A weight-related intravenous dexamethasone suppression test distinguishes obese controls from patients with Cushing's syndrome

A. B. Atkinson1, E. J. McAteer1, D. R. Hadden1, I. Kennedy1, B. Sheridan2 and A. I. Traub3

Sir George E. Clark Metabolic Unit1, Regional Endocrine Laboratory2, Royal Victoria Hospital, and Department of Obstetrics and Gynaecology3,
The Queen's University of Belfast, Belfast, Northern Ireland

Abstract. To establish a rapid test for Cushing’s syndrome we measured serum cortisol during and following iv dexamethasone infusion (5 μg · kg⁻¹ · h⁻¹ for 5 h from 10.00 h) in simple obesity (N = 19) and in Cushing’s syndrome (N = 12). We had first established that 5 μg · kg⁻¹ · h⁻¹ was the lowest dose which consistently lowered serum cortisol in simple obesity. In obesity, serum cortisols ranged from undetectable (<30) to 48 nmol/l at 17.00, <30 to 37 at 19.00 and <30 to 38 at 08.00 h the following day. Serum cortisol at these three times did not show any overlap between simple obesity and Cushing’s syndrome. Having established these findings we proceeded to study a group of patients with polycystic ovarian disease. These patients behaved differently. Their values at 17.00 and 19.00 h did not overlap those of Cushing’s syndrome. However, at 08.00 h, 5 of the 7 had values within the range seen in Cushing’s syndrome with a mean of 290 ± 99 nmol/l. In conclusion, 17.00 and 19.00 h serum cortisol levels distinguish between Cushing’s syndrome and both simple obesity and polycystic ovarian disease. However, in the latter, cortisol suppression is less prolonged than in simple obesity. This finding may be important for our understanding of the pathogenesis of the disease.

In 1960 Liddle showed that patients with Cushing’s syndrome could not suppress their urinary steroid excretion completely after the administration of 0.5 mg dexamethasone phosphate orally every 6 h for 48 h. This test remains available for the diagnosis of Cushing’s syndrome but does have certain disadvantages. It requires regular administration of the drug for 48 h, adequate absorption of the dexamethasone from the gut and an accurate collection of 24-h urine samples over the period of the test. Problems in any of these areas invalidate results. Various attempts have been made to simplify the procedure. For example, a variety of doses of dexamethasone have been administered late at night and the serum cortisol measured on the following morning. Unfortunately these tests have a false positive rate of between 5 and 15 per cent and this especially tends to happen in obese patients with whom one has the most difficulty in differential diagnosis (Tucci et al. 1967; Seidensticker et al. 1967; McHardy-Young et al. 1967; Connolly et al. 1968; Holdaway et al. 1973; Thoren et al. 1975; Meikle 1982). Measurement of simultaneous plasma dexamethasone levels is helpful but does still leave a significant group of patients with unsatisfactory dexamethasone tests which are most difficult to interpret (Meikle 1982). Measurement of serum cortisol by radioimmunoassay as an alternative to urinary steroids has been introduced during the prolonged low-dose classic test and does simplify the procedure (Kennedy et al. 1984; Ashcraft et al. 1982). However, it does not decrease the overall duration of the test. Another modification of the original test has been to use weight-related oral doses of dexamethasone. This has proved par-
particularly successful in children but has also been recommended in adults (Streiten et al. 1969).

Over 20 years there have been various descriptions of intravenous dexamethasone tests in the diagnosis and differential diagnosis of Cushing’s syndrome, but the numbers studied have been small and have often not used radioimmunoassay for measurement of serum cortisol (James et al. 1965; Croughs et al. 1973; Linquette et al. 1980; Abou-Samra et al. 1985).

Because a weight-related oral dose of dexamethasone has been shown to be helpful (Streiten et al. 1969), we have investigated the use of a weight-related intravenous infusion of dexamethasone in the diagnosis of Cushing’s syndrome. Our first aim was to find a dose of dexamethasone which reliably suppressed serum cortisol in adults with simple uncomplicated obesity on the following day and then, having found this to be 5 µg·kg⁻¹·h⁻¹, we studied that dose in a series of patients subsequently proven to have Cushing’s syndrome. Since certain patients with polycystic ovarian syndrome often present a difficult differential diagnostic group in the assessment of Cushing’s syndrome we have also studied the infusion in such a group.

