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HOW I TREAT..... CANINE INSULINOMA
Michael E Herdige MA BVSc DVSC DVR DVD DSAM DECVIM DECVDI MRCVS
Department of Veterinary Medicine,
University of Cambridge

Functional islet cell tumours (insulinomas) are the most frequently occurring tumours of the endocrine pancreas in dogs. Most insulin-secreting tumours are malignant islet cell carcinomas which metastasize to regional lymph nodes and/or the liver. Early diagnosis is important as dogs with metastases have significantly reduced survival times.

Pathophysiology
Insulinomas are composed of neoplastic β-cells which continue to release insulin despite the presence of hypoglycaemia. Hypoglycaemia is normally the major inhibitory stimulus for insulin secretion. As a result of hyperinsulinism, tissue utilization of glucose continues, the hypoglycemia worsens, and ultimately clinical signs develop. The onset and severity of clinical signs is determined by the degree of hypoglycemia and the rate at which the plasma concentration of glucose falls. A rapid decline in plasma glucose concentration may occur with fasting, exercise, or excitement in dogs with insulinomas.

The brain is an obligate consumer of glucose. Cerebral cells have limited stores of glycogen and a limited ability to utilize protein and amino acids for energy. These cells will be the first affected by hypoglycaemia. Prolonged and profound hypoglycaemia causes ischemic neuronal cell damage in a pattern similar to that caused by cerebral hypoxia.

Hypoglycemia is a potent stimulus for the release of hormones which have an antagonistic action to insulin. These include glucagon, growth hormone, glucocorticoids, catecholamines, and possibly thyroid hormones. These hormones act in concert to raise the plasma glucose concentration. Some of the clinical manifestations of hypoglycemia, such as muscle tremors, nervousness, restlessness, and hunger, may in fact result from stimulation of the sympathetic nervous system and increased levels of circulating catecholamines.

Clinical signs
Insulinomas usually occur in middle-aged to older dogs (mean age of 9.0 years) of any breed, although medium to large breeds appear to be predisposed. No sex predisposition has been reported. Insulinomas appear to be very rare in cats.

A tentative diagnosis of hyperinsulinism is generally based on fulfilment of the criteria from Whipple’s triad:

1. The presence of neurologic signs typical of hyperglycemia, which may be precipitated by exercise or excitement.
2. Hypoglycaemia (plasma glucose < 3 mmol/l [< 54 mg/dl]) at the time of the clinical signs.
3. Resolution of clinical signs following feeding or administration of glucose.

Clinical signs associated with hypoglycaemia include fatigue, generalized weakness, collapse, muscle tremors, altered behavior, confusion/disorientation, apparent blindness, ataxia, incoordination, stupor, and seizures. These signs are usually episodic in nature and may occur with fasting, exercise, or excitement in dogs with insulinomas. Provocative stimuli, such as the intravenous administration of glucagon or glucose, results in excessive secretion of insulin from neoplastic beta-cells. This response may be even greater if glucose is administered orally as numerous intestinal hormones (glucagon,
secretin, cholecystokinin, gastrin, and gastric inhibitory peptide) are secreted in response to oral glucose and these in turn increase insulin secretion. It is by this mechanism that feeding has been reported to initiate clinical signs in dogs with insulinomas.

Seizure activity is one of the most common clinical manifestations of hypoglycemia. The seizures may be grand mal or focal in nature and are normally self-limiting, lasting between 30 seconds and five minutes. Peripheral neuropathy with nerve degeneration and demyelination has also been associated with canine insulinoma in a few cases. Insulinomas are generally small tumours and do not lead to malignant cachexia. Thus weight loss is not a feature of this disease.

**Diagnosis**

**Laboratory findings.** A presumptive diagnosis of insulinoma is based on the presence of typical clinical signs in association with persistent hypoglycaemia and an inappropriately high plasma insulin concentration.

A fasting plasma glucose concentration of 3 mmol/l (≤ 54 mg/dl) or less is found in most cases. Some dogs with insulinoma show no clinical signs despite having extremely low blood glucose concentrations (< 2 mmol/l [< 36 mg/dl]) because they are able to adapt to these low concentrations over a prolonged period of time. Serum fructosamine concentrations are also reduced supporting substantial periods of hypoglycaemia even in those patients with normal or low-normal fasting blood glucose concentrations.

