Clinical Endocrinology (2001) **54**, 267–271

Hydrocortisone replacement dosage influences intraocular pressure in patients with primary and secondary hypocortisolism

J. S. W. Li Voon Chong*, J. Sen†, Z. Johnson†, G. Kyle† and I. A. MacFarlane*

**Department of Endocrinology and* †*Ophthalmology, University Hospital Aintree, Liverpool, UK*

(Received 12 April 2000; returned for revision 26 June 2000; finally revised 28 September 2000; accepted 18 October 2000)

Summary

BACKGROUND It has been suggested that the variation of intraocular pressure (IOP) during the day follows the diurnal variation of serum cortisol. There is also a higher risk of ocular hypertension and glaucoma in patients taking excessive oral steroid treatment. We assessed whether different replacement doses of hydrocortisone (HC) influenced IOP.

METHODS Seventeen patients (six Addison's disease, 11 hypopituitarism; seven males) aged 24–58 years mean 42·7 years and 20 control subjects (nine males) aged 20–59 years mean 38·7 years were studied. On the first visit, the 17 patients had been taking HC replacement doses, 20 mg morning and 10 mg afternoon. Serum cortisol and IOP in both eyes (Goldmann applanation tonometer) were measured at 0900, 1100, 1300, 1500, 1700 hours with HC 20 mg taken after the 0900 h assessment. The dose of HC was then reduced to 10 mg morning and 10 mg afternoon for 1 week and the measurements were repeated in 16 patients, with HC 10 mg taken at 0900 h.

RESULTS In the patients the peak serum cortisol occurred at 1100 h after the 0900 h HC dose. Cortisol levels were significantly higher at 1100, 1300, 1500 and 1700 h after taking 20 mg compared to 10 mg HC. The mean (SEM) IOP (mmHg) was significantly higher after 20 mg HC compared with 10 mg HC at 1300 h: 14·7(0·6) v 13·1(0·6) ($P = 0·004$) and at 1500 h: 14·4(0·6) v 13·1(0·5) ($P = 0·04$). The total mean (SEM) daily IOP score was significantly higher after 20 mg HC compared with 10 mg HC: 14·5(0·3) v 13·5(0·3) ($P = 0·0002$). The total mean (SEM) daily IOP score after the 20 mg HC dose compared with the control subjects was: 14·5(0·3) v 13·7(0·3) ($P = 0·08$).

CONCLUSION Intraocular pressures during the day are influenced by the morning hydrocortisone replacement dosage with significantly higher intraocular pressure levels in the early afternoon following 20 mg compared with 10 mg. A morning hydrocortisone dose of 10 mg leads to a more physiological intraocular pressure profile during the day. These data support the view that a daily replacement dose of 30 mg hydrocortisone may be excessive.

Patients with cortisol deficiency (either primary or secondary) have traditionally been replaced with 30 mg daily of hydrocortisone (usually 20 mg morning, 10 mg afternoon) (Besser & Jeffcoate, 1976). This replacement dosage of hydrocortisone is empirical and produces very different serum cortisol profiles from normal physiology. More recently the daily production of cortisol has been shown to be lower (5·7 mg/m^2/day) than previously thought (12–15 mg/m^2/day) (Esteban *et al*., 1991). This has led to debate about the optimum replacement daily dose of hydrocortisone and it has been suggested that most patients only require 20 mg of hydrocortisone per day (Howlett, 1997; Peacey *et al*., 1997).

One suggestion is to start the initial dose at 25 mg of hydrocortisone (15 mg early morning and 10 mg afternoon) and to decrease the daily dose to 20 or 15 mg of hydrocortisone as long as the patient feels well (Oelkers, 1996). This issue is of clinical importance because studies have suggested that chronic excessive replacement with glucocorticoids may lead to osteoporosis (Zelissen *et al*., 1994) and glucose intolerance (Al-Shoumer *et al*., 1995). Furthermore it has been argued that an increased mortality in patients with hypopituitarism may be related to excessive glucocorticoid replacement (Stewart & Sheppard, 1999).

