Serum cortisol concentrations during low dose dexamethasone suppression test to screen for Cushing's syndrome

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Abstract

Forty four subjects (23 obese controls, 11 patients with possible Cushing's syndrome, and 10 patients with definite Cushing's syndrome) underwent low dose (0·5 mg every six hours for two days) dexamethasone suppression tests during which serum cortisol concentration at 0800 and excretion of urinary free cortisol over 24 hours were measured. Serum cortisol concentration fell to below 60 nmol/l (2·2 μg/100 ml) in 31 subjects and remained above 250 nmol/l (9·1 μg/100 ml) in the 13 others. Excretion of urinary free cortisol showed a similar response, falling to below 110 nmol (40 μg)/24 h in 31 and remaining above 180 nmol (65 μg)/24 h in the 13 others. There was complete concordance between the two variables in terms of the pattern of response. Serum cortisol concentration fell to below 60 nmol/l (2·2 μg/100 ml) in at least 97% (31 of a possible 32) of subjects without Cushing's syndrome. On the other hand, a serum cortisol concentration of above 250 nmol/l (9·1 μg/100 ml) after low dose dexamethasone gave a false positive diagnosis of Cushing's syndrome in at most only one of 13 patients (7·7%).

Measurement of serum cortisol concentration during the low dose dexamethasone test is simpler than, and as accurate and reliable as, measurements of urinary steroids.

Introduction

The diagnosis of Cushing's syndrome, although obvious in patients with florid clinical features, depends on showing, by biochemical methods, hypercortisolism. Measurement of urinary excretion of 17-hydroxycorticosteroids was for many years the test most commonly used to screen for Cushing's syndrome. Unfortunately, considerable overlap may occur in this test between subjects with Cushing's syndrome and controls, leading to a false positive incidence of up to 27% among obese controls and a false negative incidence of up to 11% in patients with Cushing's syndrome.[1] In 1960 Liddle showed that suppression of urinary excretion of steroids during administration of dexamethasone at a low dose (0·5 mg every six hours for two days) was much greater in control subjects than patients with Cushing's syndrome, permitting a useful discrimination between the two groups.[2]

Measurement of urinary excretion of free cortisol has also been shown to discriminate well between patients with and without Cushing's syndrome.[1] Like 17-hydroxycorticosteroids, urinary free cortisol is suppressed in normal subjects during administration of dexamethasone,[3,4] and this serves as an excellent screening test in those subjects whose basal values are equivocal. The necessity of collecting all urine excreted over 24 hours makes the test rather cumbersome and potentially unreliable unless the patient is admitted to hospital for urine collection.

Accurate measurement of serum or plasma cortisol concentrations by radioimmunoassay has been available since the early 1970s, but the large diurnal fluctuations in serum cortisol concentrations seen in normal subjects make the interpretation of a single, random measurement of serum cortisol concentration extremely unreliable in the diagnosis of Cushing's syndrome. Serum cortisol concentrations fall during dexamethasone administration, as do urinary steroids; this forms the basis of the overnight (single dose) dexamethasone suppression test to screen for Cushing's syndrome. Unfortunately, although few patients with Cushing's syndrome show any reduction in serum cortisol concentration during this test, roughly 15-25% of obese controls also fail to show any reduction.[5-10]

Features suggesting possibility of Cushing's syndrome in patients

Feature	No of patients
Central obesity	9
Hirsutism	6
Enlarged or equivocal pituitary fossa (plain film)	5
Plethoric face	4
Hypertension	4
Easy bruising	3
Disturbed menses	3

Reports of serum cortisol concentrations during the longer two day low dose dexamethasone suppression test have been largely anecdotal, are not supported by adequate data on controls, and often antedate the use of radioimmunoassay.[11,12] We know of only one report comparing the results of this test in patients with Cushing's syndrome and in appropriate non-Cushingoid controls, and in that report the serum cortisol concentrations obtained were compared with results obtained with urinary 17-hydroxycorticosteroids.[13]

In this paper we describe the response of serum cortisol concentration to low dose dexamethasone in patients with definite and possible Cushing's syndrome and obese, non-Cushingoid controls. The results are compared with measurement of urinary free cortisol excretion during dexamethasone administration in the same groups of patients.