<table>
<thead>
<tr>
<th>Differential diagnosis of hypoglycaemia in adult dogs</th>
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<tbody>
<tr>
<td>Incorrect anticoagulant/delayed separation of serum from RBC</td>
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<tr>
<td>Functional islet cell tumour (insulinoma)</td>
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<tr>
<td>Excessive insulin administration</td>
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<tr>
<td>Extra-pancreatic tumours, particularly hepatic tumours</td>
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<td>Liver disease</td>
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<td>Septicaemic or endotoxic shock</td>
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<td>Severe polycythaemia</td>
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Plasma insulin concentrations greater than 20 mU/l in association with hypoglycaemia are inappropriate and an insulin:glucose ratio greater than 4.2 is considered diagnostic.

In borderline cases an intravenous glucose tolerance test using 0.5 g glucose/kg body weight has proved useful. Insulin-secreting tumours retain a degree of responsiveness to the glucose challenge and a glucose half-life of less than 20 minutes and/or a fractional clearance rate of more than 3%/minute is highly suggestive of insulinoma in the dog.

Although hypoalbuminaemia, hypokalaemia, and increases in alkaline phosphatase have occasionally been reported, these findings are not specific or helpful in achieving a definitive diagnosis.

**Ultrasonography.** Abdominal ultrasonography using a high quality diagnostic ultrasound machine has been used to examine the pancreas of dogs with suspected insulinomas. In one study a pancreatic mass was identified as a spherical or lobular hypoechoic nodule in 75% of dogs with insulinomas. Tumours as small as 7 mm have been identified in the pancreas. Ultrasonography, however, has proved less sensitive for the detection of hepatic or lymphatic metastases from insulinomas.

**Management**
Management of insulinomas should be directed at specific treatment of the tumour, reduction of insulin secretion, and correction of hypoglycaemia.

**Surgical management.** Surgical resection of the pancreatic tumour and metastatic tumour masses should be the first approach to therapy. Patients should be closely monitored during surgery because handling the pancreas may cause the release of large amounts of insulin. Frequent blood glucose measurements and the use of intravenous fluids containing glucose (e.g. 5% dextrose solution) perioperatively is warranted. Most insulinomas are located in the left lobe of the pancreas, with masses in the right lobe or body occurring less frequently. Tumours are usually solitary but multiple masses may occur. Rarely, there is a diffuse islet cell tumour with no discrete nodule. There does not appear to be a difference in survival in relation to tumour location within the pancreas, but there is a suggestion that tumours with a high mitotic count carry a worse prognosis.

Postoperative recovery is routine in many cases but complications including pancreatitis, hyperglycaemia, overt diabetes mellitus, and hypoglycaemia occur. In nearly all cases, hypoglycaemia will recur eventually due to metastasis becoming functional, but this can take several months.

**Medical management.** Medical management should be used if widespread metastasis is present or if hypoglycaemia recurs after surgery. Medical management can provide symptomatic control for many months and usually consists of diet, glucocorticoids and diazoxide. Dietary control consists of providing frequent small meals of a diet high in proteins, fats, and complex carbohydrates. Prednisolone, which inhibits insulin and stimulates glycogenolysis, is useful in raising blood glucose concentration and is given at a dose of 0.5 to 1.0 mg/kg daily in divided doses. Diazoxide, a non-diuretic, benzothiazine antihypertensive drug which inhibits insulin secretion, has also been used successfully at a dose of 10 mg/kg daily in divided doses increasing to 60 mg/kg daily if necessary to control hypoglycaemia.

Octreotide, a somatostatin analogue which inhibits insulin synthesis and secretion, has also been used and has been shown to be effective in some cases. Streptozotocin (streptozocin), a nitrosourea alkalating agent that is directly cytotoxic to pancreatic beta cells has been used successfully in some cases, but can cause proximal renal tubular necrosis, which is dose related and cumulative, and can lead to renal failure. Induction of diuresis by administration of 0.9% NaCl has been reported to ameliorate the renal toxic effects. Briefly, 0.9% NaCl is administered at a rate of 20ml/kg/h for 3 hours prior to the administration of streptozotocin. The dose of streptozocin (500mg/m²) is diluted with an appropriate volume and administered over the subsequent 2 hours at the same rate, and 0.9% NaCl is administered for an additional 2 hours after the streptozotocin is complete.

**Prognosis.** The prognosis is guarded due to the malignant nature of the disease. However, many dogs do well with medical and surgical management. The median time to recurrence of clinical signs after surgery is 12 months (range 4–16 months) and the median postoperative survival time is 14 months (range 10–33 months).