The intraocular pressure (IOP) in normal individuals varies during the day with the peak IOP in late morning and lower values from mid-afternoon (Kitazawa & Horie, 1975; David *et al*., 1992; Wilensky *et al*., 1993; Pointer, 1997). When

Correspondence: Dr J.S.W. Li Voon Chong, Royal Hampshire Hospital, Romsey Road, Winchester, Hampshire, SO22 5DG, UK. Fax: + 44 (0) 1962 824378.

measured over a 24-h period, the lowest IOP values have been found to be between 2 and 4 am (Henkind *et al*., 1973). It is possible that this pattern may be related to other diurnal endogenous variations in the body, such as the production of cortisol (Becker & Mills, 1963; Boyd & Mcleod, 1964; Weitzman *et al*., 1975; Kimura & Maekawa, 1976; Schwartz & Seddon, 1981; Weinreb *et al*., 1985; Wilensky, 1991). The diurnal fluctuation in IOP is increased in patients with chronic simple glaucoma, and it has been suggested that this may reflect increased sensitivity to plasma cortisol (Schwartz & Levene, 1972).

It is recognized that oral steroid treatment may be associated with ocular hypertension or open angle glaucoma (Long, 1977; Garbe *et al*., 1997a). There have also been reports of an increased risk of ocular hypertension or open-angle glaucoma in patients taking inhaled or nasal steroid treatment (Opatowsky *et al*., 1995; Dreyer, 1993; Garbe *et al*., 1997b). The rise in ocular pressure from corticosteroid therapy is thought to be due to an increase in the resistance to aqueous humour outflow (Becker & Mills, 1963; Skuta *et al*., 1996).

There is no information on whether different replacement doses of hydrocortisone influence IOP in patients with Addison's disease and hypopituitarism. Therefore we studied the daytime variation of IOP following two different replacement regimens of hydrocortisone and compared the data with a group of healthy control subjects.

Patients and methods

Patients and controls

Seventeen patients (seven males) aged 24–58 years (mean 42·7 years) who were attending the endocrine clinic were recruited. Eleven patients had hypopituitarism (seven nonfunctioning pituitary macroadenomas, four macroprolactinomas) and six had Addison's disease. The patients with Addison's disease had been taking hydrocortisone 20 mg morning, 10 mg afternoon and fludrocortisone 0·05 mg daily for at least 5 years. All patients with hypopituitarism were diagnosed in adult life and also had been taking hydrocortisone 20 mg morning, 10 mg afternoon for at least 5 years. Nine were also receiving stable replacement with thyroxine (T4), five growth hormone, five males testosterone (sustanon-250) and four females oestrogens. The four patients with prolactinomas were all taking bromocriptine. All patients had a normal serum free T4 at the time of study. Twenty control subjects (nine males) aged 20–59 years (mean 38·7 years) were also studied.

They were healthy volunteers including hospital staff and relatives of patients. None of the patients or controls had a known history of ocular hypertension or glaucoma.

Methods

The patients attended on 2 days 1 week apart. At the first visit, the serum cortisol and IOP in both eyes were measured at 0900 h, 1100 h, 1300 h, 1500 h and 1700 h and 20 mg of HC was taken after the 0900 h samples. The daily dose of HC was then reduced to 10 mg bd and the patients took this until the second visit, 1 week later. The serum cortisol and IOP were again measured at 0900 h, 1100 h, 1300 h, 1500 h and 1700 h and hydrocortisone 10 mg was taken after the 0900 h samples. Patients with Addison's disease did not take their usual morning doses of fludrocortisone at the two visits. The patients were not fasted and not fluid restricted.

The IOP was measured by an ophthalmologist using a Goldmann applanation tonometer attached to a slit lamp. Serum cortisol was measured using the direct chemiluminescent technique (Chiron Diagnostics ACS:180).

Ethical approval was granted by the South Sefton Research Ethics Committee and all patients gave informed consent.

Statistical analysis

Data are expressed as mean ± SEM. Statistical analysis was performed using paired and unpaired *t*-test as appropriate. *P*-values $< 0{\cdot}05$ were considered significant.

Results

Seventeen patients had their IOP and hydrocortisone day curve measured before and after taking hydrocortisone 20 mg at 0900 h. Sixteen patients had their IOP and hydrocortisone day curves repeated 1 week after dose reduction in hydrocortisone to 10 mg bd. One patient did not volunteer for the second occasion as she felt unwell on the lower steroid dosage.

