# Canine Insulinoma: Diagnosis and Treatment

Simon Tappin MA VetMB CertSAM DipECVIM-CA MRCVS
RCVS and European Veterinary Specialist in Internal Medicine

Dick White Referrals, The Six Mile Bottom Veterinary Specialist Centre,
Station Farm, London Road, Six Mile Bottom, Suffolk, CB8 0UH
st@dwr.co.uk

Insulinomas are rare tumours that arise from the beta cells in the pancreatic islets and lead to the excessive, and unregulated, secretion of insulin. The inappropriate release of excessive amounts of insulin, leads to signs of hypoglycaemia. Classic signs are of neurological dysfunction and include collapse, ataxia and seizures, which respond to the administration of glucose. The tumours typically release insulin episodically, with clinical signs being seen intermittently as a result. These are most often associated with prolonged starvation or prolonged periods of exertion. Insulinomas are mostly malignant (around 60%), however even those that appear benign on histopathology behave in a locally aggressive manner, and nearly always metastasis. These are found in the draining lymph nodes and liver in around half of dogs at initial presentation.

**Signalment**

Insulinomas are typically reported in medium to large breed dogs, with a reported disease predisposition in Boxers, Standard Poodles, Fox terriers and German shepherd dogs. The median age of presentation is around 9 years of age, with a reported range from 3 to 15 years. No apparent sex predisposition is reported. Insulinomas are more commonly seen in ferrets and very rarely reported in cats.

**Clinical signs**

Most animals present due to the intermittent neurological signs as a result of intermittent and excessive release of insulin, leading to neuroglycaemia. The severity of the hypoglycaemic crisis is dependent on the severity of the hypoglycaemia seen, the rate of the blood glucose decline and the duration of the hypoglycaemia. Signs are often gradual in onset and variable in there progression (over 1-6 months). Usually signs start with hind limb weakness (around 40% of cases) and lethargy, and progress to collapse, ataxia and mental confusion. A complete loss of consciousness is rarely reported, however seizures will occur as the condition progresses. Animals appear to adapt to very low blood glucose levels (1-2mmol/l) and may have no clinical for long periods, with small changes such as exercise or starvation triggering the onset of clinical signs.

Clinical examination findings are often unremarkable, although some animals will have increased body condition due to the anabolic growth hormone like effects of insulin. Post-ictal signs may still be present if there has been recent seizure activity. An insulinoma associated peripheral polyneuropathy has been reported, leading to tetraparesis and reduce reflexes. It is thought that this is related to a paraneoplastic immune mediated disorder, rather than a direct metabolic effect.

**Diagnosis**

Traditionally the diagnosis of insulinoma has been based on fore filling the 3 components of Whipple's triad. These are that clinical signs of hypoglycaemia are present, a low blood glucose level can be documented when these signs are present and that the clinical signs seen resolve with the administration of glucose. These criteria were developed in the 1930's to try to distinguish human patients that may have insulinoma and that required surgery, prior to the development of assays for insulin. With the development of reliable insulin assays, the documentation of inappropriate insulin levels is also required to make a definitive diagnosis. Differentials for hypoglycaemia are considered in the table below.

| **Differential diagnosis of Hypoglycaemia** |
|---|
| Insulinoma |
| Extrapancreatic neoplasia (e.g. hepatocellular carcinoma) |
| Sepsis |
| Neonatal hypoglycaemia |
| Toy-dog hypoglycaemia |
| Hunting-dog hypoglycaemia |
| Hepatic insufficiency |
| Hypoadrenocortisicm (primary and secondary) |
| Leucocytosis |
| Panhypopituitarism |
| Polycythaemia |
| Iatrogenic (e.g. excessive exogenous insulin or Propranolol) |
| Toxins (e.g. xylitol) |
| Delayed serum separation |

Glucose levels are usually very tightly controlled in the body and numerous hormones are implicated in the control of blood glucose levels. Insulin reduces serum glucose levels allowing glucose to be stored as glycogen within tissues. As such its secretion in the normal animal is inhibited at very low glucose levels. If an insulinoma is suspect, insulin should be measured, but in light of the serum glucose levels and it should only be measured if a low serum (<3mmol/l) glucose level is documented. An elevated insulin level in a hypoglycaemic patient is inappropriate and is consistent with an insulinoma. An insulin level with in the normal range, with a hypoglycaemic patient, is also inappropriate and is suggestive of an insulinoma. A patient with a low insulin level in response to hypoglycaemia is not consistent with an insulinoma.

