Use of proligestone in the management of three German shepherd dogs with pituitary dwarfism

Three German shepherd dogs were diagnosed with pituitary dwarfism and subsequently treated with proligestone. Treatment resulted in development of an adult hair coat, increased bodyweight and elevated insulin-like growth factor-1 concentration. Two dogs received thyroid supplementation during proligestone therapy. Adverse effects (cystic endometrial hyperplasia and acromegaly) were reported in two cases. No side effects were reported in the remaining case. This is the first report of the use of proligestone in the management of pituitary dwarfism.

C. M. KNOTTENBELT AND
M. E. HERRTAGE*

Journal of Small Animal Practice (2002)
43, 164-170

Department of Veterinary Clinical Studies, University of Glasgow Veterinary School, Bearsden Road, Bearsden, Glasgow G61 1QH

*The Queen's Veterinary School Hospital, University of Cambridge, Madingley Road, Cambridge CB3 0ES

INTRODUCTION

Pituitary dwarfism is caused by a lack of growth hormone that results in proportionate dwarfism. In German shepherd dogs, the condition is thought to be inherited as an autosomal recessive gene (Andresen and Willeberg 1976, Nicholas 1978). Lesions in the pituitary gland are thought to be responsible for the deficiency of growth hormone (Rao and Baht 1971, Capen 1993). However, pituitary cyst formation may be a secondary feature to the defect in growth hormone production (Hamann and others 1999). Pituitary cyst formation can result in deficiencies of other anterior pituitary hormones (thyroid-stimulating hormone [TSH], adrenocorticotrophic hormone [ACTH], follicle-stimulating hormone [FSH] and luteinising hormone [LH]) (Feldman and Nelson 1996) and neurohypophyseal dysfunction (antidiuretic hormone deficiency) (Ramsey and others 1999).

The use of progestins has recently been shown to induce the production of growth hormone from foci of hyperplastic ductular epithelium of the mammary gland (Mol and others 1994, 1996). These progestin-induced increases in growth hormone are also associated with elevated plasma concentrations of insulin-like growth factor 1 (IGF-1) (Mol and others 1996, 1997). Administration of medroxyprogesterone acetate to two German shepherd dog pituitary dwarfs has been shown to increase bodyweight and induce the development of adult hair coat (Kooistra and others 1998). This is the first report of the use of proligestone, a synthetic progestagen, for the management of pituitary dwarfism in dogs.

CASE HISTORIES

Two female and one male German shepherd dogs were referred to the University of Glasgow Veterinary School (case 1) and the Queen's Veterinary School Hospital, University of Cambridge (cases 2 and 3) with suspected pituitary dwarfism. All three dogs were undersized for their age (Table 1) but there was no evidence of disproportionate limb growth. The dogs had retained puppy coat and alopecia over the caudal dorsum, elbows, stifles and tail (Fig 1). Both bitches had been in season more than one month prior to referral; case 1 had been in oestrus at four months of age and again at two weeks prior to referral. Thirst, urination and defecation were normal in all three dogs. Appetite was normal in case 1, but was considered reduced in cases 2 and 3. Marked brachygnathism was evident in cases 1 and 2. Case 2 was nervous but no other behavioural problems were noted in any of the dogs.

Table 1. Age, sex and weight of the dogs at presentation

Case number	Age (months)	Sex	Weight (kg)	Normal weight for age (kg)*
1	6	F	11·0	26
2	7	F	9·4	27·5
3	6	M	16·0	26

*Normal weight of a female German shepherd dog (Randolph and others 1990)
F Female, M Male

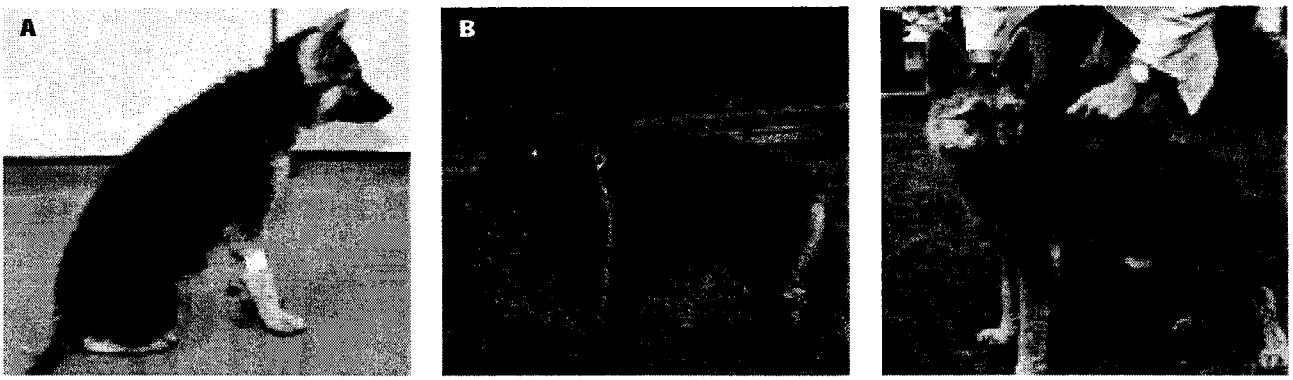

FIG 1. Appearance of the dogs at presentation: (A) case 1; (B) case 2; (C) case 3. The dogs all have puppy coats comprising secondary hairs. There are areas of alopecia over the stifles, tail and neck regions