The peak serum cortisol was at 11 am and was significantly higher at 11 am, 1300 h, 1500 h and 1700 h after taking hydrocortisone 20 mg compared to 10 mg after the 0900 h sample (Fig. 1). The mean(SEM) IOP values on the five different occasions were lower on the reduced dose of hydrocortisone. This was statistically significant at 1300 h, 14·7 (0·6) v 13·1 (0·6) mmHg ($P = 0{\cdot}004$) and at 1500 h, 14·4 (0·6) v 13·1 (0·5) mmHg ($P = 0{\cdot}04$) (Fig. 2). The total mean (SEM) IOP score combining the five occasions was significantly lower on the reduced dose profile: 14·5(0·3) v 13·5(0·3) ($P = 0{\cdot}0002$). The total mean (SEM) IOP score was higher but not significantly different comparing the patients taking the 20 mg dose of hydrocortisone at 0900 h and the controls, 14·5 (0·3) v 13·7 (0·3) ($P = 0{\cdot}08$).

There was no difference in the IOP values after taking the 10 mg HC dose compared to controls.

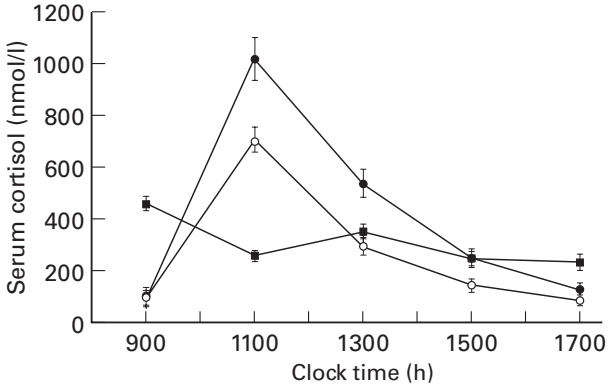

Fig. 1 Variation of serum cortisol during the day in patients with hypoadrenalism: 17 treated with hydrocortisone (HC) 20 mg at 0900 h (●); 16 with HC 10 mg at 0900 h (○); and 20 controls (■).

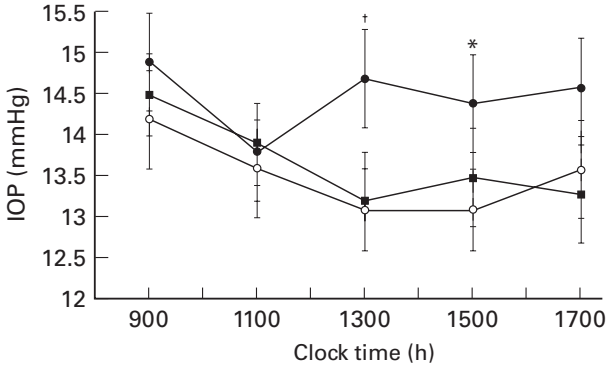

Fig. 2 Variation of intraocular pressure (IOP) during the day in patients with hypoadrenalism: 17 treated with hydrocortisone (HC) 20 mg at 0900 h (●); 16 with HC 10 mg at 0900 h (○); and 20 controls (■). *$P = 0.04$; †$P = 0.004$ 20 mg *vs.* 10 mg HC.

Analysing the patients with Addison's disease and hypopituitarism separately, the total mean IOP scores, combining the five occasions were: Addison's disease, 20 mg *vs.* 10 mg HC dose: 13·4 (0·4) *vs.* 12·6(0·4) ($P = 0·02$) and those with hypopituitarism, 20 mg *vs.* 10 mg HC dose: 15·1(0·3) v 14·0(0·4) ($P = 0·02$).

Discussion

For an individual the assessment of the optimal replacement dose or regimen of hydrocortisone is difficult and no simple tests exist. Current methods include performing a cortisol day curve, which consists of measuring serum cortisol concentrations at various times during the day (Besser & Jeffcoate, 1976; Feek *et al*., 1981). However this is time consuming and there are no accepted criteria to interpret the results and make meaningful recommendation on replacement dosages or regimens. Urinary collections for free cortisol levels have been used and it has been suggested that results correlate with plasma cortisol profiles in patients (Burch, 1982; Contreras *et al*., 1986**,** Trainer *et al*., 1993). Others however, have argued that although free urinary cortisol is a useful marker of endogenous secretion, it is unreliable in people taking replacement therapy (Jeffcoate, 1999). There is a disproportionate rise in the urine free cortisol after a dose of HC from temporary saturation of cortisol-binding globulin (Howlett, 1997).