Subjects and Methods

Three groups of subjects were investigated. The first group consisted of obese control subjects, mainly female, with a range of ideal body weight between 125 and 188% (mean 145.4%). None of the patients had the clinical features of Cushing’s syndrome apart from obesity. All had normal thyroid function. The female patients all had regular menstrual cycles. The second group consisted of 12 subjects with active Cushing’s syndrome. This was confirmed biochemically using formal low-dose dexamethasone suppression tests, urinary free cortisol to creatinine estimations, and was subsequently proven histologically by demonstration of either pituitary or adrenal pathology. Eleven patients had Cushing’s disease and one had bilateral nodular hyperplasia. The age range was between 29 and 65 years, 4 patients were male and 8 female. The range of ideal body weight was from 124–163% with a mean of 128.4%. The third group had polycystic ovarian disease. This diagnosis was based on a history of oligome-norrhea or amenorrhea and was confirmed by the finding of an elevated LH to FSH ratio and/or ultrasonic or histological evidence of polycystic ovaries. All had elevated serum testosterone and had normal routine tests of adren al function with normal serum and/or urinary cortisol estimations.

None of the patients in the above groups was receiving any medication at the time of testing. None had taken oestrogen in the previous month. None of the patients admitted to drinking alcohol to excess and none were clinically depressed.

Intravenous dexamethasone infusion procedure

If they were not already impatients, subjects were admitted at 08.30 h on the morning of the test. Two iv catheters were inserted into the forearm veins at least 30 min before any basal sampling. A calculated weight of dexamethasone phosphate was dissolved in 0.9% sodium chloride solution. It was then infused with a Harvard pump at a constant rate of 10 ml/h for 5 h, from 10.00 to 15.00 h. The patients remained supine throughout the infusion. Two basal samples were obtained for measurement of serum cortisol at 09.40 and 10.00 h, and subsequently samples were obtained hourly from 10.00 to 15.00 h. Three further samples were obtained at 17.00, 19.00 and 08.00 h.

Serum samples were stored at −20°C until estimation of serum cortisol by radioimmunoassay using reagents supplied by Diagnostic products Corporation, Los Angeles, as previously described (Atkinson et al. 1985a). Serum samples were stored at −20°C until estimation of serum cortisol by radioimmunoassay using reagents supplied by Diagnostic Products Corporation, Los Angeles. This assay has an inter-assay coefficient of variation, as determined by a precision profile, of less than 5% for values lying between 23–1000 nmol/l.

Student’s t-tests were used to compare means where appropriate.

Three doses of dexamethasone were used in the first group. These were 10 µg·kg⁻¹·h⁻¹, 5 µg·kg⁻¹·h⁻¹ and 2.5 µg·kg⁻¹·h⁻¹. In the patients with Cushing’s syndrome and polycystic ovarian disease a dose of 5 µg·kg⁻¹·h⁻¹ was used (see Results).

All patients gave informed consent. The study was approved by the Queens University of Belfast Ethical Committee.

Results

Figs. 1 and 2 show serum cortisol responses in obese subjects to 5-h infusions of dexamethasone using doses of 2.5 and 5 µg·kg⁻¹·h⁻¹, respectively. After a small number of subjects had been studied with 10 µg·kg⁻¹·h⁻¹, it was apparent that all subjects had undetectable levels of serum cortisol by 17.00 which remained undetectable on the following morning. We therefore used the two smaller doses to try to find the smallest dose of dexamethasone which would reliably suppress serum cortisol the next morning.
Serum cortisol before and during an intravenous dexamethasone infusion (2.5 $\mu$g·kg$^{-1}$·h$^{-1}$) in 8 obese subjects.

