sciences), triglycerides (Triglycerides GPO-PAP; Randox) and free glycerol (Triglyceride GPO-Trinder; Sigma-Aldrich). The triglyceride concentration was corrected for free glycerol by subtracting the free glycerol concentration from the total triglyceride concentration (Jessen and others 1990). Urine glucose was measured using semiquantitative urine dipsticks (Ames Ketodiastix; Bayer Diagnostics) and scored from 0 (no urine glucose) to 4.

Schedule

The cats were initially hospitalised for one week and examined. Blood samples for routine biochemical assay and measurement of fructosamine, beta-hydroxybutyrate and free glycerol concentrations were taken on the first three days and the sixth day of treatment. Serial blood glucose measurements were taken every two hours over a 24-hour period on the third and sixth day, and every two hours over a 12-hour period on the first, second, fourth and fifth days. Urine was collected daily and water intake was measured on the third and sixth day.

The cats were re-examined four, eight, 12, 26 and 52 weeks after the end of the initial examination period. At each recheck, 24-hour serial blood glucose measurements were made and samples were collected for biochemistry. Urine was collected, and the cats' water intake over 24 hours was measured.

Diabetic remission

If a cat had a morning preinsulin blood glucose concentration less than 10 mmol/l and was negative for urine glucose, its insulin treatment was withheld and its blood glucose was checked three times over the following 24 hours. If its blood glucose exceeded 10 mmol/l or glycosuria recurred, its insulin treatment was recommenced; otherwise, a presumptive diagnosis of diabetic remission was made, and its blood and urine glucose were retested one week and one month later. If normoglycaemia and aglycosuria were maintained, the cat was regarded as being in diabetic remission.

Statistical analysis

The data were analysed using Excel (Microsoft) and Visual Basic for Applications (Microsoft), and SigmaStat (SPSS) (Martin and Rand 2007).

RESULTS

Case outcome

During the study, seven of the cats went into diabetic remission and their insulin treatment was discontinued; none of them relapsed during the 12 months. The remissions occurred between weeks 2 and 4 in two of the cats, between weeks 4 and 8 in two, between weeks 8 and 12 in one, and within four weeks after the week 12 visit in two. Twenty-one of the 25 cats were judged to have had excellent or good response to the treatment, based on their owner's satisfaction and their general appearance, and the other four cats had an adequate response at the last follow-up. During the study, one cat died of bacterial meningitis in month 7, one died of undetermined causes in month 11, one died as a result of an accident in week 4, and one was euthanased in month 7 at the request of its owner owing to persistent behavioural problems. One cat was removed from the study after the visit in week 12 owing to its increasingly aggressive behaviour.

Dose rate

Six of the cats were started on an insulin dose of approximately 0·25 iu/kg bodyweight twice a day, 18 on 0·5 iu/kg twice a day and one on 0·9 iu/kg twice a day; this cat had been treated with the same dose of insulin once a day for several months before it entered the study. Subsequently, the median dose of insulin was 0·5 iu/kg twice a day (range 0·1 to 1·9 iu/kg twice a day). The median dose rate for all the cats did not change significantly during the study, but there were increases and decreases in dose rate for individual cats at each visit ($P<0{\cdot}05$, Kruskal-Wallis one-way analysis of variance on ranks). Two of the cats required doses of insulin greater than

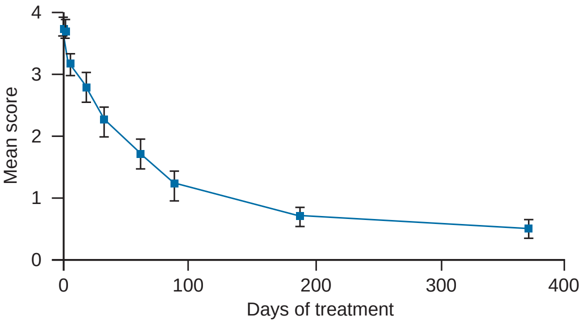

FIG 1: Mean (se) subjective clinical score of 25 diabetic cats during the study

1·0 iu/kg twice a day, but neither of them had hyperadrenocorticism on the basis of a low-dose dexamethasone suppression test.

Clinical diabetic score, body condition score and bodyweight

The cats' median clinical diabetic score decreased from 4 to 0 during the year of treatment (Fig 1). The 13 insulin-treated cats still in the study at the 52-week recheck had good or excellent diabetic control, with a diabetic score of 0 or 1, and seven of the cats were in remission.

