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Effect of octreotide on plasma concentrations of glucose, insulin, glucagon, growth hormone, and cortisol in healthy dogs and dogs with insulinoma

J.H. Robben [a,*], W.E. van den Brom [a], J.A. Mol [a], T.W. van Haeften [b], A. Rijnberk [a]

[a] *Department of Clinical Sciences of Companion Animals, Faculty of Veterinary Medicine, Utrecht University, P.O. Box 80.154, NL-3508 TD, Utrecht, The Netherlands*
[b] *Department of Internal Medicine (G 02.228), University Medical Center, Utrecht University, P.O. Box 85.500, NL-3508 GA, Utrecht, The Netherlands*

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Abstract

The inhibitory effect of the somatostatin analogue octreotide on the secretion of insulin could be used in the treatment of insulinoma. However, current information on the effectiveness of octreotide in dogs is conflicting. Therefore, the endocrine effects of a single subcutaneous dose of 50 μg octreotide were studied in healthy dogs in the fasting state ($n = 7$) and in dogs with insulinoma ($n = 12$).

Octreotide did not cause any adverse effects. In healthy dogs in the fasting state, both plasma insulin and glucagon concentrations declined significantly. Basal (non-pulse related) GH and ACTH concentrations were not affected. A slight but significant decrease in the plasma glucose concentrations occurred.

Dogs with insulinoma had significantly higher baseline insulin concentrations and lower baseline glucose concentrations than healthy dogs in the fasting state. Plasma glucagon, GH, ACTH, and cortisol concentrations did not differ from those in healthy dogs. Baseline plasma insulin concentrations decreased significantly in dogs with insulinoma after octreotide administration, whereas plasma concentrations of glucagon, GH, ACTH, and cortisol did not change. In contrast to the effects in the healthy dogs, in the dogs with insulinoma plasma glucose concentrations increased.

Thus, the consistent suppression of plasma insulin concentrations in dogs with insulinoma, in the absence of an suppressive effect on counter-regulatory hormones, suggests that further studies on the effectiveness of slow-release preparations in the long-term medical treatment of dogs with insulinoma are warranted.

Keywords: Octreotide; Canine; Glucose; Insulin; Counter-regulatory hormone

1. Introduction

Surgery is the preferred treatment for benign and malignant insulinomas in both humans and dogs (Leifer et al., 1986; Azimuddin and Chamberlain, 2001). However, medical control of hypoglycaemia is needed in the perioperative period, if the resection is incomplete or the disease is inoperable (Barrons, 1997). Diazoxide has been used to control the hypoglycaemia caused by endogenous hyperinsulinaemia, but is ineffective in about 30% of human and canine cases (Goode et al., 1986; Leifer et al., 1986). The octapeptide octreotide, a synthetic somatostatin (SST) derivative, has been used to control hormone hypersecretion and clinical symptoms in pituitary tumours, endocrine pancreatic

* Corresponding author. Tel.: +31 30 2539411; fax: +31 30 2518126.
E-mail address: j.h.robben@vet.uu.nl (J.H. Robben).

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tumours, and carcinoid tumours in man. Recently, radiolabelled octapeptide analogues have been used for radiotherapy of advanced or metastatic neuroendocrine tumours (for review: Arnold et al., 2000; de Herder and Lamberts, 2002).

In humans, octreotide is fully absorbed when administered subcutaneously and reaches maximal plasma concentrations in 25–35 min; it has an elimination half-life of 90–110 min. Rebound hypersecretion of hormones rarely occurs after octreotide administration, neither in healthy subjects nor in patients with neuroendocrine tumours (Lamberts et al., 1985; Chanson et al., 1993). Octreotide is more selective in inhibiting hormone secretion than the natural SST (Bauer et al., 1982). Growth hormone (GH) secretion is inhibited more than glucagon and glucagon more than insulin. This selectivity is probably the result of different somatostatin receptor (SSTR) populations mediating the secretion of different hormones (Rossowski and Coy, 1994; Patel, 1999; Portela-Gomes et al., 2000). In contrast to the natural SST somatostatin-14, octreotide does not bind with the same affinity to all five SSTR subtypes (Reisine and Bell, 1995; Lamberts et al., 1996). In the rat and rhesus monkey, but not in humans, octreotide is also more potent than somatostatin-14 (Bauer et al., 1982; Patel and Srikant, 1994).