When 2.5 $\mu$g·kg$^{-1}$·h$^{-1}$ was used, 6 out of 8 obese control subjects had a serum cortisol greater than 100 nmol/l at 08.00 h on the morning following (Fig. 1).

By contrast, 5 $\mu$g·kg$^{-1}$·h$^{-1}$ in 19 obese subjects suppressed cortisol to less than 40 nmol/l on the following day. Serum cortisol fell significantly (all comparisons $P<0.01$), from 311 ± 28 (mean ± SEM) nmol/l to 32 ± 1 nmol/l, (range <30 to 48) at 17.00 and to 30 ± 1 nmol/l (range <30–37) at 19.00 h. At 08.00 serum cortisol was 30 ± 1 nmol/l (range <30 to 38). Since our studies (Fig. 2) had shown that 5
μg · kg⁻¹ · h⁻¹ was the smallest dose which reliably suppressed the 08.00 serum cortisol in obese subjects, we used that dose in 12 subjects with Cushing’s syndrome. Fig. 2 also shows the response of serum cortisol to this infusion as compared to the range established in the 19 obese normal subjects. In the patients with Cushing’s syndrome, the mean basal serum cortisol were not significantly higher than those in the obese group (568 ± 41 vs 311 ± 28 nmol/l). In two subjects with Cushing’s syndrome there was a paradoxical early rise in serum cortisol following the infusion of dexamethasone. From 15.00 onward there was a clear distinction between obese subjects and patients with Cushing’s syndrome. The best separation occurred at 17.00, 19.00 and 08.00 h. At 17.00 and 19.00 h the lowest values in the Cushing’s group were 72 and 75 nmol/l, respectively, and at 08.00 h the lowest value was 94 nmol/l.

Fig. 3 shows the results of 2 and the 3 patients with Cushing’s disease who suppressed to the greatest extent during the infusion and Table 1 shows their response to an oral low-dose dexamethasone suppression test (0.5 mg). The third patient was one who was studied once it had been established that she had early recurrence of hypercortisolism after transsphenoidal surgery. In that case serum cortisol suppressed to 100, 74, 87 and 511 nmol/l, respectively, for the last four samples during the iv test. It can be seen that the two previously untreated patients were very sensitive to the administration of the drug orally, suppressing to within the normal range previously described by us in normal subjects (Table 1). Both were shown to have basophil adenomas at surgery.

Fig. 4 shows the response of patients with polycystic ovarian disease to iv dexamethasone. All patients suppressed on the day of the test, highest values at 17.00 and 19.00 being 55 and 44 nmol/l, respectively. However, by 08.00 on the following day there was a significant rise in many of the groups when compared with obese controls.
Discussion

The use of intravenous dexamethasone in the diagnosis of Cushing’s syndrome was first described by James et al. in 1965. In this and all subsequent work using this route a fixed dose of dexamethasone has been used (e mg/h) and no series has studied large numbers of patients (James et al. 1965; Croughs et al. 1973; Linquette et al. 1980; Abou-Samra et al. 1985). James et al. (1965) described separation of patients with Cushing’s syndrome from normal laboratory controls using the test. Unfortunately no comparison group of obese subjects was studied. In all the early studies of dexamethasone suppression a radioimmunoassay for serum cortisol was not available. The intravenous route was not further investigated at this time (probably because of the early reports of a rapid overnight oral suppression). However, the limitations of this overnight test have been described above (see Introduction).

Croughs et al. (1973) compared a 5-h infusion of dexamethasone phosphate using the 1 mg/h dose with James’ 3-h infusion and found that the 5-h infusion also separated Cushing’s disease from hypercortisolism due to adrenal tumours and ectopic sources of ACTH. Again, in this study a group of obese subjects was not studied.

More recently, two studies have included an obese group of controls for comparison (Linquette et al. 1980; Abou-Samra et al. 1985) using a 4-h infusion of dexamethasone phosphate 1 mg/h. These studies showed that it was possible to differentiate patients with Cushing’s disease from others with either adrenal tumours or ectopic ACTH syndrome. However, using this dose, some patients with Cushing’s disease showed suppression of serum cortisol into the range described in the obese control group. Our study is the first to use a weight-related intravenous dose of dexamethasone in obese subjects.