Recently many authors have suggested that 30 mg per day of hydrocortisone can have long-term side-effects. Long-term use of hydrocortisone replacement at this dosage may increase the risk of osteoporosis (Zelissen *et al*., 1994), hyperinsulinaemia and glucose intolerance (Al-Ashoumer *et al*., 1995). Also over-replacement with glucocorticoids may be a contributor to cardiovascular disease (Monson, 1997; Beshyah & Johnston, 1999; Stewart & Sheppard, 1999). There are, however, no long-term studies on the biological effects of lower HC replacement doses. One study has examined quality of life and well being on various daily dosages of hydrocortisone and showed no differences in these measures after taking 15, 20 or 30 mg of hydrocortisone per day (Wichers *et al*., 1999). Other studies of patients taking twice daily hydrocortisone found that some individuals have low cortisol levels and tiredness in the afternoon and felt better when they take hydrocortisone three times daily (Groves *et al*., 1988; Howlett, 1997).

In the present study the serum cortisol of the control subjects was highest in the morning at 0900 h and gradually declined thereafter (Fig. 1). In contrast, the patients taking twice daily HC replacement had completely unphysiological cortisol profiles. The serum cortisol was markedly low before the 0900 h dose of HC and peaked 2 h afterwards with significantly higher levels following 20 mg of HC compared to 10 mg HC. Other authors have showed similar cortisol profiles on twice daily HC replacement regimens (Kehlet *et al*., 1976; Scott *et al*., 1978; Feek *et al*., 1981; Al-Shoumer *et al*., 1996).

The IOP of the control subjects was highest in the morning followed by a dip at 1300 h and remained lower for the rest of the afternoon. This is similar to previous studies of IOP during the day in normal subjects (Kitazawa & Horie, 1975; David *et al*., 1992; Wilensky *et al*., 1993; Pointer, 1997). The IOP profile of the patients taking 20 mg HC showed an initial fall at 1100 h followed by a pronounced rise in the afternoon. When these patients reduced the daily dose of HC, the IOP profile after HC 10 mg at 0900 h was very similar to the control subjects (Fig. 2) with significantly lower IOP levels at 1300 and 1500 h, compared with the higher HC dose. In addition these patients had a lower total mean IOP score on the lower HC dose. These observations support the view that a

marked rise in circulating cortisol may lead to an increase in IOP some 4 h later. There cannot, however, be a simple relationship between serum cortisol and IOP. The 0900 h IOP levels in the patients were similar to the controls despite considerably lower 0900 h cortisol levels. It is possible that the 0900 h IOP levels reflect the daily glucocorticoid replacement dosage over several days in these patients.

It is important to consider the biological significance of higher IOP levels after a 0900 h dose of 20 mg HC. A study of patients with primary open-angle glaucoma who were given 20 mg of hydrocortisone at 1700 h showed a significant rise in their intraocular pressure from baseline during the night (Kimura & Maekawa, 1976). None of the patients in the present study, however, had a known history of ocular hypertension or glaucoma and we did not find a rise in the IOP above 20 mmHg (the lower limit for ocular hypertension) during the day after taking 20 mg HC. Nevertheless many patients with primary and secondary hypocortisolism are replaced with 30 mg of HC daily and it is possible that relatively high IOP levels during the afternoon may predispose to an increased risk of ocular hypertension in future years. Elderly patients taking oral glucocorticoids have a higher risk of ocular hypertension or open-angle glaucoma (Garbe *et al*., 1997a). It will therefore be of interest to study the influence of different HC replacement doses on IOP levels in elderly patients.

In conclusion, intraocular pressures during the day are influenced by the morning hydrocortisone replacement dosage with significantly higher IOP levels in the early afternoon after taking 20 mg of HC at 0900 h. A morning HC dose of 10 mg leads to a more physiological IOP profile during the day and these data support the view that 30 mg/day HC may be excessive corticosteroid replacement.