Subjects and methods

We studied three groups of patients. Group 1 consisted of 23 obese controls, including four men, in whom there was no clinical suspicion of Cushing's syndrome. Their mean (range) age was 34·6 (17-57) years. Group 2 consisted of 11 patients, including one man, with some feature or features suggestive of Cushing's syndrome (table) but in whom there was still uncertainty about the diagnosis. Their mean (range) age was 34·9 (18-62) years. None had depression as a symptom suggestive of Cushing's syndrome. In addition, none admitted to having an excessive alcohol intake, and the clinicians taking part had no reason to disbelieve this. Group 3 consisted of 10 patients, including

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one man, with clear features of Cushing's syndrome. In none of these 10 was the diagnosis in doubt, and surgical and histological confirmation was obtained subsequently in every case. Their mean (range) age was 48·2 (29-71) years. Eight of this group were shown to have Cushing's disease (pituitary dependent bilateral adrenal hyperplasia), one had an adrenal adenoma, and one an adrenal carcinoma. The mean (range) body mass indexes (weight (kg)/height (m)^2) for groups 1, 2, and 3 were 39·0 (30·8-55·8), 34·5 (23·5-44·6), and 26·9 (22·9-37·9) respectively. The patients in group 2 were followed up subsequently to establish a definite diagnosis, of either Cushing's syndrome or some other disorder, on clinical or radiological grounds or by some biochemical criteria other than the dexamethasone suppression test.

All subjects were admitted to this unit to undergo the dexamethasone suppression test, the format of which was as follows. On days 1 and 2 basal urine samples taken over 24 hours (0800-0800) were obtained for measurement of free cortisol concentration. On days 2 and 3 blood was drawn at 0800 for measurement of basal serum cortisol concentrations. Dexamethasone, 0·5 mg every six hours, was given by mouth, starting immediately after blood had been drawn at 0800 on day 3. Ingestion of tablets was ensured by nursing supervision. Urine collections over 24 hours were continued on days 3 and 4 through to 0800 on day 5, and serum cortisol concentration was measured on days 4 and 5 at 0800. Two patients in group 3, both with Cushing's disease, did not have urinary free cortisol excretion measured during the dexamethasone suppression test, and in one of these two the dose of dexamethasone given was high (2 mg every six hours rather than 0·5 mg). Their serum cortisol concentrations are included in the analysis. Another patient in group 3, a woman with an adrenal adenoma, had serum cortisol concentration measured at 0800 only on the two basal days and after 48 hours of dexamethasone—that is, on days 2, 3, and 5 of the above protocol but not on day 4.

Serum samples were stored at −20°C until estimation of serum cortisol concentration. This was by a direct radioimmunoassay featuring an iodine-125 radioligand and a solid phase antibody.[14] On completion of each 24 hour collection of urine the volume was measured and aliquots were stored at −20°C. Urine was extracted with dichloromethane and assay for free cortisol content performed on the dried solvent residue.[14]

Results

Figures 1 and 2 show basal values, and the responses during administration of dexamethasone, of urinary free cortisol excretion over 24 hours and serum cortisol concentration at 0800 for the three groups. Only one basal value is shown for each patient studied. In the case of groups 1 and 2 this is the higher of the two values obtained on the basal days and in group 3 the lower of the two values. In the obese controls (group 1) the basal urinary excretion rate of free cortisol ranged from 116 to 580 nmol (42 to 210 μg)/24 h. Eight of nine patients with definite Cushing's syndrome (group 3) had a basal urinary free cortisol excretion rate that was greater than the highest value in the controls (range 640-3800 nmol (232 1378 μg)/24 h). The other patient with Cushing's syndrome had a urinary free cortisol excretion rate of 161 nmol (58 μg)/24 h. This patient was subsequently shown to have Cushing's disease with cyclical hormonogenesis, and repeated estimations showed values fluctuating from just over 100 (36) to over 4000 nmol (1450 μg)/24 h. In contrast to urinary free cortisol excretion rates, the ranges of basal serum cortisol concentrations in groups 1 and 3 showed great overlap—315-700 nmol/l (11-25 μg/100 ml) in controls and 430-687 nmol/l (16·6-25 μg/100 ml) in patients with definite Cushing's syndrome.

