weeks using the HRS and a side effects questionnaire. Blood was taken for measuring plasma drug concentration on the day of assessment about 12 hours after the nightly dose. Five patients dropped out at one week and four more at four weeks, leaving 65 who completed the six weeks' trial. Their mean age (±SE of mean) was 49·5±6·14, HRS entry score 23·28±2·89, steady-state amitriptyline plasma concentration was 91·34±6·53 μg/l, nortriptyline 86·91±6·53 μg/l, and amitriptyline plus nortriptyline 179·14±11·95 (range 52-524 μg/l).

There was a highly significant negative correlation between plasma concentration and therapeutic response with nortriptyline but not with amitriptyline alone (table). The overall response was 60% (72% inside the range 80-200 μg/l, 42% outside). The 38 patients developing levels within the range had a highly significant improved response ($t=3{\cdot}65$-$4{\cdot}04$, $P<0{\cdot}001$) compared with those developing levels outside the range. The response of those outside the range occurred almost entirely in the first two weeks with little further response between two and six weeks. There was no simple relationship between plasma concentrations and age or side effects. Patients with high concentrations could not be identified clinically.

Correlations between plasma concentrations of amitriptyline, nortriptyline, and amitriptyline plus nortriptyline with clinical response at six weeks inside and outside the range of amitriptyline plus nortriptyline 80-200 μg/l

Mean steady-state drug plasma concentration	No	Final HRS score (6 weeks)	Amelioration of HRS score (0-6 weeks)	% Change in HRS score (0-6 weeks)
Amitriptyline (AT)	65	+0·10	−0·12	−0·13
Nortriptyline (NT)	65	+0·34*	−0·36*	−0·43†
AT + NT	65	+0·25	−0·27‡	−0·30‡
Inside range 80-200 μg/l AT + NT (mean ± SEM)	38	6·5±0·8	16·2±0·9	71·8±3·3
Outside range <80, >200 μg/l AT + NT (mean ± SEM)	27	14·4±2·0§	9·7±1·7§	42·5±7·3§

Level of significance (Student's t-test): *$P<0{\cdot}01$, †$P<0{\cdot}005$, ‡$P<0{\cdot}05$, §$P<0{\cdot}001$.

Comment

Investigating possibly complex plasma concentration response relationships is not easy. Variations in findings between trials may result from differences in the patient groups studied. These are likely to be increased by failure to record drop-outs, mixed or ill-defined diagnostic categories,[2-5] outpatients with possible compliance problems,[2-4] or small numbers.[2-4] We tried to control these sources of error. Twenty-seven out of 65 inpatients with endogenous depression taking a constant dose achieved concentrations outside the range of 80-200 μg/l of amitriptyline plus nortriptyline, and 20 of these were above the range. This allowed us to determine the significant clinical disadvantage of high concentrations and the improved response in those developing intermediate concentrations within an optimum therapeutic range. The failure of patients above this range to show further improvement between two and six weeks suggests that high concentrations may inhibit spontaneous remission, which is in line with findings with nortriptyline.[1] Our results indicate that adjustment of drug plasma concentrations to within the proposed therapeutic range would significantly improve the efficacy of treatment with amitriptyline in endogenous depression.

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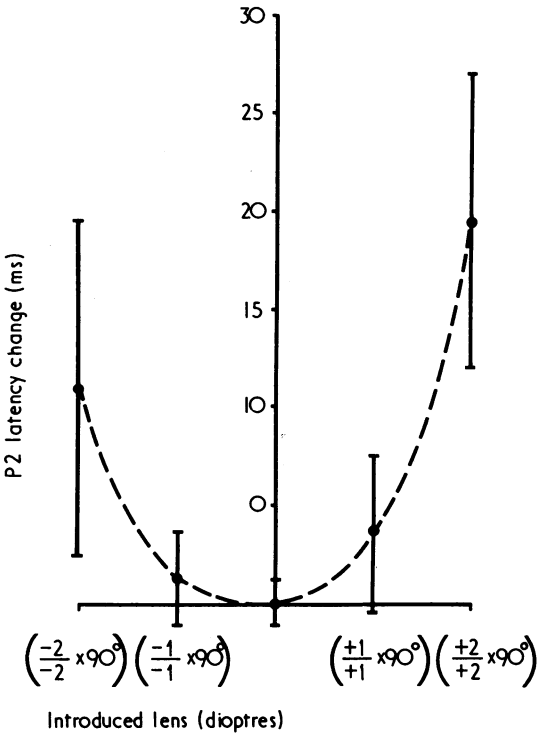
Effect of refractive error on the visual evoked response

The pattern-reversal visual evoked response (VER) technique is well established in the investigation of various neurological disorders, particularly multiple sclerosis (MS). Absolute or relative increases in the latency of the major surface positive component (P2) is almost invariably found in patients with demyelinating optic neuropathy,[1 2] and attenuation and desynchronisation of the response is a common feature of non-demyelinating lesions of the visual pathways. In view of the increasing use of this technique in neuro-ophthalmological diagnosis we have studied the effect of introduced refractive errors on the VER.

