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Insulin choice in feline diabetes mellitus

A Knowledge Summary by

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KNOWLEDGE SUMMARY

PICO question

In cats with diabetes mellitus, do protamine zinc insulin (PZI) and glargine show a similar effect in reducing clinical signs and hypoglycaemia episodes?

Clinical bottom line

Category of research question

Treatment

The number and type of study designs reviewed

The number and type of study designs that were critically appraised was one. This study was a non-randomised retrospective trial. A systematic review was also found, which analyses the influence of insulin in diabetic remission

Strength of evidence

Weak

Outcomes reported

Compared to PZI, using glargine in recently diagnosed diabetic cats fed exclusively an ultra-low carbohydrate-high protein canned diet, may result in lower fructosamine and mean 12 hour blood glucose concentrations as well as less episodes of hypoglycaemia

Conclusion

In view of the strength of evidence and the outcomes from the study the following conclusion is made: in cats with diabetes mellitus where currently licensed insulin fails to result in a good glycaemic control, glargine may be considered

How to apply this evidence in practice

The application of evidence into practice should take into account multiple factors, not limited to: individual clinical expertise, patient's circumstances and owners' values, country, location or clinic where you work, the individual case in front of you, the availability of therapies and resources.

Knowledge Summaries are a resource to help reinforce or inform decision making. They do not override the responsibility or judgement of the practitioner to do what is best for the animal in their care.

Clinical Scenario

A recently diagnosed diabetic cat shows a poor glycaemic and clinical response to protamine zinc insulin (PZI). You wonder whether there is sufficient evidence of superiority of efficacy of glargine over PZI to justify use of this insulin for avoiding hypoglycaemia whilst controlling the clinical signs.

The evidence

Only one peer-reviewed study was found where the effects of glargine were directly compared to those of PZI in diabetic cats. This study is a non-randomised trial and provides weak evidence about the superiority of glargine at reducing episodes of hypoglycaemia, lowering fructosamine levels and achieving higher rates of remission.

For completeness purposes the references were scrutinised and a relevant systematic review was found. This systematic review provides a strong level of evidence of the lack of existing evidence regarding a significant correlation between the type of insulin and diabetic remission. However, episodes of hypoglycaemia were not considered in this review.

Summary of the evidence

Marshall et al. (2009)	
Population:	Cats presenting to a feline-only veterinary practice in Australia with newly diagnosed diabetes without serious concurrent disease.
Sample size:	24 cats

Intervention details:	• Diagnosis of diabetes mellitus was based on glucose concentration, serum fructosamine and glycosuria. Presence of clinical signs consistent with diabetes mellitus was used as supporting evidence.
	• The cats were split into three insulin treatment groups of eight cats in each, at the time of first diagnosis based on breed (Burmese or non-Burmese) and previous corticosteroid administration.
	• Cats were classified as having uncomplicated diabetes if they were still eating or complicated diabetes mellitus if signs of systemic illness (depression and anorexia) and dehydration were observed.
	• Cats with uncomplicated diabetes were treated with their allocated insulin type within 12 hours. Cats with complicated diabetes were initially treated with fluid therapy and intravenous regular insulin until appetite returned and hydration status was normal.
	• All cats were placed on a sole ultra-low carbohydrate-high protein canned diet (Purina Diabetes Management) for 16 weeks or until remission was achieved. Dietary caloric restriction was recommended after the first 2 weeks of treatment for cats with body condition score (BCS)> 6 (on a scale 1–9).
	• Inclusion in the trial was confirmed at day 10. Cats were excluded up to day 10 if they did not eat the prescribed diet, or owners were unable to exclusively feed the diet or measure water intake.
	• Every group was treated with either:
	  ○ n=8 porcine lente insulin 40 U/ml (Caninsulin®; Intervet);
	  ○ n=8 PZI 40 U/ml (PZI-Vet, Idexx Pharmaceuticals USA);