Urinary free cortisol excretion rates and serum cortisol concentrations after administration of dexamethasone resulted in complete separation of groups 1 and 3. The urinary free cortisol excretion rate in controls after two days of dexamethasone administration ranged from below 15—that is, below the limit of detection—to 110 nmol (40 μg)/24 h and in patients with Cushing's syndrome from 180 to 4000 nmol (62-1450 μg)/24 h. The urinary free cortisol excretion rate was below the lower limit of detection in two controls (9%). Measurement of serum cortisol concentration at 0800 after two days' administration of dexamethasone appeared to give even clearer separation between these two groups. The highest value in any of the controls was 54 nmol/l (2 μg/100 ml), and 16 (69%) of the controls had concentrations below the lower limit of detection (20 nmol/l; 0·7 μg/100 ml). Concentrations in patients with definite Cushing's syndrome ranged from 270 to 1500 nmol/l (9·8-54 μg/100 ml). Figure 2 also shows clearly that suppression of serum cortisol concentration in the controls was almost complete after only 24 hours of dexamethasone: only one of the 23

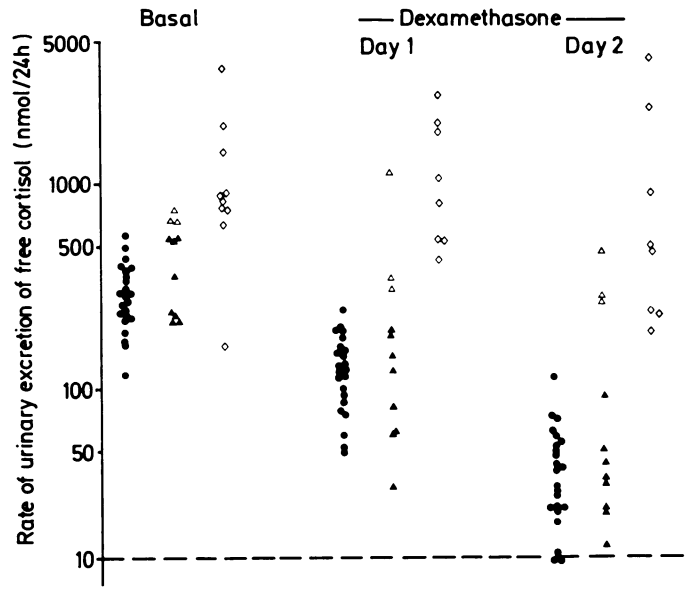

FIG 1—Twenty four hour urinary free cortisol excretion during low dose dexamethasone suppression test in 23 obese controls (●), 11 patients with possible Cushing's syndrome (▲ and △), and 10 patients (values not measured during dexamethasone in two) with definite Cushing's syndrome (◇). For patients with definite Cushing's syndrome basal value is the lower of two basal readings. For all other subjects it is the higher of the two. Dexamethasone day 1=day 3 of protocol, and dexamethasone day 2=day 4 of protocol. Broken line represents lower limit of detection of assay. The scale is logarithmic.

Conversion: SI to traditional units—Cortisol: 1 nmol/24 h ≈ 0·36 mg/24 h.