Octreotide has been used with varying success in humans with insulinoma to inhibit insulin secretion, to increase plasma glucose concentrations, and to alleviate clinical symptoms (Maton et al., 1989; Glaser et al., 1990; Timmer et al., 1991). In patients with pancreatic hyperinsulinism unresponsive to octreotide, its administration can worsen existing hypoglycaemia by suppressing the secretion of the counter-regulatory hormones glucagon and GH (Barrons, 1997). The unresponsiveness could be the result of the heterogeneous expression of SSTR subtypes in human insulinomas. SSTRs that bind octreotide with high affinity are expressed in only 50–72% of cases (Arnold et al., 2000; Breeman et al., 2001).

The short-term effect on plasma hormone concentrations of a single dose of octreotide in humans is closely correlated with the detection of neuroendocrine tumours with somatostatin receptor scintigraphy (SRS), and with the effectiveness of long-term treatment (Lamberts et al., 1988, 1990; John et al., 1996). In a previous study, we demonstrated that octreotide decreased plasma insulin concentrations with a resultant increase in plasma glucose concentrations in eight dogs with insulinoma. Furthermore, high-affinity receptors for octreotide were demonstrated by in vitro autoradiography and in vivo [^{111}In-DTPA-D-Phe^{1}]-octreotide scintigraphy (Robben et al., 1997). However, other studies of octreotide treatment in dogs with insulinoma have yielded variable results (Lothrop, 1989; Simpson et al., 1995).

Here, we report on investigations in healthy dogs and dogs with insulinoma on the acute effects of a single subcutaneous dose of octreotide on plasma concentrations of glucose and insulin, as well as the counter-regulatory hormones glucagon, GH, adrenocorticotrophic hormone (ACTH), and cortisol.

2. Materials and methods

2.1. Dogs

The tests were performed in healthy dogs (control group) and dogs with insulinoma (insulinoma group). The characteristics of the dogs in both groups are summarized in Table 1. All control dogs had been born and raised in the Department of Clinical Sciences of Companion Animals. They were housed singly or in pairs in outdoor–indoor runs, fed a standard commercial dog food twice daily, and given water ad libitum. In all control dogs, clinical chemistry variables were within the reference range. In the dogs with insulinoma, clinical chemistry variables were also within the reference range with the exception of plasma glucose concentrations, which were repeatedly below the lower limit of the reference range (4.0 mmol/l). All clinical cases had a recent history of recurrent episodes of hypoglycaemia. Hyperinsulinaemia was diagnosed by repeated measurement of low plasma glucose concentrations in the presence of inappropriately high circulating insulin concentrations. In all clinical cases, the final diagnosis of a pancreatic endocrine tumour was based on the results of histological examination of tumour samples obtained at surgery or during necropsy immediately following

Table 1
Description of healthy dogs (control group) and dogs with insulinoma (insulinoma group)

	Control group		Insulinoma group	
Number of dogs	7		12	
Breed[a]	Mixed breed (7)		Bearded Collie (2) Boxer (3) W.H.W. Terrier[d] (1) Am. Cocker Spaniel[d] (1) Beagle (1) German Shepherd (1) German Shorthair (1) Irish Setter (1) Mixed Breed (1)	
Sex[a,b]	F (2) M (4)	FN (1) MN (0)	F (2) M (4)	FN (4) MN (2)
Age (years)[c]	10.1 (8.0–13.0)		9.4 (6.0–10.7)	
Weight (kg)[c]	18.5 (15.6–22.5)		23.3 (14.8–35.6)	

[a] Number of dogs are given in brackets.
[b] F, female; FN, female neutered; M, male; MN, male neutered.
[c] Median (range).
[d] W.H.W. Terrier = West Highland White Terrier; Am. Cocker Spaniel = American Cocker Spaniel.

euthanasia. The dogs with insulinoma did not receive any treatment before the test.