	○ or n=8 glargine 100 U/ml (Lantus®; Aventis Pharmaceuticals) twice daily subcutaneously (SC). • The initial dose of 0.5 U/kg ideal body weight was given if the blood glucose concentration on admission was greater than or equal to 20 mmol/l, and 0.25 U/kg if blood glucose concentration was less than 20 mmol/l. • Blood glucose concentration was measured every 2 hours for 12 hours for each cat for the first 3 days of treatment. • After a minimum of 2 weeks, cats in remission were discharged from hospital and had their blood glucose concentration measured weekly for 3 months. • Hospital assessments were made after discharge to confirm remission on days 10, 17 and 28 and then every 2 weeks. Assessments included serial measurements of blood glucose (every 2 hours for 12 hours) and serum fructosamine measurements (every 4 weeks). Insulin was adjusted accordingly. • Trial end-point: 16 weeks of treatment or remission date.
Study design:	Non-randomised trial
Outcome studied:	Glycaemic control and remission probabilities in cats treated with either glargine, PZI or porcine lente insulin based on the mean glucose concentration, mean daily water intake and serum fructosamine using analysis or variance.
Main findings: (relevant to PICO question):	• Glargine was associated with lower mean 12 hour blood glucose concentrations. • Fructosamine concentration was significantly lower in glargine treated cats from day 56. • None of the glargine treated cats exhibited signs of hypoglycaemia despite many having biochemical hypoglycaemia. • Two cats treated with porcine lente insulin and one cat treated with PZI had severe clinical hypoglycaemia. • Daily water intake in glargine treated cats was not different in the first 28 days of therapy. • There was no difference in body weight based on type of insulin used. • The probability of remission was greater in cats treated with glargine than those treated with PZI or porcine lente insulin. By week 16, all cats in the glargine group had achieved remission while only 2/8 cats in the porcine lente insulin group and 3/8 cats in the PZI group had achieved it. • Cats with lower mean 12 hour blood glucose concentration on day 17 had a higher probability of subsequent remission than cats with higher mean glucose concentration. • Probabilities of remission were similar and did not differ significantly between Burmese and non-Burmese cats.
Limitations:	• Small group size • Cats presented at a feline only practice may not be representative of the average first opinion practice patient. • Cats with complicated diabetes were excluded, which may

	make the sample less representative of the whole population. • In first opinion practice, serial glucose measurements and early treatment are not always possible due to financial restrictions and owner's compliance. • Unequal distribution of cats that had steroid injections before the study. • Culture and sensitivity was not done on all urine samples. • Burmese breed overrepresented compared to average first opinion population. • An inherent limitation of non-randomised trials is that third factors linked to intervention or outcome cannot be excluded. • Not all factors influencing the occurrence of hypoglycaemic episodes were included.

Gostelow et al. (2017)	
Population:	111 reports assessed using eligibility criteria
Sample size:	22 studies were included
Intervention details:	Study identification and data collection following Cochrane Collaboration guidelines: • The search was carried out to answer two questions: 1. What aspects of a cat's treatment might affect the remission rate achieved? 2. What diagnostic test results or characteristics might predict remission in a diabetic cat? • An online bibliographical search for literature relevant to the two questions was performed on 18 December 2012 using three different databases (PubMed, VetMed Resource and CAB Abstracts). Bias assessment and evidence grading: • Risk of bias in each study was independently assessed by each author using bias assessment forms. Disagreement between authors was settled by subsequent discussion. • A statement describing how persistent euglycaemia was confirmed after anti-hyperglycaemic treatment had been discontinued for a minimum of 2 weeks needed to be included for the criteria for remission to be considered adequate. A minimum follow-up of 3 months was judged adequate for remission to occur. • Periodontal disease, previous diabetic ketoacidosis, and urinary tract infections for which antibiotic treatment was administered were not classified as concurrent diseases when describing the populations of included studies. Inclusion criteria: 1. published in English in a peer-reviewed journal; 2. must address one, or both, of the above research questions; 3. must contain original research (excluding review articles); 4. must describe more than three cats (excluding individual case reports and small case series).

