pISSN 1598-298X
*J Vet Clin* 30(5) : 363-365 (2013)

Journal of Veterinary Clinics
www.ksvc.or.kr

# A Case of Long-Term Management of Insulinoma in a Maltese Dog

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(Accepted: October 15, 2013)

**Abstract :** A 15-year-old, spayed female Maltese dog weighing 2.80 kg was referred with seizure of unknown origin. At presentation, serum biochemistry showed marked hypoglycemia (46 mg/dL; reference interval [RI], 65-118 mg/dL). There were, however, no abnormalities on electrolytes, complete blood counts, urinalysis, survey radiographs, and abdominal ultrasonography. In the adrenocorticotropic hormone (ACTH) stimulation test, pre-ACTH and post-ACTH cortisol concentrations were within normal reference ranges. Serum insulin level was normal and fructosamine level was slightly lower than reference ranges. The clinical signs, including seizure and collapse caused by hypoglycemia, were gradually resolved with oral administration of prednisolone (PDS) twice daily. Forty five weeks later, serum biochemistry revealed hypoglycemia with markedly increased insulin level. On abdominal ultrasonography, increased heterogenous echogenecity with hypoechoic lesion was found within pancreatic parenchyma. Based on these findings, the dog was presumptively diagnosed to insulinoma. Hypoglycemic seizure was resolved with higher dose of PDS (1 mg/kg, q12h). At 688 days after first presentation, the patient was still alive without recurrence of hypoglycemic seizure. This case describes long-term management with PDS monotherapy in a Maltese dog with insulinoma.

***Key words*** **:** dog, insulin, insulinoma, prednisolone, hypoglycemia.

## Introduction

A provisional diagnosis and staging of insulinoma are made following an inappropriately high serum insulin concentration at a time of hypoglycemia with suggestive clinical signs (2). In addition, the amended insulin:glucose ratio [AIGR, serum insulin concentration (μU/mL) × 100/blood glucose concentration (mg/dL) -30] > 30 μU/mg glucose is diagnostic of insulinoma (7). On histopathology cytology, anaplastic features are often mild or inconsistent, although most beta cells are malignant in dogs (1). A definitive diagnosis is made when suspected neoplastic tissue is evaluated (2).

When surgical resection is not applicable in patients with insulinoma, medical treatment is frequently applied to reduce the frequency and severity of clinical signs of hypoglycemia from excessive insulin level. In acute hypoglycemic crisis, intravenous dextrose bolus, dexamethasone, or glucagon can be administered. In case of chronic management, frequent feeding with small amount of food and exercise, prednisolone, glucocorticoids, diazoxide, a benzothiadiazine diuretic and potassium channel activator, and octreotide, a long-acting synthetic somatostatin analog are recommended (4). It is also reported that streptozocin, nitrosurea chemotherapeutic agent, and alloxan, an unstable uric acid derivative, can be used as chemotherapy (5). However, long-term treatment with PDS alone has not been reported in dogs with insulinomas. In this case, we describe long-term management with PDS monotherapy in a dog diagnosed to insulinoma.

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## Case

A fifteen-year-old, spayed female Maltese dog weighing 2.80 kg was referred with seizure of unknown origin. The dog had a history of collapse. At referral, there were no abnormalities on physical examination except weakness and mental dullness. Serum biochemical analyses revealed hypoglycemia (46 mg/dL; reference interval [RI], 65-118 mg/dL). In the adrenocorticotropic hormone (ACTH) stimulation test, pre-ACTH and post-ACTH cortisol concentrations were within normal reference ranges (2.88 μg/dL; RI, 0.5-4 μg/dL and 18.0 μg/dL; RI, 8-20 μg/dL), respectively. There were no abnormalities on complete blood counts, urinalysis, survey radiography, and ultrasonography (Fig 1A). Computed tomography (CT) was recommended, but the owner declined. To correct hypoglycemia, fluid therapy with 5% dextrose saline was initiated with intravenous administration of 1 mL/kg of 50% dextrose diluted to 25% in isotonic fluid as a slow bolus over 5 minutes. Dexamethasone (Dexamethasone®, Jeil, Korea, 1 mg/kg) was also administered intravenously. Prednisolone (PDS) (Solondo®, Yuhan Co., Korea, 0.5 mg/kg), ursodeoxycholic acid (Ursa®, Daewoong, Korea, 10 mg/kg), and famotidine (Famotidine®, Nelson, Korea, 0.5 mg/kg) were prescribed when the dog was discharged. The owner was asked to feed the dog with small amount of food at frequent intervals.

