Doses of carbamazepine and valproate in bipolar affective disorder

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Carbamazepine and valproate are now well established treatments for bipolar affective disorder (BAD). Both drugs are used in the acute treatment of mania and, more frequently, as longer-term mood stabilisers. The British National Formulary (BNF, Vol. 32, 1996) provides information on the use of carbamazepine in the 'prophylaxis of manic depressive illness' and suggests that the 'usual range' of doses is between 400 mg and 600 mg daily. No guidance on the use of valproate in BAD is given in the BNF because the drug is not licensed for this indication in the UK.

Perhaps because of the absence of firm prescribing advice for either drug, the doses of carbamazepine and valproate seen in practice vary considerably. In general, low doses appear to be most frequently prescribed and daily doses above 600 mg of either drug are not often seen. Doses seem to be only rarely titrated to maximise efficacy. This is possibly because the evaluation of efficacy in preventing mood changes (prophylaxis) takes months or even years.

It is apparent that more specific guidance on the dosing of carbamazepine and valproate would prove valuable and so we have examined pertinent research data in an attempt to develop more useful advice.

Table 1 lists details of important trials of carbamazepine and valproate in mania and BAD (retrieved from MEDLINE search, July 1996 and examination of reference sections of these papers). It can be seen that plasma level monitoring was used in all studies. With carbamazepine, levels above 7 or 8 mg/l were generally associated with efficacy. With valproate, levels within the range 50–100 mg/l appear to be related to response. There are two exceptions to these general observations. Stuppaecck et al (1990) noted that a mean level of 5.7 mg/l carbamazepine gave an 80% response rate in their cohort, but it is noteworthy that only seven of 25 patients had true BAD. Jacobsen (1993) showed that low levels of valproate (mean 32.5 mg/l) produced a sustained response in patients with milder forms of BAD and other disorders.

The doses of carbamazepine used were somewhat higher than those recommended by the BNF: mean daily doses ranged from 614 mg to 1400 mg. Indeed, in practices where a target plasma level of 7–12 mg/l is used, daily doses average 1000 mg (Gerner & Stanton, 1992).

With the exception of the Jacobsen study, patients in valproate trials usually received doses considerably in excess of 750 mg/day. In a selection of smaller trials reviewed by McElroy and co-workers (1992), valproate doses were of a similar magnitude and the authors felt strongly that 50 mg/l was the threshold plasma level for response.

The heterogeneity of the studies, subjects and conditions described in Table 1 makes any meaningful conclusion difficult. In addition, few of these trials attempted to discover the minimum plasma level or dose necessary for efficacy. Nevertheless, one can conclude that plasma levels of above 7 mg/l are robustly associated with response to carbamazepine, corresponding to daily doses of above 600 mg. For valproate, plasma levels above 50 mg/l appear to produce acceptable efficacy. These levels correspond to doses of 750 mg/day or (much) greater. It is interesting to note that, in the United States, where valproate (as divalproex) is licensed for the treatment of BAD, an initial dose of 750 mg/day is recommended, followed by titration to give a plasma level of between 50 and 125 mg/l. As if to confirm this, advertisements for divalproex state that 90% of patients in trials were treated with doses above 1000 mg/day.

These findings have important implications for prescribers. In the absence of data supporting the use of low doses or low plasma levels, the doses and plasma levels recommended here should be aimed for. This means that if our informal observations are a true reflection of prescribing practice, wholesale change in practice is called for.
Table 1. Dose details in trials of carbamazepine/valproate in bipolar affective disorder

| Study                  | n  | Condition                              | Design                        | Outcome                                    | Level details                        | Dose details             |
|------------------------|----|----------------------------------------|-------------------------------|--------------------------------------------|---------------------------------------|--------------------------|
| Carbamazepine          |    |                                        |                               |                                            |                                       |                          |
| Placidi et al. 1986    | 83 | Prophylactic and acute treatment of BAD| Double-blind over 3 years    | CBZ=U                                      | Target level was 7-12 mg/l             | Not given                |
| Lerner et al. 1987     | 34 | Acute mania                            | Double-blind over 4 weeks    | CBZ=U                                      | Target level was 8-12 mg/l             | Median daily dose 1400 mg|
| Joyce, 1988            | 18 | Rapid cycling                          | Open, over 6 months          | 7 showed improvement                       | Target level used but not stated      | No summary details given |
| Luznati et al. 1988     | 54 | Prophylactic and acute treatment of BAD| Double-blind over up to one year | CBZ=U                                      | Responders mean levels=8 mg/l          | Not given                |
| Frankenburg, 1988      |    |                                        | Retrospective over 3-4 years | Only 2 cases of good long term response   | All pts had levels > 8 mg/l            | Not given                |
| Okuma et al. 1990      | 105| Acute mania                            | Double-blind over 4 weeks    | CBZ=U                                      | Mean level was 7.5 mg/l                | Mean daily dose was 614 mg|
| Stuppaock et al. 1990  | 24 | Prophylaxis of 'mood disorders'        | Open, naturalistic over mean of 20.2 mths weeks | 80% improved                              | Mean level was 5.7 mg/l                | Daily doses generally 600/800 mg |
| Small et al. 1991      | 52 | Mania                                  | Double-blind over 8 weeks (2 yr follow up) | CBZ=U                                      | Mean level 8.7 mg/l at week 8          | Mean daily dose 1036 mg at week 8 |
| Valproate              |    |                                        |                               |                                            |                                       |                          |
| Brown, 1989            | 405| Manic depressive illness                | Open, community-based        | Response rate over 60% for BAD             | Target level was 50-100 mg/l           | Mean daily dose was 1200 mg |
| Calabrese et al. 1990  | 55 | Rapid cycling                          | Open, naturalistic over 7.8 months over 21 days | Marked acute/prophylactic response Valproate >> placebo | Mean level was 84 mg/l                | Mean dose was 1686 mg daily |
| Pape, 1991             | 36 | Acute mania                            | Open, naturalistic over 15.8 months over 21 days | Marked acute/prophylactic response Valproate >> placebo | Mean level was 81 mg/l                | Mean dose was 750 mg daily |
| Calabrese et al. 1992  | 78 | Rapid cycling                          | Open, naturalistic over      | 79% reported sustained response            | mean level was 32.6 mg/l               | Mean dose was 1498 mg daily |
| Jacobsen, 1993         | 33 | Cyclothymia, bipolar II, mild rapid cycling|                      |                                            | Mean level was 32.6 mg/l               | Mean dose was 351 mg daily |
| Bowden et al. 1994     | 179| Acute mania                            | Divalproex vs lithium vs placebo - 21 days | Divalproex-lithium >> placebo              | Mean on day 21=93 mg/l                 | Mean dose was 2000 mg daily (day 18) |
| Bowden et al. 1996     | 65 | Acute mania                            | Relationship of plasma levels to efficacy/toxicity | Divalproex-lithium >> placebo | Efficacy at > 45 mg/l; toxicity at > 125 mg/l | All received 1000 mg daily by day 5 |

CBZ, Carbamazepine; Li, Lithium; a=b, efficacy not statistically different; a>>b, treatment a significantly more effective than b.
Recommendations

Carbamazepine – aim for plasma level > 7 mg/l (> 600 mg/day). Start at 200 mg BD; use modified release tablets; increase slowly.

Valproate – aim for plasma level of > 50 mg/l (> 750 mg/day). Start at 500 mg OD; use modified release tablets; increase slowly.

All samples for plasma levels should be taken immediately before the next scheduled dose.

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