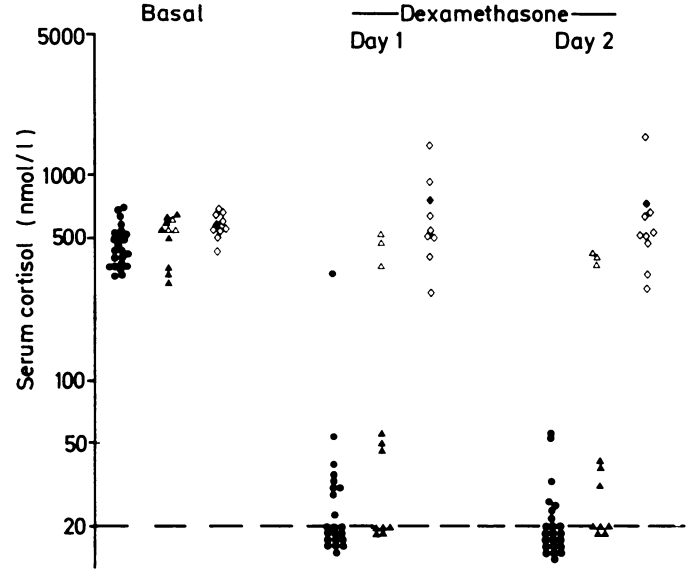

FIG 2—Serum cortisol concentration at 0800 during low dose dexamethasone suppression test in 23 obese controls (●), 11 patients with possible Cushing's syndrome (▲ and △), nine patients with definite Cushing's syndrome (◇), and one patient with definite Cushing's syndrome who underwent high dose testing (◆). Basal values selected as in fig 1. Dexamethasone day 1=0800 on day 4 of protocol, and dexamethasone day 2=0800 on day 5 of protocol. Broken line represents lower limit of detection of assay. The scale is logarithmic.

Conversion: SI to traditional units—Cortisol: 1 nmol/l ≈ 36·25 ng/100 ml.

patients had a concentration within the range seen in the patients with Cushing's syndrome at a similar stage in the test, and in 13 (56%) the serum cortisol concentration was already below detection.

Patients with possible Cushing's syndrome (group 2) had a basal range of urinary excretion rates of free cortisol intermediate between those of groups 1 and 3 and a basal range of serum cortisol concentrations at 0800 identical to that of group 1. On administration of dexamethasone these patients fell into two distinct subgroups on the basis of the responses of both urinary free cortisol excretion rate and serum

cortisol concentration. Eight patients showed suppression of both urinary free cortisol excretion rate and serum cortisol concentration to an extent similar to that seen in group 1 (controls). Follow up of these patients confirmed that they did not have Cushing's syndrome, and other diagnoses were established: two had simple obesity with an empty sella; two had the polycystic ovary syndrome; one had a prolactin secreting pituitary adenoma; one had idiopathic hirsutism; one had hypogonadotrophinism with acanthosis nigricans; and one had simple obesity, which responded to dietary treatment resulting in a loss of Cushingoid features.

Three patients with possible Cushing's syndrome (group 2) did not show a fall in either urinary excretion of cortisol or serum cortisol concentration during administration of dexamethasone. These patients are considered in greater detail. The first, a 41 year old woman, had been successfully treated for Cushing's disease two years before by selective removal of a pituitary microadenoma. The possibility of a recurrence of Cushing's syndrome was suggested by an increasingly plethoric appearance. Urinary free cortisol excretion rate and serum cortisol concentration after low dose dexamethasone were respectively 270 nmol (98 μg)/24 h and 410 nmol/l (15 μg/100 ml). In the months after this test her Cushingoid appearance intensified, with the development of skin fragility and mild proximal myopathy. Repeat measurement of urinary free cortisol excretion rate on several occasions gave values of up to 1935 nmol (701 μg)/24 h. Bilateral adrenalectomy was performed, confirming the presence of cortical hyperplasia of the adrenal glands, which had a combined weight of 21·5 g.