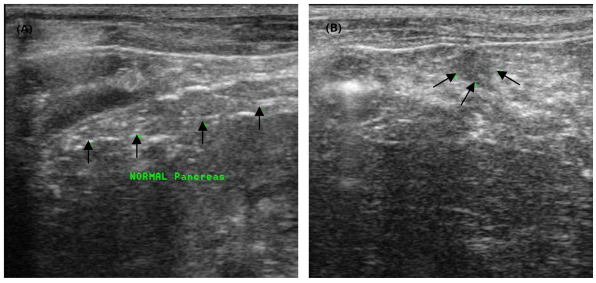


**Fig 1.** Ultrasonographic images of the pancreas obtained from the dog at presentation (A) and at 45 weeks after first presentation (B). There were no remarkable findings at presentation (A). At 45 weeks after first presentation when the dog was presumptively diagnosed to insulinoma, pancreatic parenchyma had generally increased heterogenous echogenecity with hypoechoic lesion (arrow) (B).

Three days later, serum biochemistry showed markedly increased blood glucose level (320 mg/dL). Serum insulin level was normal (5.4 μU/mL; RI, 2.1-21.0 μU/mL), and fructosamine level was slightly lower than normal ranges (242 μmol/L; RI, 258-343 μmol/L). Then, the dog was prescribed with tapered dose of PDS (0.2 mg/kg) twice daily. After that, although there was no relapse of hypoglycemic seizures, the dose was increased to 0.5 mg/kg twice a day because of too low blood glucose level (32 mg/dL).

During 2 months, the dog responded well to PDS. Liver enzymes activities were monitored carefully because steroid-induced hepatopathy might be developed by PDS. The serum biochemistry analyses revealed increased alkaline phosphatase (ALP, 1641 IU/L; RI, 29-97 IU/L) and alanine aminotransferase (ALT, 260 IU/L; RI, 21-102 IU/L). The dog's body weight increased from 3.08 to 3.45 kg, and there were also increased water intake and urine output. Additional ACTH stimulation test was performed to recheck hypoadrenocorticism, and pre-ACTH and post-ACTH cortisol concentrations were within normal reference ranges (2.7 and 7.5 μg/dL), respectively. The treatment was changed by tapering dose of PDS (0.3 mg/kg) twice a day because of increased ALP and ALT. The dog developed superficial pyoderma and otitis externa as secondary bacterial infection caused by long-term administration of PDS. These skin lesions gradually improved by anti-bacterial and anti-fungal drugs.

At 45 weeks after first presentation, the dog returned with 3 episodes of hypoglycemic seizures. On abdominal ultrasonography, pancreatic parenchyma had generally increased heterogenous echogenecity with hypoechoic lesion (Fig 1B). Evidence of metastases was not found. The blood glucose and insulin levels were 33 mg/dL and 113.6 μU/mL, respectively, with high AIGR (3665.33 μU/mg glucose). In addition, fructosamine concentration was lower than reference ranges (215 μmol/L). The dog was presumptively diagnosed to insulinoma based on clinical signs associated with hyperinsulinemia and ultrasonographic findings. One mL/kg of 50% dextrose diluted to 25% in isotonic fluid was given intravenously as a slow bolus over 5 minutes. In addition, dexamethasone (1 mg/kg) was administered. Higher dose of PDS (1 mg/kg) with famotidine (0.5 mg/kg) and ursodeoxycholic acid (10 mg/kg) were prescribed twice a day, and clinical signs disappeared. The dog was still alive at 688 days after first presentation, without recurrence of hypoglycemic seizures.