Congenital growth hormone deficiency was suspected on the basis of the proportionate dwarfism, brachygnathism and retained puppy hair coat. Serum concentrations of IGF-1 were subnormal (Table 2), confirming pituitary dwarfism in all three dogs (Eigenmann and others 1984). Serum cortisol concentrations were measured before and 30 minutes after intravenous injection of 0·25 mg of tetracosactrin (Synacthen; Alliance Pharmaceuticals). Serum thyroxine (T_4) concentrations were measured before and four hours after intravenous administration of 200 µg of thyrotrophin-releasing

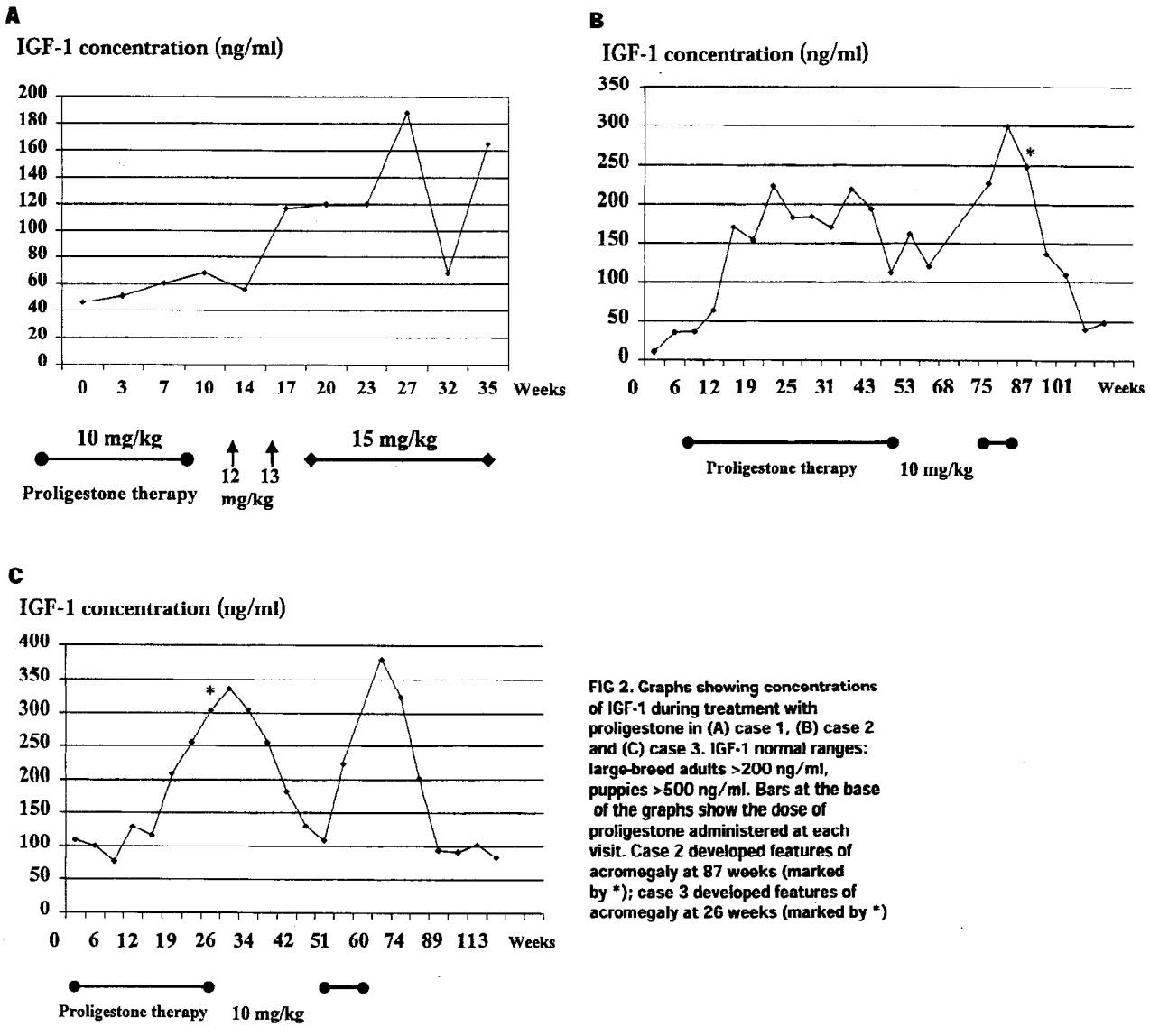

FIG 2. Graphs showing concentrations of IGF-1 during treatment with proligestone in (A) case 1, (B) case 2 and (C) case 3. IGF-1 normal ranges: large-breed adults >200 ng/ml, puppies >500 ng/ml. Bars at the base of the graphs show the dose of proligestone administered at each visit. Case 2 developed features of acromegaly at 87 weeks (marked by *); case 3 developed features of acromegaly at 26 weeks (marked by *)