The bodyweight of the cats (Table 3) was considered in conjunction with their body condition score (Table 4). On the basis of their body condition score, three of the cats were overweight, seven were in normal condition and 15 were underweight at the beginning of the study; only one of the cats was obese or had had a history of significant obesity. All 15 underweight cats gained weight during their insulin treatment. The seven with a normal body condition score at the beginning of the study maintained it, although two lost weight and five gained weight. Of the three cats that were overweight at presentation, one lost weight and its body condition score became normal, and two gained weight (Tables 3, 4).

There was no significant change in bodyweight over the 12 months of treatment when all the cats were considered as a group, but there was a statistically significant increase in their median body condition score from 2 to 3 (P<0·05) (Table 5).

Water intake

The median 24-hour water intake of the cats decreased from 54·2 to 44·5 ml/kg bodyweight during the 12 months of treatment (Tables 5, 6). Of the 18 cats that did not go into remission, 13 reached the target established for ideal diabetic control of less than 19 ml water drunk/kg bodyweight/day (Martin and Rand 2007).

Blood glucose

Mean blood glucose The cats' mean blood glucose concentration decreased from 20·5 to 14·4 mmol/l during the course of the study (Tables 7, 8). There was no significant change in the mean blood glucose concentration during the first 12 weeks, but after six and 12 months the decreases in mean blood glucose were statistically significant (P<0·05). Of the 18 cats that did not go into remission, 11 reached the target established for ideal diabetic control – a mean blood glucose less than 14·5 mmol/l (Martin and Rand 2007).

Maximum blood glucose During the year of treatment, the cats' mean maximum blood glucose decreased from 24·5 to 20·1 mmol/l (Table 7). Of the 18 cats that did not go into remission, 15 reached the target established for ideal diabetic control – a maximum blood glucose less than 20·1 mmol/l (Martin and Rand 2007).

TABLE 3: Bodyweight (kg) of 25 diabetic cats during the study

	Day		Week				
Cat	1	6	4	8	12	26	52
1	4·7	4·8	5·1	5·6	5·8	5·9	
2	4·0	4·0	4·5		4·6		
3	4·7	4·8	5·1				
4	4·4	4·9					
5	6·5	6·5	6·5	6·8			
6	5·4	5·4	5·4	5·4	5·4	5·0	5·0
7	5·4	5·8	5·9	6·4	6·2	6·0	
8	3·6	3·8	3·9	4·1	4·2		
9	4·3	4·3	4·6	4·7	4·8		
10	5·0	5·0	5·4	5·6	6·0	6·0	6·2
11	5·2	5·4	5·9	6·6	6·5	7·0	6·9
12	4·5	4·9	4·6	4·9		4·8	4·8
13	3·2	3·3	3·6	3·5	3·4	3·5	3·6
14	8·0	8·2	8·0	8·0	7·9	8·3	9·0
15	4·8	5·0	5·1	5·5	5·5	5·3	5·0
16	5·2	5·2	5·3	5·8	5·4	6·2	5·0
17	7·4	7·6	8·3	8·4	8·1	8·0	9·2
18	7·1	7·0	6·7	6·7	6·6	6·4	6·5
19	4·4	4·6	4·6	4·3	4·0		
20	5·4	5·4	5·5	5·7	6·0	6·2	
21	4·8	4·9	5·2	5·0	5·0	5·3	5·5
22	4·7	5·0	5·2	5·5	5·5	5·9	6·1
23	6·8	7·4					
24	4·2	4·3	3·6	5·5	5·4	6·6	7·2
25	3·3	3·3	3·0	3·2	3·8		

Minimum blood glucose The cats' mean minimum blood glucose had decreased significantly by the eighth week, from a mean of 14·0 to 10·6 mmol/l, and had decreased to a mean of 7·9 mmol/l by the end of the 12 months (P<0·05) (Table 7). Of the 18 cats that did not go into remission, 13 reached the target established for ideal diabetic control – a minimum blood glucose less than 6·3 mmol/l (Martin and Rand 2007).

J index The cats' median J index decreased from 177 to 112 $(mmol/l)^2$ over the 12 months (P<0·05) (Table 5). Of the 18 cats that did not go into remission, 13 reached the target established for ideal diabetic control – a J index less than 111 $(mmol/l)^2$ (Martin and Rand 2007).