The second patient was a 36 year old woman with mild hypertension, easy bruising, and a plethoric face. Urinary free cortisol excretion rate and serum cortisol concentration during low dose dexamethasone were 261 nmol (95 μg)/24 h and 390 nmol/l (14 μg/100 ml) respectively. High dose dexamethasone (2 mg every six hours for 48 hours) led to a fall in urinary free cortisol excretion rate to 45 nmol (16 μg)/24 h and in serum cortisol concentration to 52 nmol/l (1·9 μg/100 ml). Low and high dose dexamethasone suppression tests were repeated three months later with similar results, suggesting the probability of pituitary dependent Cushing's syndrome. Because she was virtually symptom free a conservative policy was adopted with frequent outpatient reviews. In the following year antihypertensive treatment was required to control the blood pressure; urinary free cortisol excretion rate measured on several occasions was in the range of 646-940 nmol (234-341 μg)/24 h; and mild proximal myopathy developed. Fifteen months after the original dexamethasone suppression test similar results were obtained during repeat low and high dose suppression tests. At this stage a computed tomogram of the pituitary suggested the presence of a microadenoma, which was subsequently confirmed and successfully removed by transsphenoidal surgery.

The third patient in group 2 in whom cortisol was not suppressed during administration of low dose dexamethasone was an 18 year old woman with oligomenorrhoea, hirsutism, weight gain, and mild generalised obesity. There was slight clitoromegaly. Urinary free cortisol excretion rate and serum cortisol concentration after low dose dexamethasone were 460 nmol (167 μg)/24 h and 360 nmol/l (13 μg/100 ml) respectively. During the next few months repeat estimations of basal rates of urinary excretion of free cortisol gave results that were generally higher than those seen in our controls—namely, 756, 1152, 1230, 2400, 543, 469, and 546 nmol (274, 418, 466, 870, 197, 170, and 199 μg)/24 h. Plasma adrenocorticotrophic hormone concentration was repeatedly measurable, within the normal range for our laboratory. Computed tomograms of the pituitary and adrenal glands showed no definite abnormality. On the assumption that she had mild Cushing's disease a trial of medical treatment (a combination of cyproheptadine and bromocriptine) was begun. Over 16 months, while she continued to receive these drugs, menstruation restarted and the hirsutism improved subjectively. Urinary free cortisol excretion rates decreased and were consistently in the range of 315-400 nmol (114-145 μg)/24 h. Drug treatment was stopped after 16 months, but information on her cortisol state was not available when this report was written. At that stage, we could not say with certainty whether she had Cushing's syndrome.

Discussion

The aims of this study were to try to establish criteria for the interpretation of serum cortisol concentrations during the low dose dexamethasone suppression test in the diagnosis of Cushing's syndrome and to compare the uses of serum concentrations and urinary free cortisol excretion rates during the test. Of the 44 patients in the three groups studied, 12 turned out to have Cushing's syndrome, 31 turned out not to have it, and, at the time of writing, one was causing legitimate uncertainty about diagnosis. On the basis of serum cortisol concentrations at 0800 after two days of administration of dexamethasone the patients could be divided into two distinct groups. Concentrations of less than 60 nmol/l (2 μg/100 ml) were seen in 31 patients who definitely did not have Cushing's syndrome, whereas the 12 patients with Cushing's syndrome plus the remaining doubtful patient had concentrations of more than 250 nmol/l (9 μg/100 ml). Thus, if the doubtful patient eventually is shown definitely to have Cushing's syndrome, the test was accurate in all cases. If she does not have Cushing's syndrome a serum cortisol concentration of less than 60 nmol/l (2 μg/100 ml) after a low dose dexamethasone suppression test was 97% (31 out of 32) accurate in excluding the diagnosis of Cushing's syndrome, while a concentration of more than 250 nmol/l (9 μg/100 ml) gave a false positive rate of 7·7% (one out of 13) in making the diagnosis of Cushing's syndrome.