Our preliminary studies showed that the minimum intravenous dose which reliably suppressed the 08.00 serum cortisol on the following morning in subjects with simple uncomplicated obesity lay between 2.5 and 10 µg · kg⁻¹ · h⁻¹ (see Fig. 1). Further studies showed very reliable suppression using 5 µg · kg⁻¹ · h⁻¹ over 5 h in a group of obese males and females.

Using a 5-h dexamethasone infusion of 5 µg · kg⁻¹ · h⁻¹ in 12 subjects with Cushing’s disease, the plasma cortisol value was only partially suppressed and escaped rapidly in 11 of the 12 (Fig. 2). Our dose of 5 µg · kg⁻¹ · h⁻¹ is smaller than those previously described and therefore less likely to show the overlap between obese patients and patients with Cushing’s disease (Linquette et al. 1980;

---

**Fig. 4.**

Serum cortisol before and during an intravenous dexamethasone infusion (5 µg · kg⁻¹ · h⁻¹) in 19 obese subjects. Individual points are also given for 7 patients with polycystic ovarian syndrome (○)
Abou-Samra et al. 1985) shown previously with the dose of 1 mg/h. However, some patients with Cushing's disease do suppress during the formal oral low dexamethasone suppression test so that occasional suppression in classic Cushing's may still occur. It is, however, interesting to note that in the previously untreated two subjects who did not escape rapidly (AT and MM) there appeared to be better separation using the intravenous rather than the classic oral low-dose test (see Table 1). It is possible that the presence of cyclical hypercortisolism may not be diagnosed by this or any type of dexamethasone suppression test (Atkinson et al. 1985a,b). Our data do not allow us to comment on whether other (higher) doses of intravenous dexamethasone will reliably distinguish Cushing's disease from other causes of hypercortisolism as our series consisted of 11 patients with Cushing's disease and one with bilateral nodular hyperplasia.

It is clear from the results shown that a 5-h infusion of dexamethasone at a dose of 5 μg·kg⁻¹·h⁻¹ reliably and rapidly separated patients with Cushing's syndrome from control subjects with simple obesity.

It is, of course, important to realise that the results of any suppression test must always be considered in conjunction with the history, examination and other biochemical data, e.g. urinary cortisol, as well as radiological data. Since intravenous dexamethasone is labour intensive, its best role may be in those patients who fail to suppress after a single overnight oral dose of dexamethasone. In an attempt to begin to study problem diagnostic patients we studied a group of patients with polycystic ovarian disease, who often represent a difficult differential diagnostic subgroup. These patients can also be separated from patients with Cushing's syndrome at 17.00 and 19.00 h. However, they demonstrate an interesting phenomenon in that they escape from suppression more readily on the following morning: This provides further evidence that an adrenal abnormality exists in this syndrome as has been suggested by other workers. Metyrapone causes excessive plasma testosterone, androstenedione and 11-deoxycortisol response in patients with polycystic ovarian syndrome (Loughlin et al. 1986), while there are increased androgen responses to exogenous ACTH (Lachelin et al. 1979). Our studies do not allow us to decide whether these abnormalities are primary or secondary phenomena.

In summary, a weight-related intravenous dexamethasone suppression test appears attractive as a rapid and reliable means of diagnosing Cushing's syndrome at 4 and 7 h after the start of an intravenous dexamethasone infusion. Patients with obesity and polycystic ovarian disease have lower values for serum cortisol than do patients with Cushing's syndrome.

Acknowledgments

We wish to thank Sister R. Humphries and the Metabolic Unit nursing staff for their help, Mrs Marie Loughran for typing the manuscript and Miss C. Gilmartin for preparing the illustrations.

References


Received April 7th, 1988.
Accepted February 27th, 1989.

Dr A. B. Atkinson,
Sir George E. Clark Metabolic Unit,
Royal Victoria Hospital,
Belfast BT12 6BA,
Northern Ireland.