SHORT REPORTS

Lithium, manic-depressive illness, and psychological test performance

For over 10 years patients responding to treatment at a lithium clinic[1] have been free from psychiatric symptoms. Little is known about the psychological performance of such patients, but a report,[2] using the Minnesota Multiphasic Personality Inventory (MMPI), confirmed that lithium produces a response in depression. Clinical impressions agree that lithium responders are patients with typical manic-depressive illness.[3] It is still not known how well patients are when taking lithium.

Patients, methods, and results

The first 20 responders to lithium attending the clinic in 1978 were studied psychologically. They had had an average (±SD) of 9·8±3·86 attacks over an average of 9·6±4·92 years before treatment. Since starting treatment they have had an average of 6·25±3·15 years attack free and an estimated average of 7·82±4·35 attacks per person prevented. The expected frequency might have been 10-20% higher, as suggested by Angst *et al.*[4] The following psychological tests were used: (1) a questionnaire measuring depression in terms of guilt, mood, impairment, and retardation[5]; (2) the Middlesex Hospital Questionnaire measuring generalised anxiety, phobic anxiety, obsessional features, somatic symptoms, depression, and hysteria. The patients were well and, except for one, had been since starting lithium. The table shows the scores from the two questionnaires for the lithium responders. Comparative data are also included. With both questionnaires the lithium responders were like normals rather than like depressives or psychiatric patients. Combined median tests on the depression questionnaire data show that the lithium responders differed from the depressed group at a significant level ($P<0·01$) on all five scores. They could not be separated statistically from the normal group. With the Middlesex Hospital Questionnaire a non-parametric analysis cannot be made since the published data do not give the individual scores for the normal and psychiatric groups. Although the use of *t* tests might not be entirely appropriate there was only one departure with such tests from the results with the depression questionnaire. On the obsessional scale lithium responders were more like psychiatric patients than normals. The lithium response might have depended on regularity in tablet taking associated with obsessional traits. The association could also mean that the normal personalities of many depressed patients have obsessional features.

Comment

These 20 manic-depressive patients had had nearly 200 admissions (many compulsorily) to a mental hospital. Since being treated with lithium (with one exception) previously severely psychotic patients are now symptom-free with normal psychological profiles. They are well and leading ordinary lives. Lithium probably prevents changes into illness and these patients, had they not been successfully treated, might well have become chronic mental hospital patients. One patient relapsed into mania twice, each time shortly after stopping her medication. Another patient (with 11 admissions in 15 years), now well for 10 years, shows features of depression on both scales. She is reactively depressed. She is living with her epileptic and subnormal daughter and her 80-year-old mother-in-law and also caring for her 80-year-old mother.

Psychological assessment indicates that these responders to lithium might be obsessional. They may be more scrupulous about complying with their treatment and more likely to respond successfully to it. Perhaps a predisposition to manic-depressive illness is associated with obsessional personalities. Would these patients have eventually become chronic mental hospital residents without lithium treatment? Their normal psychological profiles (in severely affected manic-depressives) emphasise that they are symptom-free between attacks and warrant special care to keep them well. The number of attacks and admissions prevented emphasises the importance of treating such patients with lithium and reaffirms that lithium has been effective in them. Few treatments in psychiatry are as successful, particularly when followed up for as many years.

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2 House, K M, and Martin, R L, *American Journal of Psychiatry*, 1975, **132**, 644.
3 Schou, M, *Journal of Psychiatric Research*, 1968, **6**, 67.
4 Angst, J, Dittrich, A, and Grof, P, *International Psychiatry*, 1969, **2**, 1.
5 Kerry, R J, and Orme, J E, *Journal of Clinical Psychology*, 1975, **31**, 607.