Table 2. Results of endocrine testing

Parameter	Case 1	Case 2	Case 3	Reference range
IGF-1 (ng/ml)	46	<15·0	89	<1 year >500 ng/ml, adults >200 ng/ml, dwarfs <100 ng/ml
Pre-ACTH cortisol (nmol/litre)	59	101	106	40-150 nmol/litre
Cortisol (30 minutes post-ACTH) (nmol/litre)	173	228	254	2·3 × increase (<450 nmol/litre)
Basal T_4 (nmol/litre)	15·3	30	30	10-53 nmol/litre
T_4 (4 hours post-TRH) (nmol/litre)	15·3	27	27	1·2 × basal (>25 nmol/litre)
Basal cTSH (ng/ml)	0·61	<0·01	<0·01	< 0·41 ng/ml
cTSH (30 minutes post-TRH) (ng/ml)	0·76	<0·01	<0·01	0·4-1·0 ng/ml

IGF-1 Insulin-like growth factor 1, ACTH Adrenocorticotrophic hormone, T_4 Thyroxine, TRH Thyrotrophin-realising hormone, cTSH Canine thyroid-stimulating hormone

Table 3. Results of thyroid assessment during treatment with proligestone

Case	Week	Basal total T_4 (nmol/litre)	Basal cTSH (ng/ml)
1	0	15·3	0·61
	7	32·2	NA
	27	43·3	NA
2	0	30	<0·01
	29	46	NA
	68	55	<0·01
3	0	30	<0·01
	19	61	NA
	60	31	<0·01
	83	37	<0·01
Reference ranges		10-53	<0·41

Cases 2 and 3 were receiving thyroxine (Soloxine; Arnolds Veterinary Products) at a dose of 0·02 mg/kg once and twice daily, respectively, throughout treatment with proligestone. T_4 Thyroxine, cTSH Canine thyroid-stimulating hormone, NA Not assessed

hormone (TRH, Cambridge Laboratories). Canine thyroid-stimulating hormone (cTSH) concentrations were measured before and 30 minutes after TRH administration (Scott-Moncrieff and Nelson 1998). The results of endocrine testing are shown in Table 2.

Treatment with proligestone (Delvosteron; Intervet UK) by subcutaneous injection at 10 mg/kg every three weeks was instituted once the diagnosis of pituitary dwarfism was confirmed (cases 1 and 2) or after thyroxine therapy failed to result in a significant improvement in coat quality (case 3). Case 1 was treated with proligestone alone. Case 3 was initially treated with thyroxine (Soloxine; Arnolds Veterinary Products) alone at a dose of 0·02 mg/kg twice daily orally for 37 weeks prior to proligestone therapy. Case 2 received concurrent thyroxine treatment at a dose of 0·02 mg/kg once daily orally during proligestone therapy. Thyroid supplementation was continued after proligesterone therapy was withdrawn in cases 2 and 3. At each visit any change in weight, hair coat, thirst, appetite or urination was recorded. The mammary glands were palpated and the vulva was examined for discharge. Blood was collected for measurement of serum IGF-1 concentrations (Fig 2).

FIG 3. Appearance of case 3 at 26 weeks. The increased soft tissue around the head and neck and forelimb thickening are consistent with the development of acromegaly

No mammary development or other adverse effects were recorded during therapy in case 1. Mammary development was noted in cases 2 and 3 after 12 and 9 weeks, respectively. Treatment with proligestone was withheld from week 48 in case 2 due to the development of heavy breathing at exercise. Treatment was reinstituted at week 68 but withheld again from week 81 due to development of the clinical features of acromegaly (increased soft tissue formation around the head and neck, inspiratory stridor, enlargement of the limbs, heavy muscle development and increased interdental spaces).