AUC 24-hour blood glucose The cats' mean AUC decreased from 490 to 344 mmol/h/l, and the decrease was statistically significant at six months (P<0·05) (Table 7). Of the 18 cats that

TABLE 4: Body condition scores of 25 diabetic cats during the study

	Day		Week				
Cat	1	6	4	8	12	26	52
1	2	2	2	3	3	3	
2	2	2	3		2·5		
3	2	2	3				
4	3	3					
5	3	3	3	3·5			
6	3	3	3	3	3	3	3
7	2	2	2	2	2	2	
8	2	2	2·5	3	3		
9	3	3	3	3	3		
10	1	1	2	2	2·5	2·5	2·5
11	2	2	3	3	3	3	3
12	2	2	2	2·5		2·5	2·5
13	1·5	1·5	2	2·5	2	2	2·5
14	4	4	4·5	4·5	4	5	5
15	3	3	3	3	3	3	3
16	2·5	2·5	2	2	2·5	2·5	2
17	4	3	3·5	3·5	3·5	4	4
18	3	3	3	3	3	3	3
19	4	4	3	3	3		
20	2	2	3	3	3	3	
21	2	2	2·5	2·5	2·5	3	3
22	1·5	1·5	2·5	3	3	3	3·5
23	3	3					
24	1·5	1·5	2	2	2·5	3	3
25	2·5	2·5	3	3	3		

TABLE 5: Median and ranges of parameters of blood glucose and fructosamine assessed non-parametrically in 25 diabetic cats during the study

	Day 1	2	3	6	Week 4	8	12	26	52	Ideal control target*	Number of cats with ideal control†
Water intake (ml/kg BW/day)‡	–	–	54·2 (4·6-135·0) n=23	50·0 (5·4-129·6) n=23	41·5 (0-242) n=22	52·9 (0-129) n=20	42·9 (3·1-184) n=18	48·8 (1·7-154) n=16	44·5 (0-193) n=12	19	13
J index (mmol/1)^2	–	–	177 (68-427) n=25	163 (41-360) n=25	156 (26-405) n=23	163 (19-372) n=20	145 (37-265) n=18	134 (24-302) n=16	112 (33-365) n=13	111	13
Beta-hydroxybutyrate (mmol/l)§	0·1 (0·1-10·6) n=23	1·0 (0·1-9·2) n=19	1·1 (0·1-5·7) n=23	0·5 (0·1-5·1) n=22	0·2 (0-8·9) n=24	0·3 (0-7·4) n=23	0·2 (0-5·5) n=21	0·2 (0-1·5) n=15	0·1 (0·1-5·7) n=13	–	–
Condition score‡	2 (1-4) n=25	2 (1-4) n=25	2 (1-5) n=22	2 (1-4) n=21	3 (2-4) n=23	3 (2-4) n=20	3 (2-4) n=19	3 (2-5) n=16	3 (2-5) n=13	3	

* Targets for ideal control are taken from Martin and Rand (2007)
† Data from cats in diabetic remission excluded
‡ Data for cats after diabetic remission was achieved within the study were not included
§ Due to poor correlation with clinical signs, ideal control targets were not established for this parameter
BW Bodyweight

did not go into remission, 11 reached the target established for ideal diabetic control – an AUC less than 302 mmol/h/l (Martin and Rand 2007).

Nadir blood glucose The clinical decision to adjust a cat's insulin dose was based on the lower of the two blood glucose nadirs during any 24-hour test period. The lowest blood glucose concentration was significantly higher during the night than during the day ($P<0·05$), although the insulin was given in equal doses morning and evening (results from cats whose morning and evening doses differed were excluded). There was no significant difference between the time to the blood glucose minima during the day and night.

Biochemical parameters

Fructosamine There was no significant change in the cats' mean fructosamine concentration during the 12 months (Tables 7, 9). Of the 18 cats that did not go into remission, 15 reached the target established for ideal diabetic control – a fructosamine concentration less than 422 μmol/l (Martin and Rand 2007).