The dogs in the control group were fasted overnight (fasting state). Dogs with insulinoma are usually given several (6–8) small meals throughout the day to control hypoglycaemia. For this experiment, these animals were given a final small meal 4–6 h before the test. Food was withheld from all dogs during the test, that is, for 4 or 4.5 h.

The Committee for the Ethical Care of Animals of the Utrecht University approved the experiments in this study.

2.2. Octreotide test

To study the effect of a single injection of octreotide, at $T = 0$ min, 50 μg of octreotide (Sandostatin®: Novartis Pharma B.V., Arnhem, the Netherlands) was administered subcutaneously in all dogs. In a previous study, this dose had a significant effect on plasma insulin and glucose concentrations (Robben et al., 1997).

Blood samples were collected for the measurement of plasma glucose, insulin, glucagon, GH, ACTH, and cortisol at −30, −15, 0, 15, 30, 60, 120, and every 30 min thereafter up to 240 min after the administration of octreotide. Blood samples were collected by jugular venipuncture into oxalate fluoride-coated tubes for measurement of plasma glucose concentration and into precooled EDTA-coated tubes with 500 KIU/ml aprotinin (Trasylol®: Bayer B.V., Mijdrecht, the Netherlands) for measurement of plasma hormone concentrations. The samples were centrifuged at 4 °C and plasma for determination of hormone concentrations was stored at −20 °C until used for assay.

2.3. Assay methods

The glucose concentration in plasma was measured with a hexokinase method on a Beckman Synchron CX® System (Beckman Coulter Nederland B.V., Mijdrecht, the Netherlands) (Kunst et al., 1984). Details on the assays used to determine plasma hormone concentrations are summarized in Table 2.

2.4. Calculation and statistical analysis

The results of the octreotide test are presented as median and range as the data were not normally distributed. Median baseline plasma glucose and hormone concentrations were calculated from the −30, −15, and 0 min values. Differences in baseline values between the control and insulinoma group were assessed with the non-parametric Mann–Whitney U test (two-tailed). Plasma glucose and hormone concentrations in the octreotide test are expressed as the incremental area-under-the-curves (AUC/240 – BL; AUC = area-under-the-curve during 240 min (the trapezoidal method), BL = the baseline value). The significance of results was determined with the non-parametric Wilcoxon signed-rank test (two-tailed). Differences between control and insulinoma group were assessed with the Mann–Whitney U test (two-tailed).

The differences between each time point and the baseline value for plasma glucose, insulin, and glucagon concentrations in each group were first assessed by analysis of variance (ANOVA) for repeated measures. When significant changes were found, multiple comparisons were performed using the Dunnett test. A $P < 0.05$ was considered significant.

3. Results

3.1. Octreotide test

There were no signs that the dogs were disturbed by the injection and/or sampling procedure. Neither the control dogs nor the clinical cases had signs of hypo-

Table 2
Description of assay methods used for plasma hormone measurement

Hormone	Assay		Variation coefficients		LQ[a] (pmol/l)
	Type	Product	Intra-assay (%)	Inter-assay (%)	
Insulin	Two-site IRMA[b]	INS-IRMA: BioSourceEurope SA, Nivelles, Belgium[c]	4.5	4.7	7
Glucagon	Heterologous RIA[b]	Double Antibody Glucagon: Diagnostics Products Co., Los Angeles, CA, USA[d]	6.5	11.9	3.7
GH	Homologous RIA	Eigenmann and Eigenmann (1981)	3.8	7.2	27
ACTH	Two-site IRMA	ACTH Radioisotopic Assay: Nichols Institute Diagnostics, San Juan Capistrano, CA, USA	3.2	7.8	0.22
Cortisol	Solid-phase RIA	Count-A-Count Cortisol: Diagnostics Products Co., Los Angeles, CA, USA	5.1	6.4	6×10^2