	22 included studies were included in two categories: 1. those assessing the effect of pharmaceutical intervention and diet on remission rate; 2. those assessing diagnostic tests and cat characteristic as predictors of remission.
Study design:	Systematic review
Outcome studied:	The strength of evidence regarding the following remission related aspects were studied: • Factors influencing remission rate pharmaceutical intervention: Oral anti-hyperglycaemic agents, insulin glargine, porcine lente insulin, PZI, insulin detemir, Neutral Protamine Hagedorn, home glucose monitoring. • Factors influencing remission rate: diet • Predictors of remission: diagnostic tests, cat characteristics and treatment regime
Main findings: (relevant to PICO question):	GLARGINE • Glargine was the most commonly investigated insulin • The study published by Marshall et al. (2009) is the only trial to directly compare remission rates achieved with different twice-daily insulins. An evaluation of the level of evidence of the pharmaceutical intervention revealed several limitations: ○ Bias: 1. The study population was potentially not comparable to general population. 2. A small sample reduced the power of the study. 3. High risk of inclusion of acromegalic cats. 4. Presence of possible confounding factors. ○ Confounding factors: 1. The protocol for porcine lente insulin was different from that of glargine and PZI, making dosing protocol a potential confounding factor. 2. There were differences between groups in the number of cats with urinary tract infections. 3. Since reversible forms of insulin resistance can lead to a greater chance of remission, previous corticosteroid treatment was considered a confounding factor too. ○ Lack of blinding. ○ Positive findings in studies with low statistical power are at greater risk of being false-positives compared to those in studies with high statistical power. • The evidence provided by the review regarding the influence of glargine in diabetic remission was classified as 3a (1 being the highest and 4d the lowest level of evidence in the grading system used (Centre for Evidence-Based Medicine (CEBM), 2011)).

	PZI • Marshall et al. (2009): same limitations mentioned above. • One study documented no episodes of remission after 45 days, but cats were most likely normoglycaemic by the end point. • A non-randomised trial designed to assess the effect of dietary composition reported a remission rate of 68% in in cats predominantly treated with twice-daily PZI and fed a low-carbohydrate, low fibre diet. • The evidence provided by the review regarding the influence of use of PZI in diabetic remission was classified as 3b. Overall pharmaceutical intervention: weak evidence for correlation between insulin type and remission.
Limitations:	• Questions cannot be clearly addressed because of difficulties such as a general lack of consensus about the definition of diabetic remission, its duration and characteristics. • Some of the studies were designed for purposes different to remission. • The process of assessment is clearly described. However the combination of different interventions (dietary and pharmaceutical) could have interfered with the assessment and conclusions. • Hypoglycaemia or other complications of diabetic treatment were not taken into account.

Appraisal, application and reflection

Long acting insulin (PZI, glargine or detemir) and high-protein/low-carbohydrate diets are recommended for the management of diabetic cats (Behrend et al. 2018; and Sparkes et al. 2015). Diabetes mellitus is a common disorder that affects a cat's quality of life and survival. An appropriate management is key to positively contribute to their welfare and the cat-human bond.

The UK veterinary prescription cascade precludes the use of human insulin (e.g.: glargine, detemir) as first line treatment. ProZinc® (Boehringer Ingelheim Vetmedica), a human PZI produced by recombinant DNA technology (PZIR), is the only long acting insulin licensed for use in cats in the UK. However, a large part of the literature about diabetic management and remission in cats involves glargine trials (Gostelow et al. 2014).

A shift regarding feline diabetic remission is taking place and seems to be considered a main goal by many experts (Marshall et al. 2009; and Gostelow et al. 2014). However, the tight glycaemic control (Nack & DeClue, 2014) needed to achieve that period of time in which symptoms of diabetes are absent, is potentially concerning, as it may result in episodes of hypoglycaemia which may affect the cat's quality of life. Whereas in 2015 the ISFM guidelines (Sparkes et al., 2015) highlighted the convenience of 'avoiding hypoglycaemia at the expense of allowing periods of hyperglycaemia', in 2018 Behrend et al. stated that 'In cats, diabetic remission is a reasonable goal'.