Fructosamine and glycosylated haemoglobin A1c levels have been used to strengthen the clinical suspicion of prolonged periods of hypoglycaemia. The remainder of haematology and serum biochemistry results are usually normal, although mild reductions in albumin, potassium and phosphate, and increases in liver enzymes have been reported. There is no clear correlation between elevations in liver enzymes and hepatic metastasis.

If normal blood glucose levels are present initially the animal is carefully observed, but fasted for a 12-24 hour period and samples taken every 1-2 hours. Patient side glucometers will be adequate for initial evaluation; however they often under estimate

glucose at low levels and a sample should be stored in a fluoride oxalate tube for analysis at a reference laboratory. When blood glucose levels fall paired samples for glucose and insulin analysis can be taken and the animal fed. Repeated measurement of insulin may be needed in some cases (1 measurement found 76% of insulinomas, with 2 samples confirming 91% in one study). Insulin to glucose ratios are not recommended as they do not add to the clinical interpretation of the insulin and glucose values. Tolerance and stimulation tests (such as the glucagon, glucose or tolbutamide tolerance tests and the epinephrine stimulation test) are not recommended due to the risk of potentially fatal hypoglycaemia.

**Diagnostic Imaging**

Where possible the treatment of choice for insulinoma is its surgical excision, so imaging to help locate its presence, support the endocrine diagnosis and establish the presence of metastasis is essential for treatment planning. Radiographs are rarely helpful in the evaluation of insulinoma, both in the evaluation of pancreatic masses (due to their location and small size, usually <3cm at diagnosis) and that the lungs are a very late site for metastasis (the local lymph nodes, mesentery and omentum, and liver being more commonly affected.

Ultrasound is a good way of imaging the pancreas and is successful at identify pancreatic masses in around half of dogs with defined insulinoma. A larger mass (>2cm diameter) is more likely to be seen on ultrasound and the sensitivity of ultrasound is greatly affected by the equipment used and the experience of the operator. Ultrasound may give both false positive (due to non-neoplastic pancreatic nodules) and false negative (the mass is not apparent) results. Metastatic changes can also be identified and are seen on ultrasound in around 20% of cases.

CT is used in people due to its increased sensitivity for detecting small pancreatic lesions. Small studies using CT in dogs have been published and it appears better than ultrasound at diagnosing pancreatic masses that have been confirmed at surgery, with around 70% of tumours seen. Metastases are also detected by CT, however due to the higher resolution the chance of false positive results in much greater. The use of dual phase and Positron Emission Tomography (PET-CT) are currently being evaluated.

Scintigraphy using the radiolabelled somatostatin analogue $^{111}$Indium pentetreotide has been used to evaluate insulinoma in people, however is rarely used for to the low likelihood of stomatostatin receptor expression. In dogs scintigraphy usually reveals areas of abnormal activity, however tumour localisation is poor. A positive scan result may be helpful in predicting if a tumour is likely to respond to treatment with stomatostatin analogues such as octeride.

**Treatment**

Treatment for insulinoma falls into the management of the acute hypoglycaemic crisis and long term management. Ideally surgery to remove the primary tumour will be curative, however is still indicated in the face of metastatic disease. If surgery is not possible, due to tumour location or owner constraints medical management can lead to good long term survival times.

*Acute management of hypoglycaemic crisis*

Symptoms of hypoglycaemia normally resolve quickly with the administration of intravenous glucose or dextrose (1ml/kg of 50% glucose solution diluted 1:2 in 0.9% sodium chloride). This should be given slowly (as tumours retain some degree of responsiveness to insulin levels and rapid boluses of glucose may lead to further release of insulin) and followed with a constant rate infusion (2.5 – 5% glucose in an isotonic crystalloid solution). The infusion can be discontinued when clinical signs abate, usually this is relatively rapid. If there is a failure to respond to glucose alone, then injection of dexamethasone (0.1mg/kg i/v BID), octeride (10-50µg/kg s/c TID) or a glucagon constant rate infusion (5-10ng/kg/min) could be considered. In severe seizures or those that do not respond to glucose diazepam or phenobarbitone loading may need to be considered. Mannitol should be considered if cerebral oedema is suspected.

*Surgery*

Where possible surgery should be considered to try to remove as much of the insulin secreting tumour as possible. Medical signs should be controlled as much as possible prior to explorative laparotomy. Studies have shown roughly even distribution of tumours to the left (42%) and right (41%) limbs, with 17% present in the central area around the pancreatic and bile ducts; tumours in this location are not amenable to surgery. Confirming the presence of an insulinoma should be done visually and by palpation of the pancreas (around 15% of dogs have multiple nodules). The use of intraoperative ultrasound and possibly the injection of new methylene blue can increase the chances of finding the mass. If a mass is not found surgical resection of either the right or left lobe could be considered in the hope of removing the bulk of the tumour. As there will be extensive handing of the pancreas at surgery post-operative pancreatitis is a significant concern and diabetes mellitus is seen in around 10% of patients, in some patients the need for insulin will resolve over time.