[a] LQ, limit of quantification.
[b] IRMA, immunoradiometric assay; RIA, radioimmunoassay.
[c] The degree of cross-reactivity with human pro-insulin is 0% (according to information supplied by the manufacturer). Serial dilutions of canine plasma were parallel to the standard curve of human insulin.
[d] Serial dilutions of canine plasma were parallel to the standard curve, based on a standard preparation containing synthetic human glucagons in a protein-based matrix.

glycaemia during or after the test. Acute adverse effects similar to those reported in humans were not noticed in these dogs during or immediately after the test.

3.2. Plasma glucose concentrations

The insulinoma group had significantly lower baseline plasma glucose concentrations than the control group (Table 3). In the control group, plasma glucose concentrations decreased significantly over the 240-min test period. In the insulinoma group, plasma glucose concentrations increased significantly 120 min after octreotide administration and remained high (Table 3, Fig. 1).

3.3. Plasma insulin concentrations

Baseline plasma insulin concentrations were significantly lower than in the insulinoma group compared to the control group (Table 3). Plasma insulin concentrations decreased significantly over the 240-min test period in the control group and the insulinoma group. Plasma insulin concentrations reached a nadir at 15, 30 and/or 60 min in both groups. For the control group, the median nadir value at 30 min was 13 (range, 7–27) pmol/l. In the insulinoma group, the 30-min nadir value was 27 (range, 20–47) pmol/l.

3.4. Plasma glucagon, GH, ACTH, and cortisol concentrations

Baseline plasma glucagon concentrations of the control group and the insulinoma group did not differ significantly (Table 3). After octreotide administration plasma glucagon concentrations in the control group decreased significantly whereas those of the insulinoma group did not (Table 3, Fig. 1).

Baseline plasma GH, ACTH, and cortisol concentrations did not differ between the control group and the insulinoma group (Table 3) and did not change in response to octreotide administration, with the exception of a significant decline in plasma cortisol concentrations in the control group (Table 3).

4. Discussion

The subcutaneous administration of octreotide in humans can cause pain at the injection site and may also give rise to more generalized adverse effects such as nausea, abdominal cramps, diarrhea, and flatulence (Chanson et al., 1993). Moreover, in patients with insulinoma hypoglycaemia may be aggravated (Maton et al., 1989; Stehouwer et al., 1989). The absence of noticeable side effects or signs of hypoglycaemia indicates that administration of a single dose of 50 μg octreotide to dogs with insulinoma may be with less risk than in man.

The effect of octreotide on plasma insulin concentrations in our dogs with insulinoma differs from the effect in humans with insulinoma. Our dogs responded with decreased plasma insulin concentrations, while in humans insulin concentrations show a variable response to octreotide. This has been related to SSTR heterogeneity. In this respect, it is intriguing that canine insulinomas are primarily malignant (>95%), whereas in humans both benign and malignant tumours were studied (Maton et al., 1989). It has been suggested that malignant pancreatic endocrine tumours in humans respond better to octreotide than do benign tumours (Glaser et al., 1990).

There is evidence that insulin release from insulinomas is more sensitive to suppression by octreotide and can be inhibited for longer than insulin release from non-tumourous β-cells, both in vitro and in vivo (Oosterom et al., 1987). Although our study was not specifically designed to test this hypothesis, the suppressive effect of octreotide on plasma insulin concentrations did not appear to last longer in dogs with insulinoma

Table 3
Baseline and response[a] values of plasma glucose and insulin in the control group (fasting state) and the insulinoma group after a single subcutaneous injection of octreotide