TABLE 6: Daily water intakes (ml/kg) of 25 diabetic cats during the study

Cat	Day 1	2	3	6	Week 4	8	12	26	52
1						20	16	5	
2					67				
3		43	15	10	24				
4	32	22	83	69					
5	7	11	18	36	6				
6	40	6	5	63	19	20	43	81	31
7	78	49	27	25	47	95	49	154	
8	78	50	87	50	28	46	54		
9	56	41	11	10	1	7			
10	132	184	81	61	71	94	58	65	71
11	85	146	104	66	115	66	20	7	6
12	87	80	60	34	47	7		2	17
13	56	38	78	95	39	17	13	13	60
14	50	14	20	5	25	38	11	2	3
15	23	23	6	9	44	69	13	45	58
16	140	79	84	63	76	80	114	114	193
17	3	4	6	9	0	0	3	17	0
18	70	54	54	56	72	37	43	97	82
19	61	89	52	5	16	129	89		
20	30	37	106	130	117	76	55	67	
21	154	134	135	124	38	75	72	94	6
22			20	20	28	16	4	2	
23			51	25					
24			117	127	242	119	184	52	215
25			88	64	48	59	26		

Between-day variations in fructosamine During the first week of the study, there were significant differences between the median fructosamine concentrations on days 1 and 2, 1 and 3, 1 and 7, 2 and 3, and 2 and 7, but not between days 3 and 7. In three of the cats, the fructosamine concentrations fluctuated above and below the upper limit of the reference range for fructosamine (406 μmol/l) during the first week of testing.

Beta-hydroxybutyrate The cats' median concentration of beta-hydroxybutyrate decreased significantly from 1·1 mmol/l at the start of the study (day 3) to 0·1 mmol/l after 12 months ($P<0·05$) (Table 5).

Cholesterol, glycerol, triglycerides, and corrected triglycerides There were no significant changes in the cats' median concentrations of cholesterol, glycerol, triglycerides and triglyceride corrected for free glycerol during the 12 months of the study.

Urine glucose The cats' median urine glucose concentration decreased from 3 to 1 during the 12 months (Table 10), and the decrease was statistically significant after six months of treatment ($P<0·05$). Of the 18 cats that did not go into remission, 11 reached the target established for ideal diabetic control, a urine glucose of 1 or less (Martin and Rand 2007).

DISCUSSION

The results of this study show that the dose rate and duration of action of porcine insulin zinc suspension were similar to those reported for beef-pork NPH and another lente insulin, both of which have been administered twice a day for the treatment of diabetes mellitus in cats (Moise and Riemers 1983, Bertoy and others 1995).

Seven of the 25 cats went into diabetic remission within 15 weeks of their treatment beginning, in accordance with studies that have shown that it takes several weeks for the pancreatic β cells to recover from the effects of glucose toxicity (Link and Rand 1995, 1996). Furthermore, although their general appearance had improved, some of these cats still had marked hyperglycaemia, polydipsia and polyuria even a week or two before going into diabetic remission. Although the cats in remission were not glycosuric, a small number of the insulin-treated diabetic cats whose clinical signs were

TABLE 7: Means (se) and ranges of parameters of blood glucose and fructosamine measured parametrically in 25 diabetic cats during the study

	Day				Week					Ideal control target*	Number of cats with ideal control†
	1	2	3	6	4	8	12	26	52		
Mean blood glucose (mmol/l)‡	19·1 (0·9) (9·7-27·8) n=25	19·4 (0·8) (10·2-28·3) n=25	20·5 (0·8) (13·2-30·1) n=25	17·7 (0·9) (9·1-27·3) n=25	16·3 (1·0) (7·0-27·4) n=23	18·5 (1·4) (6·2-29·1) n=20	15·7 (1·0) (8·0-25·0) n=18	15·0 (1·1) (7·4-23·3) n=16	14·4 (1·5) (7·4-25·4) n=13	14·5	11
Maximum blood glucose (mmol/l)‡	24·5 (1·1) (15·4-33·2) n=25	24·8 (0·8) (17·6-33·6) n=25	24·5 (1·0) (15·6-35·3) n=25	24·7 (1·1) (12·6-37·0) n=25	24·1 (1·3) (10·7-35·7) n=23	25·2 (1·6) (7·9-34·8) n=20	23·1 (1·3) (13·3-32·4) n=18	21·8 (1·9) (8·7-33·1) n=16	20·1 (1·8) (10·6-31·6) n=13	20·1	15
Minimum blood glucose (mmol/l)‡	14·0 (0·9) (9·7-27·8) n=25	14·0 (0·8) (3·2-22·8) n=25	14·9 (0·9) (5·2-22·1) n=25	10·5 (0·9) (2·8-18·7) n=23	8·1 (0·9) (1·2-16·5) n=25	10·6 (1·3) (3·0-22·5) n=20	9·0 (1·0) (3·5-19·1) n=18	8·5 (0·9) (3·5-15·7) n=16	7·9 (1·1) (3·3-16·3) n=13	6·3	13
AUC 24-hour blood glucose (mmol/h/l)‡			490 (20) (309-174) n=25	419 (22) (214-646) n=25	387 (23) (163-641) n=23	424 (36) (145-697) n=21	368 (25) (183-597) n=18	321 (25) (175-476) n=16	344 (37) (170-592) n=12	302	11
Fructosamine (µmol/l)	475 (17) (327-689) n=23	488 (19) (370-713) n=18	463 (17) (329-659) n=24	465 (21) (326-739) n=21	441 (27) (238-793) n=23	462 (33) (210-827) n=23	425 (30) (216-771) n=22	453 (32) (202-695) n=15	459 (30) (279-594) n=13	422	15