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Amitriptyline plasma concentration and clinical response

The case for monitoring plasma nortriptyline concentrations to maximise antidepressant effect[1] has been put. The relationship between plasma concentrations and clinical response is more complex with amitriptyline, the most widely prescribed antidepressant. This is because amitriptyline undergoes demethylation in vivo to produce variable quantities of nortriptyline, its active metabolite. Braithwaite *et al*[2] reported a simple linear relationship between response and concentrations of amitriptyline plus nortriptyline. But an alternative analysis suggested there was an improved response with intermediate concentrations. Montgomery and Braithwaite[3] found a significantly better response with amitriptyline plus nortriptyline concentrations between 80 and 200 μg/l. Ziegler *et al*[4] reported findings that supported the concept of this "therapeutic window". The recent WHO multicentre trial[5] suggested there was little justification for routine monitoring of concentrations although a significant negative correlation between percentage change on the Hamilton (HRS) and nortriptyline concentrations was reported.

Patients, methods, and results

Seventy-four patients suffering from primary affective disorder with endogenous depression (defined by Newcastle inventories after our earlier design[1]) who remained moderately to severely depressed after a placebo period were treated with a constant dose of 150 mg amitriptyline at night for six weeks. Patients were rated after the placebo period and every two

Mean scores (and standard deviations) of lithium and other groups on two questionnaires

		Depression questionnaire				
	No	Total score	Guilt	Mood	Impairment	Retardation
Lithium responders	20	6·20 (5·77)	1·85 (2·08)	1·05 (1·28)	1·45 (1·50)	1·85 (1·96)
Normals	35	5·07 (3·32)	2·31 (1·47)	0·91 (0·77)	1·11 (1·12)	0·74 (1·31)
Depressed patients	34	23·88 (8·45)	5·06 (3·51)	5·65 (3·18)	6·35 (2·42)	6·82 (2·69)

		Middlesex Hospital Questionnaire					
	No	Anxiety	Phobic	Obsessional	Somatic	Depression	Hysteria	Total
Lithium responders	20	4·7 (2·1)	3·4 (1·72)	8·3 (2·68)	3·9 (3·06)	4·3 (2·88)	3·5 (2·62)	28·1 (12·90)
Normals	39	5·2 (3·5)	3·7 (2·3)	6·4 (2·7)	4·2 (2·7)	3·8 (2·8)	3·9 (3·0)	27·2
Psychiatric inpatients	24	12·5 (1·9)	9·0 (4·1)	9·3 (3·1)	9·3 (4·3)	8·2 (2·8)	7·4 (3·8)	55·7

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.

[1] Montgomery, S, *et al*, *Clinical Pharmacology and Therapeutics*, 1978, **23**, 309.
[2] Braithwaite, R A, *et al*, *Lancet*, 1972, **1**, 1297.
[3] Montgomery, S A, and Braithwaite, R A, Meeting of British and Scandinavian Associations of Psychopharmacology, London, 1975.
[4] Ziegler, V E, Clayton, P J, and Biggs, J T, *Archives of General Psychiatry*, 1977, **34**, 607.
[5] Coppen, A, *et al*, *Lancet*, 1978, **1**, 63.

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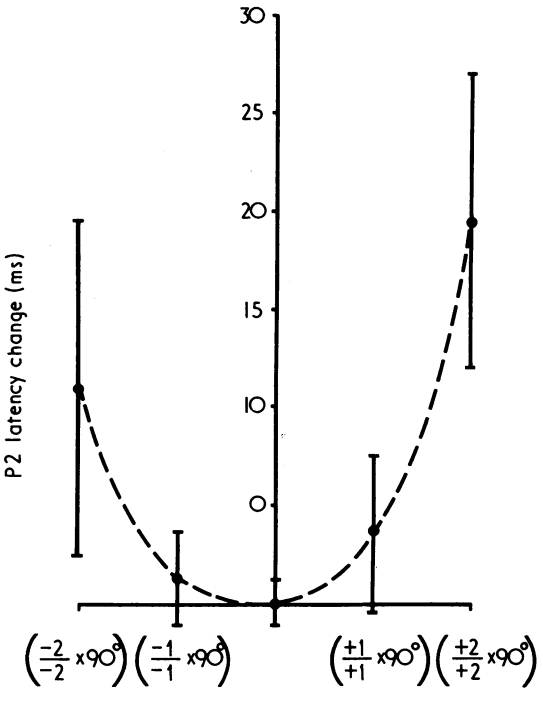
Effect of refractive error on the visual evoked response

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.