Subjects, methods, and results

Five women and eight men aged 19 to 45 years were selected after a thorough ophthalmological assessment. Visual acuity (VA) was 6/6 or better in all subjects and none had dyschromatopsia or significant astigmatism. Refractive errors were created by introducing the following combined standard lenses: $(+2/+2\times90°)$, $(+1/+1\times90°)$, $(-1/-1\times90°)$, and $(-2/-2\times90°)$ dioptres. The VA of each eye was measured for each lens. Using three-degree radius field stimulation and 12-minute checks, monocular pattern-reversal VERs were recorded without and then with each introduced refractive error by a computer-based data collection system described elsewhere[2 3] and compared with previously established normal values.[2] Of these the most important response parameters were the P2 latency (113 ms) and the interocular latency difference (6 ms), being the 99·7% limits. At least seven recordings were made for each eye and 16 records were obtained for each introduced lens.

The VA was reduced to 6/60 or worse with the $(+2/+2\times90°)$ dioptre lens and to 6/24 or worse with the $(-2/-2\times90°)$ dioptre lens in all subjects, and there was a pronounced effect on the P2 component of the VER with these introduced refractive errors. The P2 latency change for each refractive error is shown in the figure. The P2 latency was abnormally prolonged in 31% (5/16) of recordings with the $(-2/-2\times90°)$ dioptre lens and in 87·5% (14/16) with the $(+2/+2\times90°)$ dioptre lens. The maximum P2 latency was 126 ms. For all other recordings the P2 latency was less than 113 ms but there was considerable temporal dispersion and reduction in amplitude of the P2 component, especially for the convex lenses. Indeed, the VER was almost abolished in some of the recordings when a $(+2/+2\times90°)$ dioptre lens was used. When the P2 latency recorded with introduced refractive error was compared with that recorded from the other eye without refractive



Change in latency of major surface positive component (P2) in pattern-reversal visual evoked response with introduced refractive errors.

error the interocular latency for the ($-1/-1\times90°$) dioptre lens was within the normal range of 6 ms for all subjects. However, 31% of recordings with the ($+1/+1\times90°$) dioptre lens, 56% with the ($-2/-2\times90°$) dioptre lens, and 100% of the identifiable responses recorded with the ($+2/+2\times90°$) dioptre lens showed an abnormally increased interocular delay. The maximum relative delay observed was 32 ms.

Comment

Reduction in amplitude of the VER with refractive error has previously been reported.[4] Our study, using the pattern-reversal method, confirms that finding. More importantly, our study illustrates the significant changes in absolute and relative latency of the P2 component when refractive errors which approximate to those found in the population at large are introduced to defocus a small stimulus field and high spatial frequency pattern. This effect is greatest for refractive errors of ($+2/+2\times90°$) dioptres. Because a relative or absolute prolongation of P2 latency is often found in cases of suspected MS, and because of their similarity to the findings of our study, we would emphasise that refractive errors should be reduced or eliminated to minimise false-positive results. Furthermore, the VA must be considered in the interpretation of the VER.

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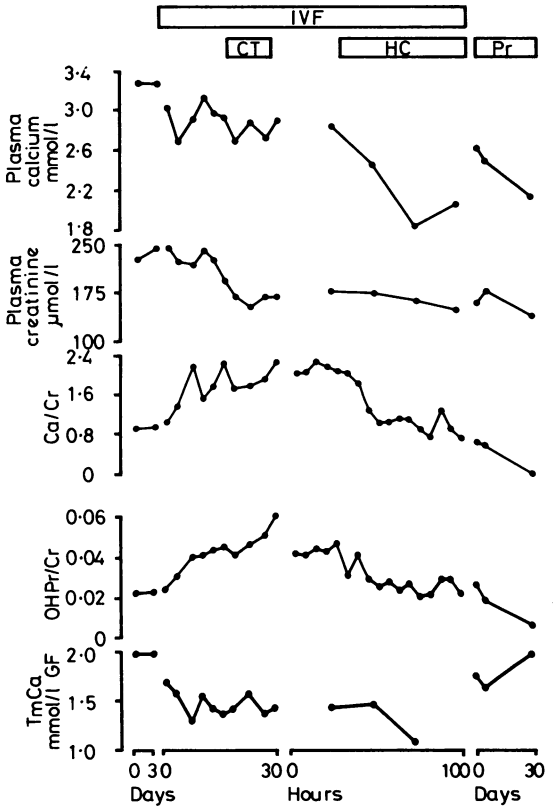
Acute effects of saline, calcitonin, and hydrocortisone on plasma calcium in vitamin D intoxication