* Targets for ideal control are taken from Martin and Rand (2007)
† Data from cats in diabetic remission excluded
‡ Data for cats after diabetic remission was achieved within the study were not included
AUC Area under curve

completely controlled but were not in remission had mean blood glucose concentrations less than 10 mmol/l and were not glycosuric. A definitive predictive indicator of diabetic remission is still lacking for diabetic cats, but if a cat becomes aglycosuric it should be checked to determine whether it is in remission (Nelson and others 1999).

The diabetic cats took approximately three months for their clinical signs to resolve significantly (Fig 1), and this time scale needs to be considered when assessing the response of diabetic cats to treatment. During the first weeks of treatment, until the clinical signs of diabetes are well controlled, the dose rate of insulin should be adjusted according to the blood glucose nadir concentration, to avoid hypoglycaemia. Increases in the dose based on the clinical signs alone, without measuring blood glucose, may lead to inappropriately high doses of insulin being given.

It is not known why the nadir blood glucose was higher at night than during the day. However, this means that clinicians need to take serial blood glucose measurements only during the day from diabetic cats being treated twice a day with porcine insulin zinc suspension, and can assume that the risk of nocturnal hypoglycaemia is low if the daytime minimum blood glucose level is within the reference range for blood glucose. However, incorrect clinical decisions would have been made in a few cases if they had been based on a daytime blood glucose curve rather than a 24-hour blood glucose curve; for example, the dose would not have been increased as required in three of 139 decisions, it would not have been decreased as required in eight of 139 decisions, and it would have been increased when it should have been decreased in two of 139 decisions; this last type of mistake would pose the highest potential risk.

The characteristics of the cats when they began the study were similar to those described by Crenshaw and Peterson (1996), although there was a markedly smaller proportion of obese cats in the present study. The over-representation of male and Burmese cats is in agreement with previous epidemiological studies on diabetes mellitus in cats (Panciera and others 1990, Rand and others 1997).

As in previous studies, the owners' satisfaction, the improvement in clinical signs and the increase in average body condition score were greater than would have been expected on the basis of the results of biochemical tests, including blood glucose and fructosamine concentrations (Goossens and others 1998). Although there were improvements in the average values of many of the measurements during the study, in many cases the improvements were not statistically significant. However, in the group of cats whose clinical signs were controlled completely, there were significant improvements in the biochemical parameters. Unfortunately, biochemical parameters are not necessarily good indicators of the clinical control of diabetes (Goossens and others 1998). The variability of urine glucose concentrations may be related to the variability of the renal threshold for glucose (Ruhnau and others 1997). In the absence of an accurate and reliable indicator of diabetic control, the clinical signs and a combination of biochemical parameters should be considered when evaluating the response of diabetic cats to treatment (Martin and Rand 2007).

During the 12 months, two of the 25 cats died of non-accidental causes, a smaller proportion than would have been expected in a group of diabetic cats (Goossens and others 1998). The exclusion of cats with significant other illness or ketoacidosis may account for this higher survival rate.