Division of patients into two subgroups on the basis of urinary excretion rate of free cortisol during administration of dexamethasone was identical with that on the basis of serum cortisol concentrations. In other words, there was complete concordance between the two variables as far as suppressibility during administration of dexamethasone was concerned. The difference, which is apparent from inspection of figures 1 and 2, was that the degree of separation of the two groups was smaller with urinary free cortisol excretion rates. The upper value for this variable among the 31 patients in whom suppression occurred was 110 nmol (40 μg)/24 h, and the lowest value in the remaining 11 in whom urinary free cortisol excretion rate was measured was 185 nmol (67 μg)/24 h. Clearly, therefore, replacing measurement of excretion of urinary free cortisol over 24 hours with the simpler measurement of serum cortisol concentration during a low dose dexamethasone suppression test would not be detrimental and might even enhance the discriminatory value of the test.

Ashcraft *et al* came to a similar conclusion when comparing serum cortisol concentrations with urinary excretion of 17-hydroxycorticosteroids during suppression with low dose dexamethasone.[13] The serum cortisol concentration of 138 nmol/l (5 μg/100 ml), which they suggested as the upper limit in patients who showed suppression during administration of dexamethasone, was considerably higher than the value of 60 nmol/l (2 μg/100 ml) found in our study. We have no ready explanation for this difference, although in the study of Ashcraft *et al* the serum cortisol concentration was measured at 1600 on the second day of administration of low dose dexamethasone rather than at 0800 the next morning, as in our study. The advantage of sampling in mid-afternoon rather than early morning is obvious, particularly in the outpatient setting. The timing of samples in our study was chosen to fit in with established ward routine and to dovetail with the 24 hour urine collections. We see no reason why, for an outpatient test, the initial dose of dexamethasone could not be given at 1400, with serum cortisol concentration measured at the same time two days later, six hours after the last dose of dexamethasone.

Measurement of plasma dexamethasone concentration has been advocated in identifying patients in whom results are misleading because of altered dexamethasone metabolism.[15] The results of our study suggest that, when administration of dexamethasone is carefully supervised, misleading results are probably extremely rare. A possible disadvantage of an outpatient dexamethasone test would be uncertainty about compliance in taking the dexamethasone. The problem that non-compliance would cause is apparent non-suppressibility in a subject who does not have Cushing's syndrome. In that event measurement of plasma dexamethasone concentration would be helpful, though recourse to inpatient testing might be required.

Interestingly, our patient with Cushing's syndrome and cyclical hormonogenesis had an appropriate response (that is, failure of suppression) of both urinary free cortisol excretion rate and serum cortisol concentration during dexamethasone

administration despite having intermittently normal values for both serum cortisol concentration and urinary free cortisol excretion rate. We believe that cyclical hormonogenesis could possibly give rise to misleading responses during dexamethasone suppression tests, though this is likely to be as true for measurement of urinary free cortisol excretion or 17-hydroxycorticosteroids as it is for serum cortisol concentration.

In summary, we suggest that the low dose dexamethasone suppression test, incorporating measurement of serum cortisol concentration rather than of urinary cortisol or steroid excretion rate, is highly reliable in screening for Cushing's syndrome and may be of considerable financial benefit in facilitating outpatient rather than inpatient investigation.

We thank Sister R Humphries and the nursing staff of this unit for their careful and conscientious help during this study; and Paula Robinson for preparing the manuscript.

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(*Accepted 14 August 1984*)

SHORT REPORTS

Television induced seizures in alcoholics

Television induced seizures usually occur in patients with photosensitive epilepsy. This epilepsy is usually idiopathic and has a well known genetic predisposition.[1] We describe three chronic alcoholics who during a period of abstinence had a grand mal seizure while watching or adjusting the television set. So far as we know environmentally induced photic seizures have not been reported as a manifestation of alcohol withdrawal.