Hydrocortisone reduces plasma calcium in hypercalcaemic states other than primary hyperparathyroidism.[1] The mechanisms, however, are not entirely clear. Calcium absorption and renal tubular reabsorption of calcium are reduced and a direct reduction in bone resorption has been suggested. On the other hand, chronic administration of cortisol increases bone resorption and predisposes to osteoporosis.[2 3] We report the case of a patient with vitamin D intoxication in whom acute administration of hydrocortisone resulted in a rapid reduction in bone resorption with consequent abolition of hypercalcaemia. All methods used have been described.[4]

Case report

A woman aged 36 developed hypoparathyroidism after a thyroidectomy in 1964. She was maintained on vitamin D_2 (200 000 U/day) and calcium supplements. Three years after the thyroidectomy she developed hypothyroidism and was maintained on thyroxine 0·3 mg/day. In 1978 she was noted to be hypercalcaemic. Vitamin D and calcium supplements were withdrawn, but her plasma calcium concentration remained high and she was referred for further management. Initial investigation (figure) suggested that the hypercalcaemia (plasma calcium concentration 3·28 mmol/l (13·1 mg/100 ml); normal range 2·22-2·60 mmol/l (8·9-10·4 mg/100 ml)) was due to a combination of increased bone resorption (fasting urinary OHPr:Cr 0·023; normal <0·017) and decreased glomerular filtration (creatinine concentration 223 μmol/l (2·5 mg/100 ml)). She had low absorption of radiocalcium (0·39 fraction of dose absorbed per hour; normal range 0·3-1·2) and plasma 25-hydroxy vitamin D concentration was raised at 650 ng/ml (normal range 5-72·5 ng/ml). The concentration of parathyroid hormone was unmeasurable and of alkaline phosphatase normal at 6·2 KA units/100 ml (normal range 3-13), as was that of plasma phosphate at 1·12 mmol/l (3·47 mg/100 ml); normal range 0·8-1·45 mmol/l (2·5-4·5 mg/100 ml)). The patient was clinically and biochemically hyperthyroid (T4=255 mmol/l (normal range 60-140)), and thyroxine was discontinued.



Changes in plasma and urinary biochemistry after saline 3 l/day (IVF), calcitonin (CT), hydrocortisone infusion (HC), and prednisone (Pr). Doses used and normal ranges described in the text.

Conversion: SI to traditional units—Calcium: 1 mmol/l ≈ 4 mg/100 ml. Creatinine: 1 μmol/l ≈ 0·0113 mg/100 ml. Ca:Cr: 1 ≈ 0·353. OHPr:Cr: 1 ≈ 1·16. TmCa: 1 mmol/l GF ≈ 4 mg/100 ml GF.

She was put on a low calcium diet and rehydrated with intravenous saline, which resulted in a fall in plasma calcium due to improved glomerular filtration and reduced renal tubular reabsorption of calcium. Bone resorption, however, remained high and the patient remained hypercalcaemic. Frusemide (two consecutive daily doses of 40 mg) and calcitonin in low doses (20 U/day for 12 days) did not affect the hypercalcaemia. Hydrocortisone sodium succinate 50 mg was added to each litre of saline given for a period of three days, the fluid regimen remaining otherwise unchanged. Within four hours of starting hydrocortisone there was a reduction in urinary hydroxyproline and urinary calcium concentrations accompanied by a reduction in plasma calcium concentration, which became subnormal by the second day. Renal tubular reabsorption of calcium fell further but glomerular filtration rate remained unchanged. The patient was later discharged taking prednisone 5 mg and thyroxine 0·1 mg daily, having become clinically and biochemically hypothyroid (T4<10 mmol/l). She has remained normocalcaemic with no evidence of increased bone resorption, but mild renal impairment has persisted.

Comment

The plasma calcium concentration was reduced by the established effects of saline infusion on glomerular filtration rate and renal tubular reabsorption of calcium. The low calcium absorption in the face of a high plasma 25-OHD_3 concentration and the increase in bone resorption during saline infusion, which was related to improvement in renal function, are unexplained. Neither frusemide nor calcitonin reduced renal tubular calcium reabsorption or bone resorption. The effect of hydrocortisone on the plasma calcium concentration was due mainly to a reduction in bone resorption, although it also decreased the tubular reabsorption of calcium. The rapid onset of action