The results of the study show that the administration of porcine insulin zinc suspension twice a day was an effective treatment for diabetes mellitus in these cats. On average, the

TABLE 8: Mean daily blood glucose concentrations (mmol/l) of 25 diabetic cats during the study

	Day				Week				
Cat	1	2	3	6	4	8	12	26	52
1	18·2	18·9	19·9	23·3	10·2	8·4	9·4	7·4	
2	9·7	10·2	18·3	10·5	10·8				
3	18·5	18·7	23·9	17·9	19·9				
4	14·2	20·0	27·7	25·5					
5	15·4	17·4	19·1	18·3	14·9				
6	11·9	13·2	15·2	18·2	15·1	14·4	15·3	18·2	12·8
7	19·9	17·9	17·1	16·3	17·8	17·4	16·6	16·4	
8	23·1	22·6	30·1	14·1	17·2	20·3	16·8		
9	12·9	16·0	13·3	9·1	7·0	6·2			
10	19·7	19·6	19·2	14·9	17·2	17·5	17·9	17·5	20·6
11	16·9	21·7	19·9	16·4	18·1	17·9	16·0	10·7	12·0
12	17·3	23·0	22·0	20·9	20·2	17·3		12·1	15·0
13	17·9	16·1	20·7	20·4	17·3	18·2	14·8	17·1	16·1
14	23·3	17·9	18·2	12·5	17·1	15·9	14·5	8·3	8·0
15	20·8	19·5	15·7	16·9	18·5	24·9	16·9	17·8	19·5
16	21·5	22·7	22·2	18·6	21·4	25·8	21·4	20·5	25·4
17	19·5	18·4	20·0	17·0	9·1	8·9	9·5	18·3	14·5
18	25·2	28·3	26·1	23·5	20·9	16·2	15·1	16·8	16·3
19	22·4	23·4	22·2	12·4	9·9	27·2	25·0		
20	16·7	19·0	25·8	27·3	27·4	25·0	19·6	23·3	
21	24·4	23·9	23·4	20·1	12·7	21·9	16·7	14·5	9·1
22			13·2	12·4	12·7	12·8	9·9	10·7	10·9
23			17·8	14·7					
24			20·9	18·2	18·1	25·2	18·5	11·0	7·4
25			23·8	23·2	21·8	29·1	8·0		

TABLE 9: Serum concentrations of fructosamine (µmol/l) recorded in 25 diabetic cats during the study

	Day				Week				
Cat	1	2	3	6	4	8	12	26	52
1	462				238	244	247	202	
2	362		381		471	318	259		
3	382	373	372	372	426				
4	589	539	573	578	253	236	240		
5	327		329	443	425	210	216		
6	476		429	420	504	507	548	504	484
7	480	474	422	406	408	496	538	458	
8	490	471	443		333	282	255		
9	448	448	434	420	380	294	268		
10	419		441	427	472	458	407		353
11	404	437	384			434	420	371	554
12	446	432	440	445	393	481		464	594
13	469	458	450	354	360	476	505	571	562
14	510	509	479	419	326	410	439	263	279
15	389	370	339	326	398	463	387	601	569
16	489	491	469	411	436	492	400	397	503
17	429	420	403	373	300	425	471	422	336
18	544	568	556	576	570	507	508	695	405
19	489	487	473	465	422	639	771		
20	689	713	659	739	659	720	600	535	
21			506	572	473	595	520	466	324
22	492	465	442	407	518	436	460	406	385
23	625	610	577	553					
24	523	512	507	513	793	827	543	442	541
25			612	538	587	683	369		

TABLE 10: Urine glucose (dipstick readings) of 25 diabetic cats during the study

		Week				
Cat	Day 1	4	8	12	26	52
1	3+	1+	0	0	0	
2		3+				
3	2+	3+				
4	3+					
5	2+	2+	0			
6	3+	3+	3+	3+	3+	3+
7	3+	3+	3+	4+	3+	
8	3+	3+	2+	3+		
9	3+	2+	0	0		
10	4+	3+	3+	3+	2+	Trace
11	3+	3+	3+	2+	3+	1+
12	3+	2+	2+		2+	1+
13	3+	3+	3+	2+	2+	3+
14	4+	2+	2+	2+		0
15	3+	2+	3+	3+	3+	2+
16	3+	3+	3+		2+	3+
17	3+	1+	1+	1+	2+	1+
18	3+	2+	2+	1+	2+	1+
19	4+	1+	3+	3+		
20	3+	3+	2+	2+	2+	
21	4+	2+	3+	2+	1+	1+
22	3+	2+	3+	0	Trace	Trace
23	3+					
24	3+	4+	4+	3+	2+	2+
25	3+	3+	3+	0		

cats required a dose of 0·5 iu/kg bodyweight twice a day, but serial blood glucose measurements should be assessed to help establish the dose rate for individual cats with diabetes.

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