Case 3 developed a recurrent bacterial pyoderma after 16 weeks which was treated with a variety of antibiotics including ampicillin (Amfipen; Intervet UK), cephalexin (Ceporex; Schering-Plough Animal Health) and enrofloxacin (Baytril; Bayer). Features of acromegaly were detected 26 weeks after the start of treatment in case 3 (Fig 3) and treatment was therefore withheld for 20 weeks. Treatment was re-instituted at 46 weeks due to a reduction in IGF-1 concentration (Fig 2C); however, treatment was withdrawn again from week 60 due to a recurrence of the signs of acromegaly. Case 2 developed a recurrent vulval discharge 87 weeks after starting therapy. Ovariohysterectomy was performed at week 96 and the presence of cystic endometrial hyperplasia was confirmed on histopathology. Case 3 was castrated at 117 weeks due to recurrence of hair loss (oestrogens and androgens have been shown to suppress initiation of the anagen phase of the hair cycle in rats; Scott and others 1995).

During the treatment of case 1, the dose of proligestone was gradually increased from week 14 as no adverse effects had been reported and treatment had failed to increase IGF-1 concentrations to any marked degree. The dose was maintained at 15 mg/kg from week 20 of treatment. A voided urine sample was collected at 35 weeks to determine if glucosuria was present. Dipstick analysis showed no abnormalities; specific gravity was 1·024. No adverse side effects were reported during treatment. Total T_4 concentrations were measured intermittently in all dogs and basal cTSH in cases 2 and 3 (Table 3).

Improvement in the coat quality was noted within 10 weeks of starting treatment in all three cases (Fig 4). Primary hairs initially developed over the tail and subsequently appeared over the dorsum and flanks. Hair regrowth at sites of clipping was noted by week 14 in case 1. A recurrence of hair loss was noted in case 2 after proligestone therapy had been withheld for 10 weeks and in case 3 after therapy had been withheld for 14 weeks. All dogs showed a steady increase in bodyweight during treatment and even after treatment had been withdrawn in cases 2 and 3 (Fig 5). An increase in paw size was noted in case 1 at 10 weeks.