However, limiting the cat's clinical signs, using a treatment that fits into the owner's daily life and preventing clinically significant hypoglycaemia and other complications are clear goals in both current guidelines of management of feline diabetes (Sparkes et al., 2015; and Behrend et al., 2018).

Most long-term effects on health, quality of life and cost effectiveness of a near-euglycaemic management and remission paradigm is unknown (Nack & DeClue, 2014). On the other hand, more comorbidities are included in the diagnostic work up nowadays. Over the last few decades new feline pathologies influencing the onset and

management of diabetes have been identified and technical instruments are more readily available making it possible to diagnose these diseases. A close monitoring of the glycaemic levels and the work up of these comorbidities result in additional expenses and difficulties to achieving stabilisation of the feline diabetic patient (Gostelow et al., 2014).

Hence, when cost and effectiveness are outweighed, remission may be considered a goal but most veterinarians priorities may still be reducing clinical signs and likelihood of hypoglycaemic episodes. To avoid controversy, 'remission' has not been included as a keyword in the search but remission related evidence was not excluded from the search results and was taken into account.

At the time of writing, the study of Marshall et al. (2009) is the only peer-reviewed publication where PZI and glargine are directly compared. The evidence provided by this non-randomised trial regarding the superiority of glargine compared to PZI at reducing clinical signs in diabetic cats is weak.

With respect to the clinical signs, daily water intake in glargine treated cats was not different in the first 28 days of therapy, despite being associated with lower mean 12 hour blood glucose concentrations than porcine lente insulin and PZI. An extended trial period would have been necessary to assess the medium to long-term effects, since fructosamine concentrations were reported to be significantly lower in glargine treated cats from day 56. There was no significant effect of insulin type on change in body weight from initial hospital discharge to trial end.

However, the trial provides stronger evidence about influence of insulin type on the development of hypoglycaemia. During the trial, two cats treated with porcine lente insulin and one cat treated with PZI had severe clinical signs associated with low blood glucose levels, whereas none of the glargine treated cats exhibited signs of hypoglycaemia.

To ensure the completeness of the Knowledge Summary, references of selected search results were scrutinised. A relevant systematic review about feline diabetic remission (Gostelow et al., 2014) was found amongst them and included in the search table after applying the exclusion criteria.

The systematic review does not fully answer the PICO question because hypoglycaemia or other complications of treatment were not taken into account.

It was included in the Knowledge Summary because it analyses the evidence in the study published by Marshall et al. (2009). However, one of three confounding factors described in the review was unrelated to this PICO question as it was linked to the porcine lente insulin dosing protocol, which is not a type of insulin included in this Knowledge Summary. With respect to the confounding factor associated with the use of steroids, as explained by Marshall et al. (2009), the glargine group was disadvantaged with respect to the probability of remission compared to the other groups and that disadvantage could compensate the bias.

Regarding the overall conclusion, the systematic review shows a slightly lower existing evidence for remission in cats treated with PZI (3b) compared to glargine (3a), 1 being the highest and 4d the lowest grade of evidence (Table 1 in Gostelow et al., 2014).

Another potentially relevant study (Gostelow et al., 2017) was found during scrutinisation of the references. The results were included in the 2017 ACVIM Forum Research Abstract Forum, but were excluded from this summary as were other non-peer-reviewed publications since a detailed description of the study was not available and an assessment of possible biases could not be made.

A limitation of this Knowledge Summary could be the omission of the keyword 'remission'. However, a similar search including this keyword was made and the results were not significantly different and did not include the systematic review published by Gostelow et al. (2014) either.