	Baseline		Response		Difference control and insulinoma	
	Control	Insulinoma	Control	Insulinoma	Baseline	Response
Glucose (mmol/l)	5.4 (4.7 to 5.6)	3.1 (2.3 to 3.5)	−1.65* (−1.86 to −1.33)	+0.65* (−0.14 to 1.69)	$P < 0.001$	$P < 0.001$
Insulin (pmol/l)	43 (34 to 63)	117 (56 to 371)	−26* (−37 to −10)	−63** (−252 to −17)	$P < 0.001$	$P < 0.01$
Glucagon (pmol/l)	24.5 (19.5 to 27.2)	23.6 (15.2 to 34.8)	−8.7* (−15.0 to −6.7)	−3.2 (−9.2 to 10.7)	ns	$P < 0.005$
GH (pmol/l)	123 (27 to 224)	49 (27 to 132)	−13.1 (−142.2 to 51.1)	−6.2 (−97.3 to 85.1)	ns	ns
ACTH (pmol/l)	11.9 (3.9 to 19.6)	6.9 (2.3 to 24.9)	−1.45 (−8.91 to 2.61)	−0.32 (−10.44 to 5.54)	ns	ns
Cortisol (nmol/l)	88 (30 to 117)	54 (27 to 238)	−34.2* (−75.1 to 4.1)	−6.7 (−86.2 to 23.9)	ns	ns

Results are presented as median (range). ns, not significant.
[a] Response is defined as the incremental area-under-the-curve.
* Significant response: $P < 0.05$.
** Significant response: $P < 0.001$.