## Discussion

In the present case, the dog was diagnosed to insulinoma based on clinical signs, laboratory and ultrasonographic findings, which are consistent with earlier reports (11). The dog responded well to treatment with PDS alone, although there were 3 times of recurrence of seizure for continuous administration of PDS. Chemotherapy for treatment of insulinoma was not performed, because clinical signs induced by hypoglycemia were controlled with administration of PDS alone.

In hypoglycemic crises, dextrose, dexamethasone or glucagon bolus can be administered (5). In the present case, dextrose and dexamethasone were effective when hypoglycemic seizure recurred. However, stabilization in patients with insulinoma may be difficult to manage since the dextrose bolus can exacerbate insulin release resulting in unpredictable fluctuations in blood glucose concentrations and worsened hypoglycemia. Therefore, alternative therapies to dextrose are recommended for chronic management of hypoglycemia (5). This dog was prescribed with PDS in conjunction with diet modifications for the long-term management of insulinoma, and blood glucose concentration was successfully controlled.

PDS stimulates hepatic gluconeogenesis and glycogenolysis, and interferes with the interaction between cellular insulin receptors and glucose. These effects result in an increase in blood glucose levels, especially in chronic management of hypoglycemia (10). However, several side effects by chronic use of PDS have also been reported, such as glucocorticoid-induced hepatopathy and secondary skin problems (4). Hypoglycemia in this case was controlled well by PDS alone, although steroid-induced hepatopathy and secondary bacterial infection of skin and ears also had developed.

On ultrasonography, insulinomas are usually either spherical or lobular and hypoechoic compared with the surroundings tissues (5). The sensitivity of ultrasonography in detection of insulinoma in dogs was reported to be 75% (6). In this case, there were no abnormal findings on ultrasonography when the dog was firstly referred. However, 45 weeks later, ultrasonographic imaging of pancreas revealed hypoechoic lesion in heterogenous parenchyma. At that time, insulin level was remarkably high, although it was initially within reference ranges. Given the low sensitivity of ultrasonography, we presumed that this dog might have a small size of insulinoma at first presentation, which became larger gradually. It indicated that enlarged lesions of pancreas might result in subsequent increased insulin level. This suggests that serial monitoring of pancreas on ultrasonography and frequent measurement of serum insulin level are necessary,

even if there are no abnormal ultrasonographic findings and serum insulin level is within normal ranges.

There are limitations to this study. Although the sensitivity of CT for localization of primary insulinoma depends on tumor size, CT is better than ultrasonography in detecting primary or metastatic neoplasia (3). Because of the owner rejection, extrapancreatic neoplasia, such as hepatocellular carcinoma or hepatoma, leiomyosarcoma or leiomyoma, hemangiosarcoma, and carcinoma could not be ruled out. Limitation does also exist that the laboratory which measured serum insulin and fructosamine level at 3 days after first presentation was different from the one at 45 weeks after first presentation.

Survival time of this dog appeared to be longer than previously reported survival times (8). This strongly supports that administration of appropriate dose of PDS may be effective in the long-term control of hypoglycemia by insulinoma.

## Conclusion

The case reported here describes that the hypoglycemia resulted from insulinoma can be managed by monotherapy with PDS for 688 days despite side effects of PDS. It also emphasizes the importance of serial monitoring of serum insulin and fructosamine levels, ultrasonographic imaging of pancreas, and any side effects resulted from long-term use of PDS. This case suggests that medical management with PDS alone may be a reasonable option for long-term management of insulinoma in dogs.

## Acknowledgements

This work was supported by the research grant of the Chungbuk National University in 2012.