Case reports

Case 1—A 26 year old man had a grand mal seizure when he was adjusting the television set. In the hours before the fit he had noticed tremulousness and irritability. Six months earlier he had suffered an identical seizure, which had also occurred while he was adjusting the television. He had been a heavy beer drinker for several years and on both occasions he had not had a drink since the day before. There was no other past medical history or family history of epilepsy and he was not taking medication. Examination showed a coarse tremor of both arms, spider angiomas, palmar erythema, and a lip bite lesion. Laboratory findings on admission contained the following abnormal values: mean corpuscular volume 100 fl (100 μm^3), γ-glutamyltransferase activity 153 IU/l (normal <40 IU/l), and creatine kinase activity 482 IU/l (normal <100 IU/l). Serum electrolyte, glucose, and ammonia concentrations were normal, as were renal function values. An electroencephalogram the day after the seizure showed an α rhythm of 10 Hz and no abnormalities on intermittent light stimulation. A computed tomogram of the brain was normal. Liver biopsy disclosed cirrhosis.

Case 2—A 40 year old chronic alcoholic had a first grand mal seizure when watching television. A few minutes after regaining consciousness he had a second fit. Two days earlier he had stopped alcohol because of an upper respiratory tract infection. There was no family history of epilepsy and he was not taking medication. Examination showed mild confusion and a postural tremor of both arms. Abnormal findings on routine laboratory investigation were: potassium concentration 2·9 mmol(mEq)/l, γ-glutamyltransferase activity 650 IU/l, and creatine kinase activity 152 IU/l. Serum electrolyte and glucose concentrations, renal function values, and haematological measurements were normal. Four days after admission the electroencephalogram showed fast, low voltage activity and no abnormalities on intermittent light stimulation. CT scan of the brain was normal.

Case 3—A 31 year old man with a history of delirium tremens five years before had a first grand mal seizure the moment that he started watching television. He usually drank about 15 bottles of beer daily. There was no family history of epilepsy and he was not taking medication. He had not had a drink since the day before the seizure. Examination showed only tremor of both hands. γ-Glutamyltransferase activity was 1020 IU/l and creatine kinase activity 225 IU/l. Serum electrolyte and glucose concentrations, renal function values, and haematological measurements were normal. Four days after admission an electroencephalogram showed an α rhythm of 9 Hz and no abnormalities on intermittent light stimulation. CT scan of the brain was normal.

The table gives the circumstances of the seizures in the three patients.

Circumstances of seizures in the three patients

Case No		Television set (transverse diameter of screen)	Distance (and angle) of person to screen	Background lighting	Interference on screen
1	First seizure	Colour (30 cm)	Close (horizontal)	Dim	None
	Second seizure	Colour (66 cm)	Close (horizontal)	Dim	None
2		Colour (66 cm)	2·5 m (horizontal)	Dim	None
3		Colour (56 cm)	3 m (horizontal)	Dim	None

Comment

Seizures after alcohol withdrawal are usually grand mal attacks which occur between six and 48 hours after the last drink. Liability to this type of seizure is often accompanied by heightened stroboscopic flicker sensitivity with photomyoclonic or photoconvulsive responses in the electroencephalogram.[2] The occurrence of seizures in our patients when watching or adjusting the television set may have been simple coincidence. Nevertheless, in view of the heightened photosensitivity observed in the electroencephalograms of patients after alcohol withdrawal it is tempting to assume that their seizures were television induced. In our first patient simple coincidence seems especially unlikely because he twice had a seizure under identical circumstances. In none of our patients did the electroencephalogram show abnormal responses on intermittent light stimulation. This agrees with the notion that photic induced electroencephalographic abnormalities in the alcohol withdrawal period may occur only at the time of the seizure.[2]

Evidence suggests that central dopaminergic neurotransmission is implicated in the pathophysiology of generalised photosensitive epilepsy. Apomorphine, a dopamine agonist, blocks epileptic photosensitivity in patients with generalised photosensitive epilepsy.[3] The mechanism by which dopamine acts in the visual cortex has still to be elucidated. Interestingly, other studies have shown that dopaminergic neurotransmission is also impaired in the alcohol withdrawal period. In ethanol dependent rats release of dopamine in the striatum is reduced during alcohol withdrawal.[4] Although this has not been shown in man, we may assume that there is also a reduced dopaminergic turnover in the visual cortex in patients during abstinence from alcohol. Intermittent photic stimulation by itself reduces the release