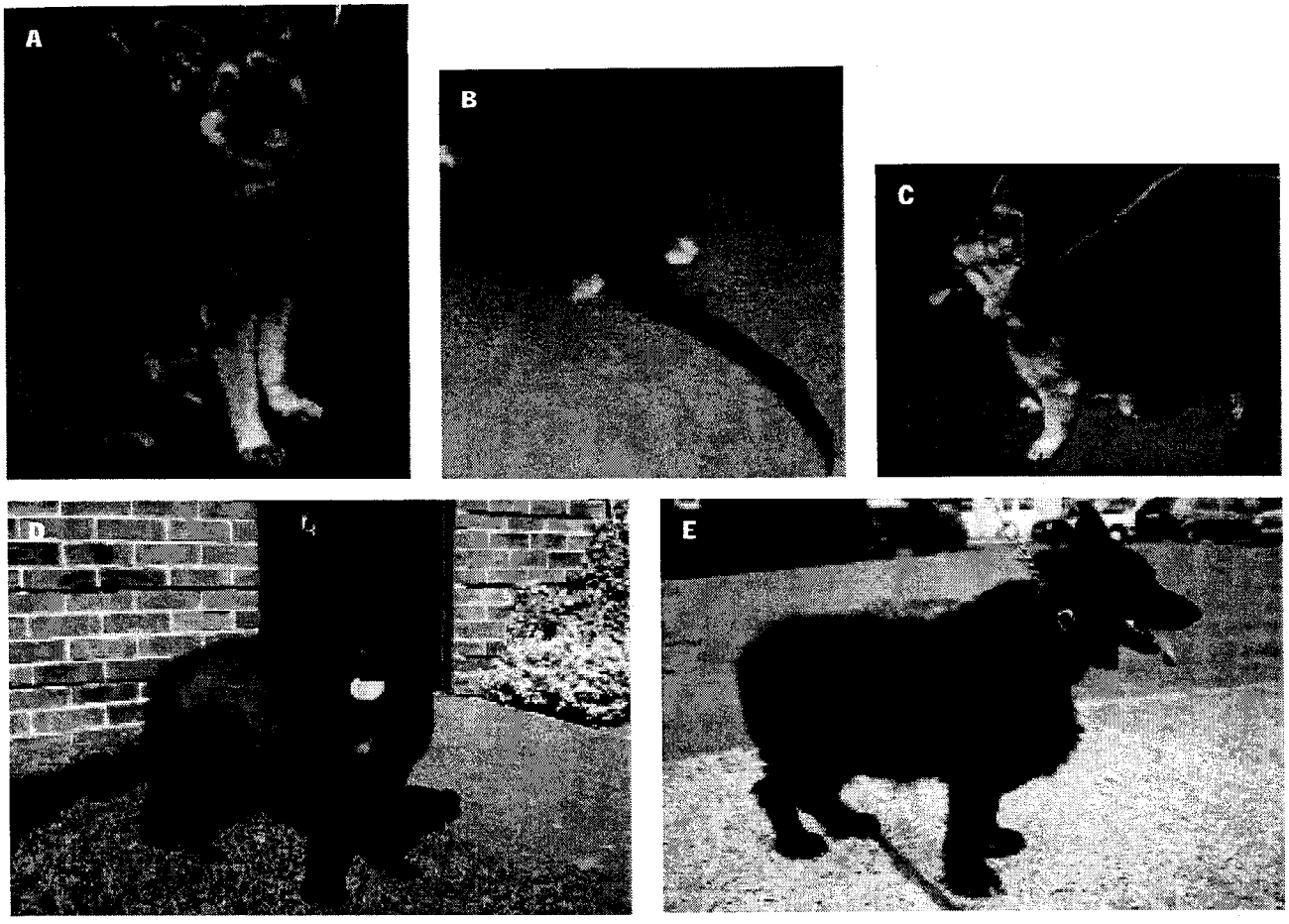

FIG 4. Appearance of the dogs during and after treatment:
(A) Case 1 at four weeks. The puppy haircoat still predominates but primary hairs are evident over the hindquarters. Alopecia is evident over the stifles. Hair clipped from the jugular area has failed to regrow;
(B) Tail and hindquarters of case 1 at four weeks. Primary hairs are growing down the length of the tail and over the hindquarters. The area of alopecia on the tail has reduced in size compared to the pre-treatment appearance;
(C) Case 1 at nine weeks. The tail has an adult appearance and is completely covered with primary hairs. The growth of primary hairs over the dog's body has increased dramatically. Primary hairs now predominate over the dorsum and flanks;
(D) Case 2 at 43 weeks. Primary hair growth is evident on the face, forelimbs and tail. Some increase in primary hair growth is evident on the trunk;
(E) Case 2 at 64 weeks. The dog has developed a full adult hair coat. A dramatic improvement in hair growth was noted three weeks after ovariohysterectomy;
(F) Case 3 at 113 weeks. The dog has developed a full adult hair coat

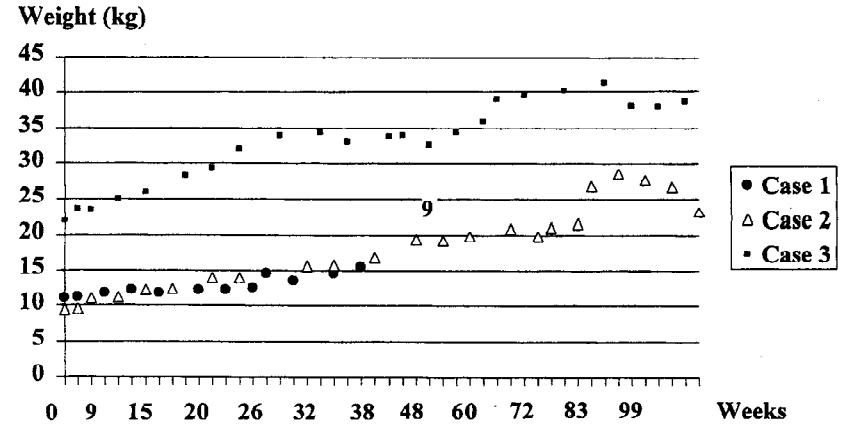

FIG 5. Graph showing changes in weight recorded during and after treatment

DISCUSSION

Pituitary dwarfism is caused by a failure of production of growth hormone by the anterior pituitary lobe. The condition is often associated with other endocrine abnormalities including failure of ACTH and TSH production (Feldman and Nelson 1996, Kooistra and others 2000). Canine growth hormone treatment is not available for therapeutic use. Studies using heterologous non-canine growth hormone have shown an increase in secondary hair growth with little effect on primary hair growth (Kooistra and others 1998); there is the additional disadvantage that biosynthetic human growth hormone administration in the dog results

in the production of antibodies against growth hormone (van Herpen and others 1994). The majority of pituitary dwarfs, therefore, receive only thyroid supplementation and/or glucocorticoids as indicated by the results of endocrine testing.

The use of progestins has recently been shown to induce the production of growth hormone from foci of hyperplastic ductular epithelium of the mammary gland (Mol and others 1994, 1996). These progestin-induced increases in growth hormone are also associated with elevated plasma concentrations of IGF-1 (Mol and others 1996, 1997). Treatment of canine pituitary dwarfs with medroxyprogesterone acetate at doses of 2·5 to 5·0 mg/kg bodyweight has been reported to improve hair coat and increase body size, but is associated with the development of intermittent pyoderma and cystic endometrial hyperplasia (Kooistra and others 1998). The increase in bodyweight and the development of an adult hair coat, seen in the present three cases, is similar to that reported previously (Kooistra and others 1998). The dramatic improvement reported after ovariohysterectomy and castration in cases 2 and 3, respectively, was attributed to removal of oestrogens and androgens which have been shown to suppress the initiation of the anagen phase of the hair cycle in rats (Scott and others 1995).