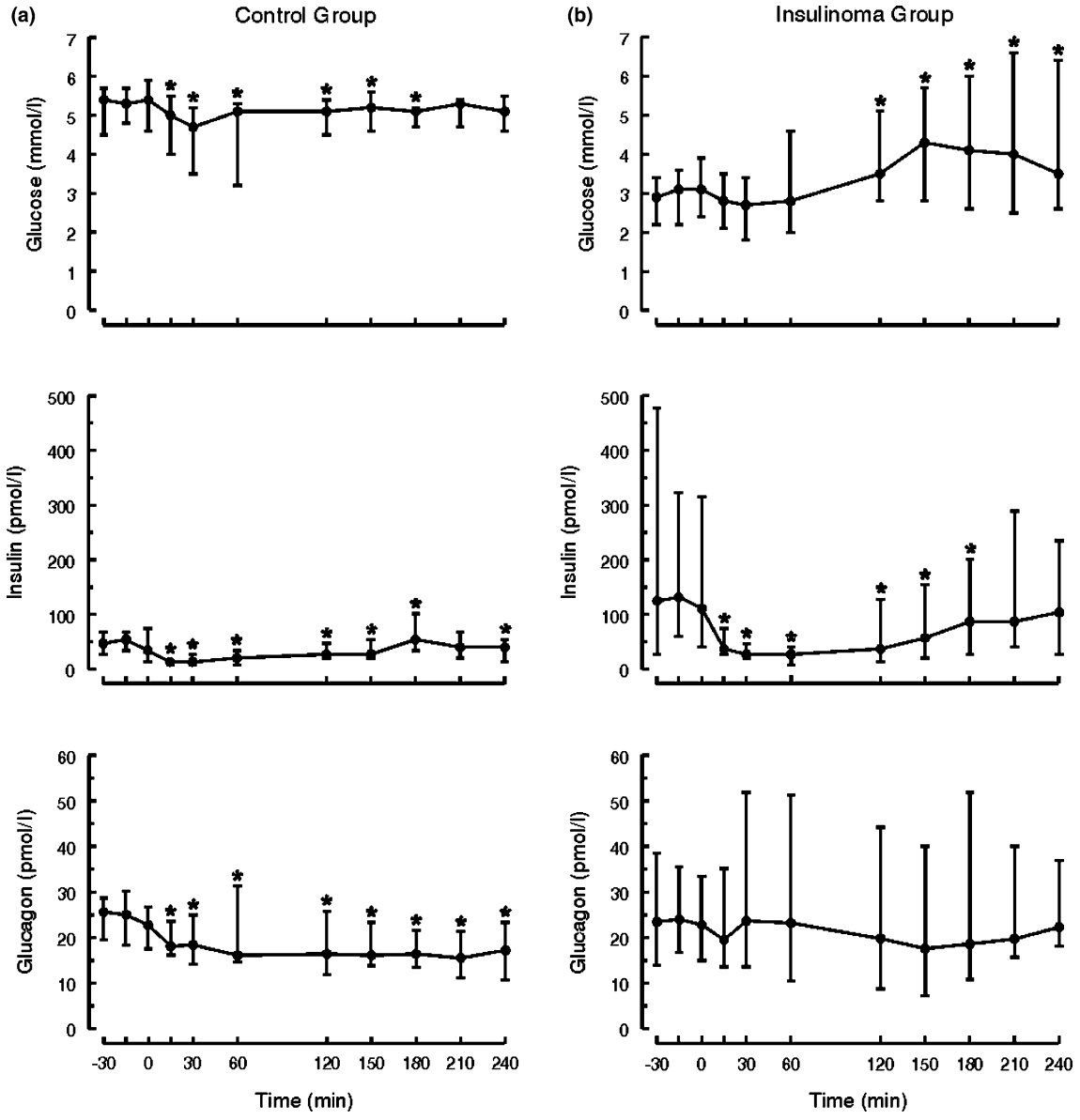

Fig. 1. Plasma concentration (median and range) of glucose, insulin and glucagon after a single subcutaneous injection of 50 μg octreotide at $T = 0$ min in healthy dogs after an overnight fast (Control Group) (left panels) and dogs with insulinoma and food withheld for 4–6 h prior to the test (Insulinoma Group) (right panels). Note the wide range of baseline plasma insulin concentrations in the dogs with insulinoma as compared to the healthy dogs. * Significantly different from baseline values.

than in healthy dogs and lasted about 3–4 h in all animals. This relatively short effect may explain the earlier reported therapeutic failure of octreotide treatment in dogs with insulinoma (Lothrop, 1989; Simpson et al., 1995). In humans, continuous octreotide infusion is more effective than administration at 8-h intervals (Glaser et al., 1990). The effectiveness of a slow-release formulation of octreotide in controlling plasma insulin concentrations in dogs with insulinoma has not yet been studied (Tomassetti et al., 2000).

Baseline concentrations of the counter-regulatory hormones glucagon, GH, and cortisol were similar in control dogs and dogs with insulinoma. Thus, chronic hypoglycaemia does not lead to persistently increased plasma concentrations of these hormones. In healthy humans with acute hypoglycaemia, the plasma glucose thresholds for activation of different counter-regulatory systems lie just below the physiological plasma glucose concentration (between 3.6 and 3.9 mmol/l) (Cryer, 2003). However, glucose thresholds decrease during sustained (56 h) hypoglycaemia in healthy volunteers and in humans with insulinoma, most likely because brain glucose uptake is enhanced at lower plasma glucose concentrations (Mitrakou et al., 1993; Boyle et al., 1994).

In humans, octreotide suppresses basal and stimulated plasma glucagon concentrations in both healthy

subjects and patients with insulinoma (Del Pozo et al., 1986; Johnston et al., 1986; Stehouwer et al., 1989). Octreotide suppressed plasma glucagon concentrations in the control dogs but not in the dogs with insulinoma. This may have prevented the occurrence of clinical signs of hypoglycaemia during the test in the dogs with insulinoma. Octreotide did not affect plasma glucagon concentrations in four humans with benign insulinoma (Timmer et al., 1991). Possibly, the inhibitory effect of octreotide on glucagon secretion may have been counteracted by the simultaneous reduction in insulin secretion. Insulin suppresses glucagon secretion and therefore a decrease in plasma insulin may have had a stimulatory effect on glucagon release (Gerich et al., 1976). The initial tendency of plasma glucose concentrations to decrease, although not significantly, could also have triggered glucagon secretion.