References

Al-Shoumer, K.A.S., Ali, K., Anyaoku, V., Niththyananthan, R. & Johnston, D.G. (1996) Overnight metabolic fuel deficiency in patients treated conventionally for hypopituitarism. *Clinical Endocrinology*, **45,** 171–178.

Al-Shoumer, K.A.S., Beshyah, S.A., Niththyananthan, R. & Johnston, D.G. (1995) Effect of glucocorticoid replacement therapy on glucose tolerance and intermediary metabolites in hypopituitary adults. *Clinical Endocrinology*, **42,** 85–90.

Becker, B. & Mills, D.W. (1963) Corticosteroids and intraocular pressure. *Archives of Ophthalmology*, **70,** 500–507.

Beshyah, S.A. & Johnston, D.G. (1999) Cardiovascular disease and risk factors in adults with hypopituitarism. *Clinical Endocrinology*, **50,** 1–15.

Besser, G.M. & Jeffcoate, W.J. (1976) Endocrine and metabolic diseases. Adrenal diseases. *British Medical Journal*, **1,** 448–451.

Boyd, T.A.S. & Mcleod, L.E. (1964) Circadian rhythms of plasma corticoid levels, intraocular pressure and aqueous outflow in normal and glaucomatous eyes. *Annals of the New York Academy of Science*, **117,** 597–613.

Burch, W.M. (1982) Urine free-cortisol determination. A useful tool in the management of chronic hypoadrenal states. *Journal of the American Medical Association*, **247,** 2002–2004.

Contreras, L.N., Hane, S. & Tyrell, J.B. (1986) Urinary cortisol in the assessment of pituitary-adrenal function: utility of 24 hour and spot determinations. *Journal of Clinical Endocrinology and Metabolism*, **62,** 965–969.

David, R., Zanghill, L., Briscoe, D., Dagan, M., Yagev, R. & Yassur, Y. (1992) Diurnal intraocular pressure variations: an analysis of 690 diurnal curves *British Journal of Ophthalmology*, **76,** 280–283.

Dreyer, E.B. (1993) Inhaled steroid use and galucoma. *New England Journal of Medicine*, **329,** 1822.

Esteban, N.V., Loughlin, T., Yergey, A.L., Zawadzki, J.K., Booth, J.D., Winterer, J.C. & Loriaux, D.L. (1991) Daily cortisol production rate in man determined by stable isotope dilution/mass spectrometry. *Journal of Clinical Endocrinology and Metabolism*, **72,** 39–45.

Feek, C.M., Ratcliffe, J.G., Seth, J., Gray, C.E., Toft, A.D. & Irvine, W.J. (1981) Patterns of plasma cortisol and ACTH concentrations in patients with Addison's disease treated with conventional corticosteroid replacement. *Clinical Endocrinology*, **14,** 451–458.

Garbe, E., LeLorier, J., Boivin, J. & Suissa, S. (1997a) Risk of ocular hypertension or open-angle glaucoma in elderly patients on oral glucosteroids. *Lancet*, **350,** 979–982.

Garbe, E., LeLorier, J., Boivin, J. & Suissa, S. (1997b) Inhaled and nasal glucosteroids and the risks of ocular hypertension or open-angle glaucoma. *Journal of the American Medical Association*, **277,** 722–727.

Groves, R.W., Toms, G.C., Houghton, B.J. & Monson, J.P. (1988) Corticosteroid replacement therapy: twice or thrice daily? *Journal of the Royal Society of Medicine*, **81,** 514–516.

Henkind, P., Leitman, M. & Weitzman, E. (1973) The diurnal curve in man: new observations *Investigative Ophthalmology*, **12,** 705–707.

Howlett, T. (1997) An assessment of optimal hydrocortisone replacement therapy *Clinical Endocrinology*, **46,** 263–268.

Jeffcoate, W.J. (1999) Chronic fatigue syndrome and functional hypoadrenia-fighting vainly the old ennui. *Lancet*, **353,** 424–425.

Kehlet, H., Binder, C. & Blichert-Toft, M. (1976) Glucocorticoid maintainance therapy following adrenalectomy: assessment of dosage and preparation. *Clinical Endocrinology*, **5,** 37–41.