Cases 2 and 3 received oral thyroxine supplementation during administration of proligestone and case 3 had also received thyroxine for 21 weeks prior to proligestone therapy. Thyroid administration can cause an increased rate of hair growth in dogs without hypothyroidism (Gunaratnam 1986, Muller and others 1989). The coat changes seen in these patients may have been related to thyroid supplementation, although this explanation does not seem likely based on the time scale. The dramatic response seen in case 1 and the further improvement in coat quality noted in case 3 would suggest that the improvement in hair coat was due to administration of proligestone and not solely to thyroid supplementation.

Pituitary cyst formation can result in deficiencies of other anterior pituitary hormones (Feldman and Nelson 1996) and neurohypophyseal dysfunction (Ramsey and others 1999). Magnetic resonance imaging and computed tomography studies can be used to confirm the presence of a pituitary cyst. These investigations were not performed as they require general anaesthesia and the results would not have altered the treatment options. The results of the ACTH stimulation tests in all three cases revealed no evidence of glucocorticoid deficiency. Thyroid axis function was assessed using the T_4 and TSH responses to intravenous TRH. Basal TSH concentrations were undetectable in cases 2 and 3. In both these cases, TSH concentrations failed to increase after administration of TRH, suggesting a possible diagnosis of secondary hypothyroidism (pituitary failure of TSH release). Thyroid supplementation was therefore administered prior to (case 3) and/or concurrently with proligestone therapy (cases 2 and 3). Basal TSH was elevated in case 1 and increased by only 65 per cent following TRH administration, while T_4 failed to increase following TRH, suggesting that this dog was suffering from primary hypothyroidism (thyroid gland failure of thyroid hormone release) (Scott-Moncrieff and Nelson 1998). Thyroid supplementation was withheld as TSH concentrations were normal and further assessment of basal T_4 was performed at weeks 7 and 27.

After treatment with proligestone, serum total T_4 concentrations increased in case 1. This may have been associated with the dog's reproductive status as it was reported to have been in oestrus two weeks prior to endocrine testing. Females in dioestrus have elevated concentrations of total T_4 compared to females at other stages of the reproductive cycle (Riemers and others 1984, 1990). This may have resulted in a false elevation of total T_4 concentration at week 7. Alternatively, administration of proligestone may have resulted in an increase in T_4 at weeks 7 and 27, since endogenous progesterone is known to increase T_4 and T_3 concentrations (Riemers and others 1984, 1990). Although post-treatment thyroxine was also assessed in cases 2 and 3, both were receiving thyroid supplementation at the time of sampling, which makes interpretation of these results difficult.

The response of serum TSH to TRH administration in pituitary dwarfs appears to be highly variable. Ramsey and others (1997) diagnosed secondary hypothyroidism in one pituitary dwarf with a TSH concentration of <0·1 ng/ml, which increased to 0·2 ng/ml after TRH. Scott-Moncrieff and Nelson (1998) reported a pituitary dwarf with an increase in TSH concentration from 0·03 ng/ml to 0·57 ng/ml following TRH, a result consistent with euthyroidism. This post-TRH TSH concentration is similar to that of case 1 in this study. With the advent of new methods of assessing the thyroid axis, such as cTSH assays, further studies are required to determine which cases of pituitary dwarfism are associated with thyroid dysfunction and whether administration of proligestone results in a change in thyroid axis function.

Proligestone was selected as the progestin of choice due to the absence of mammary or uterine disease associated with its use (Evans and Sutton 1989). Medroxyprogesterone acetate administration has been associated with a high incidence of cystic endometrial hyperplasia and pyometra and is therefore not recommended for use in an intact bitch (von Berky and Townsend 1993). Despite the reported apparent safety of proligestone, its use was associated with cystic endometrial hyperplasia in one of the bitches treated in this study.

The initial dose of proligestone used in these cases (10 mg/kg) was based on the dose recommended in the manufacturer's (Intervet UK) data sheet for postponement of oestrus. The dosing interval (three weeks) was based on previous recommendations (Kooistra and others 1998). In humans with growth hormone deficiency, the dose of growth hormone required is based on serum IGF-1 concentration prior

to treatment (Murray and others 2000). Further studies are required to determine if pre-treatment IGF-1 concentrations can be used to determine the dose of proligestone required in canine pituitary dwarfs.

IGF-1 is produced and released by the liver. Its secretion is under direct control of growth hormone. IGF-1 has been reported to be a more sensitive indicator of the effect of treatment than growth hormone concentrations as the latter is released in a pulsatile manner (Kooistra and others 1998). Serum IGF-1 concentrations were therefore used to monitor the response to treatment. Since stimulation of growth hormone secretion by progestins appears to be dose related (Scott and Concannon 1983), the dose of proligestone was increased in case 1 when the IGF-1 concentration failed to increase above 100 ng/ml. This dose was associated with an increase in IGF-1 concentration to over 100 ng/ml. Further studies are required to determine if IGF-1 concentration during treatment should be used to determine the dose of proligestone. In this study, the results of the IGF-1 assay were available two to three weeks after collection. Treatment was therefore altered on the basis of the serum IGF-1 concentration from the previous visit. The dose of proligestone was increased in an attempt to bring the IGF-1 concentration into the normal range for an adult German shepherd dog (>200 ng/ml). The IGF-1 results, however, never exceeded 200 ng/ml.