*Medical management*

In some case of insulinoma frequent feeding of complex carbohydrates, and diets high in protein and fat, may control the clinical signs of hypoglycaemia, the gradual release of post-prandial carbohydrate may decrease the potential for insulin release.

Prednisolone should be started is dietary management alone does not control signs and the dose increased as needed (0.5-2mg/kg/day in divided doses). Glucocorticoids increase blood glucose levels by increasing gluconeogenesis, elevating glucose 6-phosphatase activity, decreasing blood glucose uptake into tissues and stimulating glucagon release. Steroids are cheap and effective, but as the tumour progresses signs of iatrogenic hyperadrenocortisicm may limit their use.

Diazoxide is used in patients that stop responding to steroids and acts by inhibiting insulin release, but also by increasing glycogenolysis, gluconeogenesis and inhibiting tissue uptake of glucose. Treatment usually starts at 10mg/kg in divided doses (2-3 times a day) and is titrated up to effect to 50-60mg/kg/day. Around 70% of dogs will respond to treatment with diazoxide, but in comparison to prednisolone is much more expensive. It is generally not recommended but the use of thiazide diuretics (e.g. chlorothiazide 2-4mg/kg/day) may potentiate the effects of diazoxide. Common potential side effects

include vomiting and inappetance; other potential adverse effects include bone marrow suppression, sodium retention, diarrhoea, tachycardia, aplastic anaemia, hyperglycaemia and cataract formation.

Octeride is a long acting stomatostatin analogue which inhibits insulin secretion and has been used successfully in canine patients. Octeride inhibits the release of insulin from pancreatic beta cells by acting on the stomatostatin receptor. Not all patients with insulinoma express this receptor, so a very variable response to octeride administration can be seen. No adverse side effects are reported in dogs, but in people side effects include pain at the injection site, nausea, vomiting, constipation and steatorrhea. It is also costly and needs to be injected frequently (starting dose of 10µg/dog s/c every 8-12 hours, increasing to 50µg/dog/dose, depending in response). Longer acting slow release forms of stomatostatins are available in people and may be more convenient for use in dogs, however their efficacy has not yet been evaluated.

*Chemotherapy*
Streptozotocin has been used a cytotoxic treatment for insulinoma. It is a nitrosourea antibiotic that is derived from the bacteria *Streptomyces achromogenes* and selectively destroys the beta cells in the pancreas and at distant metastatic sites. Initial reports in dogs suggested that dogs did not well tolerate streptozotocin, however more recent studies have shown it can be given safely is given with aggressive diuresis and it is infused over a prolonged period, to avoid its nephrotoxic effects. The suggested protocol is to premedicate with anti-emetics, give pretreatment diuresis (0.9% sodium chloride for 3 hours at 18ml/kg/hour), then infuse the streptozotocin (500mg/$m^2$ in saline to be given as an infusion at 18ml/kg/hour over 2 hours) and followed by a further 3 hours of diuresis at the initial rate. Although efficacious in some dogs the handling of animals hospitalised excreting large amounts of cytotoxic urine has limited the use of this protocol. The use of doxorubicin is reported in some human patients with insulinoma. It use in veterinary patients could be considered but as yet its effectiveness is unknown.

**Prognosis**
The long term prognosis for dogs with insulinoma is guarded, due to the likelihood of the development of metastasis and associated clinical signs. Median survival times for dogs undergoing partial pancreatectomy is around a year, with a range of 0 days to 5 years. Reported survival times are longer for dogs treated with surgery initially compared to medical management (MST 381 days c.f. 74 days) used alone. A more recent study has reported better survival times for dogs undergoing surgery (MST 785 days) and much longer survival times is prednisolone was used with signs of hypoglycaemia recurred (1316 days). Dogs with metastatic disease have significantly short disease free intervals compared to those without at surgery (20% expected to be normoglyceamic with metastasis 14 months after surgery, compared to 50% without metastasis at surgery). In people mitotic rate appears to be associated with the long term prognosis, this has yet to be shown in dogs. Young dogs have a worse prognosis compared to older dogs, but no other factors (breed, body weight, clinical signs, tumour location, gross presence of metastatic disease, blood glucose or insulin level) have been associated with outcome. Dogs that have normal or elevated blood glucose levels after surgery have much significantly better prognosis.