Another limitation could be that the PZI used in the trial published by Marshall et al. (2009) is a mixture of 90% beef and 10% pork insulin (PZI-Vet, Idexx® Pharmaceuticals USA, Westbrook, Maine USA) and not the PZIR (Boehringer Ingelheim). However, there is some evidence about similar results of PZI-Vet and PZIR (Nelson et al., 2009).

An observation made whilst reviewing these papers was a low level of satisfaction of owners with their veterinarian's knowledge of diabetes 'which may reflect owner access to the rapidly changing body of knowledge on the Internet' (Aptekmann et al., 2014). There is also a possible bias in the veterinary literature, where the importance of temporary remission seems overestimated compared to that of limitation of clinical signs and hypoglycaemia.

Complete studies with large samples are difficult to perform due to the lack of adequate cases and it is possible that investigating other treatments and formulations such as incretins and glargine 300 U/mL (Gilor et al., 2016; and Saini et al., 2020) may be more appealing to researchers now. Multiple factors affect the prognosis of diabetes in cats that deserve some attention too and may be understandably leading the way in research.

There is more literature about glargine than about any other insulin type in cats and its use has been demonstrated to be safe and effective. There is weak evidence about glargine helping to achieve lower fructosamine levels as well as possibly reducing the likelihood of hypoglycaemia when it is directly compared to PZI. However, the results are mainly based on newly diagnosed diabetes, what may not reflect the situation of the majority of the population.

Methodology Section

Search Strategy	
Databases searched and dates covered:	CAB Abstracts on OVID Platform 1973 – Week 07 2021] VetMed 1973 – February 2021 Pubmed 1973 – February 2021
Search terms:	CAB Abstracts and VetMed: (cat OR cats OR feline OR felines OR queen OR tom) AND (diabetes mellitus OR diab*)) and (PZI OR protamine zinc insulin OR human recombinant protamine zinc insulin OR ProZinc) and (improvement OR glycaemic control OR glycemic control OR hyperglycaemia OR hyperglycemia OR hypoglycaemia OR hypoglycaemia OR blood glucose OR weight OR body condition score OR clinical signs OR polyuria OR polydipsia) (cat OR cats OR feline OR felines OR queen OR tom) AND (diabetes mellitus OR diab*)) and (PZI OR protamine zinc insulin OR human recombinant protamine zinc insulin OR ProZinc) and (Glargine OR Lantus OR iGlar) PubMed: (cat OR cats OR feline OR felines OR queen OR tom) AND (diabetes mellitus OR diab*))(PZI OR protamine zinc insulin OR human recombinant protamine zinc insulin OR ProZinc) AND (Glargine OR Lantus OR iGlar) AND (improvement OR glycaemic control OR

	glycemic control OR hyperglycaemia OR hyperglycemia OR hypoglycaemia OR hypoglycaemia OR blood glucose OR weight OR body condition score OR clinical signs OR polyuria OR polydipsia)
Dates searches performed:	22 Feb 2021

Exclusion / Inclusion Criteria	
Exclusion:	• Excel was initially used to find duplicates. Duplicates that this initial approach failed to find were removed along the exclusion process. • Studies that did not involve domestic cats were excluded. Studies that only included either iGlar or PZI were not included. • Case reports, clinical reviews, guidelines, congress abstracts only were excluded to achieve a certain level of scientific evidence. • Studies where the PICO question was not addressed were excluded.
Inclusion:	• Studies that involved both PZI and iGlar in domestic cats with diabetes mellitus were included. • A thorough scrutinisation of the references was made and relevant studies offering a strong level of evidence were included.

Search Outcome

Database	Number of results	Excluded – Duplicates	Excluded – Non feline, non PZI or iGlar related	Excluded – Non-English, case reports, clinical reviews, guidelines, congress abstracts	Excluded – Did not address the PICO question	Total relevant papers
CAB Abstracts	62	28	10	7	17	0
VetMed	195	106	45	12	31	1
PubMed	387	46	312	23	6	0
Total relevant papers when duplicates removed						**1**

CONFLICT OF INTEREST

The author declares no conflicts of interest.
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