Cortical excitability during prolonged antiepileptic drug treatment and drug withdrawal

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Abstract

Objective: Previous reports characterized the effects of administration of single oral doses of antiepileptic drugs (AED) on cortical excitability. However, AED effects on cortical excitability, and their relationship to plasma blood levels, during chronic drug administration at therapeutic doses are not known. The objective of the study was to determine whether plasma blood levels during chronic administration at therapeutic doses would accurately predict changes in corticomotor excitability.

Methods: We used transcranial magnetic stimulation (TMS) to measure cortical excitability during 5 weeks administration of carbamazepine (CBZ) and lamotrigine (LTG), and subsequent AED withdrawal in 20 healthy volunteers. Data were analyzed using ANOVA\textsubscript{RM} and regression analysis.

Results: Resting motor thresholds (r-MT) increased with increasing total and free CBZ and LTG levels during drug administration, but not drug withdrawal. After acute AED withdrawal, r-MT elevation persisted in most individuals with CBZ despite undetectable plasma levels, compared to a rapid normalization with LTG. In contrast, acute drug withdrawal resulted in a transient decrease in r-MT in 3/10 individuals with CBZ and 2/10 with LTG.

Conclusions: Plasma levels provide information on motor cortical function during active treatment phases but not during AED withdrawal.

Significance: The transient decrease in r-MT associated with acute AED withdrawal could represent a physiological substrate contributing to AED withdrawal seizures.

Key words: Cortical excitability; Transcranial magnetic stimulation; Plasma blood levels; Antiepileptic drug treatment; Drug withdrawal

1. Introduction

Plasma blood levels, a standard clinical measure for tracking the therapeutic effects of antiepileptic drugs (AEDs), may not always provide direct information on cortical excitability. Drug levels usually measure total (protein-bound) drug in peripheral blood, and may not reflect the portion crossing the blood brain barrier that influences cortical function. The pharmacokinetic relation between oral dosage and drug blood level is not constant across patients, and can be affected by differences in absorption, protein binding, and biotransformation. These factors may vary over time within individuals. Moreover, the pharmacodynamic relationships between drug levels and actual effects are quite variable from person to person. Some patients may have good therapeutic effects without toxicity at low blood levels, while others may have little efficacy at toxic levels.

Transcranial magnetic stimulation (TMS) has been used to characterize motor cortex excitability changes associated with administration of AEDs (mostly single doses) in healthy volunteers (Chen et al., 1997; Rizzo et al., 2001;...
Ziemann et al., 1996). Na\(^{+}\) channel blockers such as carbamazepine (CBZ) and lamotrigine (LTG) lead to increased motor thresholds (Chen et al., 1997; Manganotti et al., 1999; Ziemann et al., 1996) while gabapentin (GBP), structurally related to GABA, increase intracortical inhibition and decrease intracortical facilitation (Rizzo et al., 2001; Ziemann et al., 1996). Unlike CBZ or LTG, GBP may increase GABAergic inhibitory potentials (Goldlust et al., 1995; Petroff et al., 1996), and/or decrease the L-type excitatory inward Ca\(^{2+}\) current (Stefani et al., 1998). One study evaluated the effects of up to 1 week administration of riluzole which led to an increase in short-latency intracortical inhibition (Schwenkreis et al., 2000). The applicability of these results to chronic drug therapy is very limited given known changes in the rate of metabolism, drug-induced changes in receptor density or efficiency of receptor coupling, and sensitization.

Additionally, the effects of abrupt AED withdrawal on cortical excitability are of particular interest, given the documented rebound exacerbation of seizures that occasionally follows (Duncan et al., 1988; Fernandez-Torre, 2001; Marciani et al., 1985; So and Gotman, 1990). Because of obvious ethical concerns in addressing this issue in a patient population, we studied changes in corticomotor excitability in a group of healthy volunteers undergoing a 5 week administration of the Na\(^{+}\) channel blockers CBZ and LTG (induction, steady state peak drug levels, and acute withdrawal). The objective of the study was to test the hypothesis that plasma blood levels during chronic administration at therapeutic doses would accurately predict changes in corticomotor excitability.