The lack of a suppression of basal plasma GH concentrations by octreotide has been reported earlier, in both healthy dogs and humans (Johnston et al., 1986; Watson et al., 1987; Selman et al., 1991). However, spontaneous (nocturnal) GH peaks (in humans) and stimulated GH responses to clonidine and human Growth Hormone Releasing Hormone (hGHRH, in dogs) and arginine (in humans) are lowered by octreotide (Del Pozo et al., 1986; Johnston et al., 1986; Selman et al., 1991). In dogs with insulinoma, a more detailed study of the pulsatile pattern of GH secretion is necessary to elucidate the effect of octreotide on spontaneous pulsatile GH release (Kooistra et al., 2000).

In healthy dogs in the fasting state, octreotide administration did not affect ACTH concentrations, but caused a significant decrease in plasma cortisol concentrations. However, this decrease started before the injection of octreotide suggesting that the initial stress response to the test subsided during the test. Octreotide does not influence basal and stimulated ACTH and cortisol concentrations in healthy humans (Maton et al., 1989; Lamberts, 1988). It has been hypothesized that only in the absence of physiological feedback regulation by glucocorticoids, such as in Addison's disease, SST has an inhibitory effect on ACTH secretion (Lamberts, 1988).

The effect of octreotide on plasma glucose concentrations is not only the result of its influence on hormone release. Octreotide may also influence gastrointestinal absorption and hepatic and peripheral metabolism of glucose, as well as indirectly affect other glucoregulatory mechanisms (epinephrine, neural and substrate factors) (Johnston et al., 1986). In healthy dogs in the postprandial state, plasma glucose concentrations do not change after octreotide administration (Watson et al., 1987). This may be explained by a reduction in plasma insulin concentrations on the one hand and a reduction in plasma glucagon concentrations and intestinal absorption of carbohydrates on the other. In the fasting state, plasma glucagon concentrations could become more important even though the plasma insulin concentration is still an important determinant of the plasma glucose concentration (Cryer, 2003). In the control dogs in the fasting state the decrease in plasma glucose concentrations may have been primarily determined by the decreased plasma glucagon concentrations. Thus, in healthy dogs, the effect of a single dose of octreotide on plasma glucose concentrations appears to depend on the metabolic state.

The differences between each time point and the baseline value for plasma glucose indicate a delayed rise in plasma glucose concentrations in dogs with insulinoma after a single injection with octreotide. During the first 2 h, plasma glucose concentrations did not change or decreased slightly, whereas in the last 2 h of the test plasma glucose concentrations increased significantly. A transient decrease followed by a rise in plasma glucose after a single dose of octreotide has been observed in two humans with insulinoma (Stehouwer et al., 1989). The delayed glucose response could be the result of sustained metabolic effects of insulin after plasma concentrations are lowered. Indeed, the action of insulin on the liver and peripheral tissues may persist for 40 min or longer (Sherwin et al., 1997). Additionally, the delayed increase in glucose could also result from a time-dependent change in the interaction of insulin and SST derivatives. Findings in humans indicate that the action of insulin is intensified in the first hour and is counteracted after 2 h of continuous SST infusion (Adamson et al., 1982). This biphasic effect could also contribute to the rise in plasma glucose concentrations despite the simultaneous increase in plasma insulin concentrations. Furthermore, an initial rise in glucose concentrations as a result of insulin suppression could be counteracted by a parallel decrease in plasma glucagon concentrations (Sherwin et al., 1997). Although this has been demonstrated in humans with insulinoma (Stehouwer et al., 1989), glucagon concentrations did not decrease in our dogs with insulinoma. As there were no major changes in GH, ACTH, and cortisol concentrations, it is most likely that the alterations in plasma glucose concentration were mainly the result of changes in insulin release and the interaction of insulin with octreotide.

In dogs with insulinoma, octreotide decreases plasma insulin concentrations and increases plasma glucose concentrations. This indicates that octreotide, when used together with other measures to raise plasma glucose concentrations, could be useful for controlling the acute life-threatening hypoglycaemia of dogs with insulinoma. The consistent suppression of plasma insulin concentrations in dogs with insulinoma, in the absence of an effect on counter-regulatory hormones, suggests that further studies on the effectiveness of slow-release preparations in long-term medical treatment are warranted.

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