Kimura, R. & Maekawa, N. (1976) Effect of orally administered hydrocortisone on the ocular tension in primary open-angle glaucoma subjects. *Acta Ophthalmologica*, **54,** 430–436.

Kitazawa, Y. & Horie. T. (1975) Diurnal variation of intraocular pressure in primary open-angle glaucoma. *American Journal of Ophthalmology*, **79,** 557–566.

Long, W.F. (1977) A case of elevated intraocular pressure associated with systemic steroid therapy *American Journal of Optometry and Physiological Optics*, **54,** 248–252.

Monson, J.P. (1997) The assessment of glucocorticoid replacement Therapy, *Clinical Endocrinology*, **46,** 269–270.

Oelkers, W. (1996) Adrenal insufficiency. *New England Journal of Medicine*, **335,** 1206–1212.

Opatowsky, I., Feldman, R.M., Gross, R. & Feldman, S.T. (1995) Intraocular pressure elevation associated with inhalation and nasal corticosteroids. *Ophthalmology*, **102,** 177–179.

Peacey, S., Guo, C.Y., Robinson, A., Price, A., Giles, M.A., Eastell, R. & Weetman, A.P. (1997) Glucocorticoid replacement therapy: are patients over treated and does it matter? *Clinical Endocrinology*, **46,** 255–261.

Pointer, J.S. (1997) The diurnal variation of intraocular pressure in non-glaucomatous subjects: relevance in a clinical context. *Ophthalmic and Physiological Optics*, **17,** 456–465.

Schwartz, B. & Levene, R.Z. (1972) Plasma cortisol differences between normal and glaucomatous patients: before and after dexamethasone suppression. *Archives of Ophthalmology*, **87,** 369–377.

Schwartz, B. & Seddon, J.M. (1981) Increased plasma cortisol levels in ocular hypertension. *Archives of Ophthalmology*, **99,** 1791–1794

Scott, R.S., Donald, R.A. & Espiner, E.A. (1978) Plasma ACTH and cortisol profiles in Addisonian patients receiving conventional substitution therapy. *Clinical Endocrinology*, **9,** 571–576.

Skuta, G.L. & Morgan, R.K. (1996) Corticosteroid-induced glaucoma. In: (Ritch, R. Sheilds, M.B. Krupin, T., eds.) *The Glaucomas* pp.1177–1188. Mosby, St Louis.

Stewart, P.M. & Sheppard, M.C. (1999) Mortality and hypopituitarism *Growth Hormone and IGF Research*, **9,** 15–19.

Trainer, P.J., McHardy, K.C., Harvey, R.D. & Reid, I.W. (1993) Urinary free cortisol in the assessment of hydrocortisone replacement therapy. *Hormone and Metabolic Research*, **25,** 117–120.

Weinreb, R.N., Polansky, J.R., Kramer, S.G. & Baxter, J.D. (1985) Acute effects of dexamethasone on intraocular pressure in glaucoma. *Investigative Ophthalmology*, **26,** 170–175.

Weitzman, E.D., Henkind, P., Leitman, M. & Hellman, L. (1975) Correlative 24- hour relationships between intraocular pressure and plasma cortisol in normal subjects and patients with glaucoma. *British Journal of Ophthalmology*, **59,** 566–572.

Wichers, M., Springer. W., Bidlingmaier, F. & Klingmuller, D. (1999) The influence of hydrocortisone substitution on the quality of life and parameters of bone metabolism in patients with secondary hypocortisolism. *Clinical Endocrinology*, **50,** 759–765.

Wilensky, J.T. (1991) Diurnal variation in intraocular pressure *Transactions of the American Ophthalmological Society*, **89,** 757–790.

Wilensky, J.T., Gieser, D.K., Dietsche, M.L., Mori, M.T. & Zeimer, R. (1993) Individual variability in the Diurnal Intraocular Pressure Curve. *Ophthalmology*, **100,** 940–944.

Zelissen, P., Croughs, R., Van Rijk, P. & Raymakers, J. (1994) Effect of glucocorticoid replacement on bone mineral density in patients with Addison disease. *Annals of Internal Medicine*, **120,** 207–210.