Adverse effects were noted in cases 2 and 3 and were thought to be related to increases in growth hormone (acromegaly) and direct progesterone effects (vulval discharge and cystic endometrial hyperplasia). Papules and secondary bacterial pyoderma frequently develop in the adult pituitary dwarf and are probably a result of altered skin immunity (Feldman and Nelson 1996) rather than the use of a progestin. Clinical signs consistent with acromegaly were noted after the IGF-1 concentration exceeded 200 ng/ml on two consecutive samples. These side effects have previously been attributed to the continuous production of growth hormone by the mammary gland following progestin therapy (Kooistra and others 1998). Growth hormone secretion from the normal pituitary gland is pulsatile (Watson and others 1987), whereas its secretion from the mammary gland is continuous which may more easily result in an increased total daily secretion (Yoshida and others 1996) with an increased risk of side effects. Withholding proligestone therapy appeared to be associated with a reduction in IGF-1 concentration. The absence of adverse effects in case 1 could reflect the relatively low levels of growth hormone and IGF-1 achieved during treatment or the difficulty in diagnosing subclinical side effects. Further studies are required to determine the dose rate and frequency that will optimise development of an adult hair coat and increased bodyweight while minimising the risk of adverse effects.

Conclusions

This is the first report of the use of proligestone in dogs diagnosed with pituitary dwarfism. Proligestone may provide an alternative, relatively cheap treatment, which, if monitored carefully, could induce fewer adverse effects than other progestins. Based on the results presented here, treatment should be tailored to ensure that IGF-1 concentration does not exceed 200 ng/ml. Further studies are required to determine the optimum dose, the optimum age at which treatment should be instigated, how long therapy should be maintained and whether proligestone has an effect on thyroid axis function in pituitary dwarfs.

Acknowledgements

The authors would like to thank Dr I. K. Ramsey for his assistance in the management of case 1.

References

ANDRESEN, E. & WILLEBERG, P. (1976) Pituitary dwarfism in German shepherd dogs: additional evidence of simple autosomal recessive inheritance. *Nordisk Veterinæ Medicin* **28**, 481-486

CAPEN, C. C. (1993) The endocrine glands. In: Pathology of Domestic Animals, 4th edn. Eds K. V. F. Jubb, P. C. Kennedy and N. Palmer. Academic Press, San Diego. pp 267-347

EIGENMANN, J. E., ZANESCO, S., ARNOLD, U. & FROESCH, E. R. (1984) Growth hormone and insulin-like growth factor I in German shepherd pituitary dwarf dogs. *Acta Endocrinologica* **105**, 289-293

EVANS, J. M. & SUTTON, D. J. (1989) The use of hormones, especially progestagens to control oestrus in bitches. *Journal of Reproduction and Fertility* – (Supplement) **39**, 163-173

FELDMAN, E. C. & NELSON, R. W. (1996) Disorders of growth hormone. In: Canine and Feline Endocrinology and Reproduction, 2nd edn. Eds E. C. Feldman and R. W. Nelson. W. B. Saunders, Philadelphia. pp 38-66

HAMANN, F., KOOISTRA, H. S., MOL, J. A., GOTTSCHALK, S., BARTELS, T. & RIJNBERK, A. (1999) Pituitary function and morphology in two German shepherd dogs with congenital dwarfism. *Veterinary Record* **144**, 644-646

GUNARATNAM, P. (1986) The effect of thyroxine on hair growth in the dog. *Journal of Small Animal Practice* **27**, 17-29

KOOISTRA, H. S., VOORHOUT, G., MOL, J. A. & RIJNBERK, A. (2000) Combined pituitary hormone deficiency in German shepherd dogs with dwarfism. *Domestic Animal Endocrinology* **17**, 177-190

KOOISTRA, H. S., VOORHOUT, G., SELMAN, P. J. & RIJNBERK, A. (1998) Progestin-induced growth hormone (GH) production in the treatment of dogs with congenital GH deficiency. *Domestic Animal Endocrinology* **15**, 93-102

MOL, J. A., SELMAN, P. J., RUTTEMAN, G. R., VAN GARDEREN, E. & RIJNBERK, A. (1994) Progestin-induced growth hormone excess in the dog originates in the mammary gland. *Endocrinology* **134**, 287-292

MOL, J. A., SELMAN, P. J., SPRANG, E. P., VAN NECK, J. W. & OOSTERLAKEN-DIJKSTERHUIS, M. A. (1997) Progestin-induced hypersecretion of growth hormone: an introductory review. *Journal of Reproduction and Fertility* (Supplement) **51**, 339-344