## References

1. Brandt KR, Charboneau JW, Stephens DH, Welch TJ, Goellner JR. CT- and US-guided biopsy of the pancreas. Radiology 1993; 187: 99-104.
2. Caywood DD, Klausner JS, O'leary TP, Withrow SJ, Richardson RC, Harvey HJ, Norris AM, Henderson RA, Johnston SD. Pancreatic insulin-secreting neoplasms: clinical, diagnostic and prognostic features in 73 dogs. J Am Anim Hosp Assoc 1988; 24: 577-584.
3. Chiti A, Fanti S, Savelli G, Romeo A, Bellanova B, Rodari M, van Graafeiland BJ, Monetti N, Bombardieri E. Comparison of somatostatin receptor imaging, computed tomography and ultrasound in the clinical management of neuroendocrine gastro-entero-pancreatic tumours. Eur J Nucl Med 1998; 25: 1396-1403.
4. Feldman EC, Nelson RW. Canine and feline endocrinology and reproduction, 3rd ed. St. Louis (MO): Saunders. 2004: 616-644.
5. Goutal CM, Brugmann BL, Ryan KA. Insulinoma in dogs: a review. J Am Anim Hosp Assoc 2012; 48: 151-163.
6. Lamb CR, Simpson KW, Boswood A, Matthewman LA. Ultrasonography of pancreatic neoplasia in the dog: a retrospective review of 16 cases. Vet Rec 1995; 137: 65-68.
7. Leifer CE, Peterson ME, Matus RE. Insulin-secreting tumor: diagnosis and medical and surgical management in 55 dogs. J Am Vet Med Assoc 1986; 188: 60-64.
8. Polton GA, White RN, Brearley MJ, Eastwood JM. Improved survival in a retrospective cohort of 28 dogs with insulinoma. J Small Anim Pract 2007; 48: 151-156.
9. Robben JH, Pollak YW, Kirpensteijn J, Boroffka SA, van den Ingh TS, Teske E, Voorhout G. Comparison of ultrasonography, computed tomography, and single-photon emission computed tomography for the detection and localization of canine insulinoma. J Vet Intern Med 2005; 19: 15-22.
10. Steiner JM, Bruyette DS. Canine insulinoma. Compend Contin Educ Vet 1996; 18: 13-25.
11. Vallee IK. Insulin-secreting beta cell neoplasia in a 10-year-old dog. Can Vet J 2003; 44: 592-594.

# 말티즈 개에서 인슐린종의 장기간 관리 증례

**박소영 · 강병택 · 강지훈 · 장동우 · 양만표**[1]

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**요 약** : 15살, 중성화 암컷 2.80 kg의 말티즈 개가 불명의 경련 및 허탈로 내원하였다. 내원시, 혈청화학적검사에서 심한 저혈당이 나타났으나 전해질검사, 전혈구검사, 뇨분석 및 방사선과 복부초음파에서는 특이적인 소견이 관찰되지 않았다. 인슐린 수치는 정상이었으며, 프락토스아민은 정상범위보다 약간 낮았다. 저혈당의 교정을 위해 프레드니솔론이 처방되었고, 임상증상은 개선되었다. 처음 내원한지 45주 후에, 저혈당성 경련의 재발로 다시 내원하였고, 이때 낮은 혈당치와 매우 높은 인슐린농도가 측정되었다. 복부 초음파 상에서, 췌장은 실질이 전반적으로 증가된 균질하지 않은 에코를 보였으며, 실질 내에 저에코성의 병변이 관찰되었다. 이러한 소견을 근거로, 이 개는 인슐린종으로 임상적 진단되었다. 더 높은 용량의 프레드니솔론을 하루에 2회씩 투여하였고, 경련 등의 임상증상은 개선되었다. 처음 내원한지 688일 후, 환자는 인슐린종으로 인한 저혈당성 경련의 재발 없이 아직 생존해있다. 이 사례는 말티즈 개에서 인슐린종의 진단과 프레드니솔론 단독으로 인슐린종의 장기간 관리에 대한 좋은 예를 보여준다.

**주요어** : 개, 인슐린, 인슐린종, 프레드니솔론, 저혈당증