MOL, J. A., VAN GARDEREN, E., RUTTEMAN, G. R. & RIJNBERK, A. (1996) New insights into the molecular mechanism of progestin-induced proliferation of mammary epithelium: induction of the local biosynthesis of growth hormone (GH) in the mammary glands of cats, dogs and humans. *Journal of Steroid Biochemistry and Molecular Biology* **57**, 67-71

MULLER, G. H., KIRK, R. W. & SCOTT, D. W. (1989) Cutaneous endocrinology. In: Small Animal Dermatology, 4th edn. Eds G. H. Muller, R. W. Kirk and D. W. Scott. W. B. Saunders, Philadelphia. pp 575-657

MURRAY, R. D., HOWELL, S. J., LISSETT, C. A. & SHALET, S. M. (2000) Pre-treatment IGF-1 level is the major determinant of GH dosage in adult GH deficiency. *Clinical Endocrinology* **52**, 537-542

NICHOLAS, F. (1978) Pituitary dwarfism in German Shepherd Dogs: a genetic study of some Australian data. *Journal of Small Animal Practice* **19**, 167-174

RAMSEY, I. K., DENNIS, R. & HERRTAGE, M. E. (1999) Concurrent central diabetes insipidus and panhypopituitarism in a German shepherd dog. *Journal of Small Animal Practice* **40**, 271-274

RAMSEY, I. K., EVANS, H. E. & HERRTAGE, M. E. (1997) Thyroid stimulating hormone and total thyroxine concentration in euthyroid, sick euthyroid and hypothyroid dogs. *Journal of Small Animal Practice* **38**, 540-545

RANDOLPH, J. F., MILLER, C. L., CUMMINGS, J. F. & LOTHROP, C. D. (1990) Delayed growth on two German Shepherd Dog littermates with normal serum concentrations of growth hormone, thyroxine, and cortisol. *Journal of the American Veterinary Medical Association* **196**, 77-83

RAO, R. R. & BAHT, N. G. (1971) Incidence of cysts in

pars distalis of mongrel dogs. *Indian Veterinary Journal* **48**, 128-133

RIEMERS, T. J., LAWLER, D. F., SUTARIA, P. M., CORREA, M. T. & ERB, H. N. (1990) Effects of age, sex and body size on serum concentrations of thyroid and adrenocortical hormones in dogs. *American Journal of Veterinary Research* **51**, 454-457

RIEMERS, T. J., MUMMERY, L. K., MCCANN, J. P., COWAN, R. G. & CONCANNON, P. W. (1984) Effects of reproductive state on concentrations of thyroxine, 3,5,3'-triiodothyronine and cortisol in serum of dogs. *Biology of Reproduction* **31**, 148-154

SCOTT, D. W. & CONCANNON, P. W. (1983) Gross and microscopic changes in the skin of dogs with progestagen-induced acromegaly and elevated growth hormone levels. *Journal of the American Animal Hospital Association* **19**, 523-527

SCOTT, D. W., MILLER, W. H. & GRIFFIN, C. E. (1995) Endocrine and metabolic diseases. In: Small Animal Dermatology, 5th edn. Eds D. W. Scott, W. H. Miller and C. E. Griffin. W. B. Saunders, Philadelphia. pp 627-644

SCOTT-MONCRIEFF, J. C. & NELSON, R. W. (1998) Change in serum thyroid-stimulating hormone concentration in response to administration of thyrotropin-releasing hormone to healthy dogs, hypothyroid dogs and euthyroid dogs with concurrent disease. *Journal of the American Veterinary Medical Association* **213**, 1435-1438

VAN HERPEN, H., RINJBERK, A. & MOL, J. A. (1994) Production of antibodies to biosynthetic human growth hormone in the dog. *Veterinary Record* **134**, 171

VON BERKY, A. G. & TOWNSEND, W. L. (1993) The relationship between the prevalence of uterine lesions and the use of medroxyprogesterone acetate for canine population control. *Australian Veterinary Journal* **70**, 249-250

WATSON, A. D. J., RUTTEMAN, G. R., RIJNBERK, A. & MOL, J. A. (1987) Effect of somatostatin analogue SMS 201-995 and antiprogestin agent RU486 in canine acromegaly. *Frontiers of Hormone Research* **17**, 193-198

YOSHIDA, T., SHIMATSU, A., SAKANE, N., HIZUKA, N., HORIKAWA, R. & TANAKA, T. (1996) Growth hormone (GH) secretory dynamics in a case of acromegalic gigantism associated with hyperprolactinemia: non-pulsatile secretion of GH may induce elevated insulin-like growth factor-I (IGF-I) and IGF-binding protein-3 levels. *Journal of Clinical Endocrinology and Metabolism* **81**, 310-313