2. Methods

Twenty healthy normal volunteers aged 21–38 years (mean 28 yrs) were recruited. Ten subjects were assigned to each of two drugs, carbamazepine (CBZ) or lamotrigine (LTG). All subjects underwent the following drug intake schedule; (a) 100 mg CBZ twice a day for the initial 7 days, 200 mg twice a day for the next 7 days, 300 mg twice a day for 7 days, and 400 mg twice a day thereafter; (b) 25 mg LTG twice a day for 7 days, 50 mg twice a day for 7 days, 75 mg twice a day for 7 days, and 100 mg twice a day thereafter. Subjects who could not tolerate a given dose reverted to the next lower level. In our study, we used the most common clinical dosage schedules. Body weights of the subjects ranged between 53 and 89 kg. Dosages were 8–15 mg/kg for CBZ (800 mg/day) and 2–5 mg/kg for LTG (200 mg/day). All subjects stopped the AED abruptly after 5 weeks of drug intake (2 weeks at the highest dose).

We measured cortical excitability using TMS at baseline, during the AED induction period (days 3, 7, 10, 17), at the maximum dosage (days 24, 31), and 3, 6, and 12 half-lives after (days 35, 38, 44), and finally 3 weeks after abrupt drug withdrawal (day 54) (Fig. 1). Blood sampling for drug levels was obtained at each TMS study. Total and unbound drug levels were measured by membrane separation immunoassay, and CBZ-epoxide and LTG levels were measured using high pressure liquid chromatography. All subjects completed a drug adverse events profile and Beck depression inventory (Beck et al., 1961) at each study visit.

TMS indices obtained included resting motor threshold (r-MT), MEP amplitudes, intracortical inhibition (ICI) and facilitation (ICF). TMS was applied to the non-dominant hemisphere using two Magstim 200 stimulators connected via a Bistim module (Magstim Company, UK) and a figure of 8-shaped coil (7 cm wing diameter). Surface EMG was recorded (bandpass 10 Hz–2 kHz) from the first dorsal interosseus (FDI) muscle of the non-dominant hand using disposable Dantec surface EMG electrodes placed in a belly-tendon montage and data acquisition set (LabVIEW \textsuperscript{TM}, National Instruments Corp., USA). The raw signal was digitized at a rate of 5 kHz and stored on a personal computer for off-line analysis). The intersection of the two wings of the coil was placed tangentially to the scalp with the handle pointing backward and laterally at a 45° away from the midline in order to activate optimally the corticospinal pathways (Brasil-Neto et al., 1992). The coil was moved to determine the optimal position for eliciting motor evoked potential (MEP) of maximal amplitude in FDI and the position of the coil was marked on a well-fitting cap on the subject’s head with a soft tip pen to ensure consistent coil placement throughout the experiment.

The r-MT, tested in each experimental session, was defined as the minimum stimulator output to evoke a MEP of > 50 \mu V in at least 5 out of 10 consecutive trials (Chen et al., 1997; Ziemann et al., 1996). Peak-to-peak MEP amplitude was determined at a stimulus intensity of 100, 120, and 140%
(10 pulses of each) of the r-MT of the FDI muscle and averages were calculated for each intensity. The intertrial interval during TMS was 5 s. Paired stimuli were delivered at interstimulus intervals (ISIs) of 2 ms for ICI and 15 ms for ICF (10 pairs of stimuli for each ISI) (Chen et al., 1998; Kujirai et al., 1993; Ziemann et al., 1998a). The intensity of the conditioning stimulus was 70% of the r-MT of the FDI determined in each particular session. The intensity of the test stimulus was adjusted to produce MEPs of 1 mV peak-to-peak amplitude in the FDI in each session. Paired pulses at ISIs of 2 and 15 ms were delivered 5 s apart in a random order. The amplitude ratio of the mean conditioned MEP to unconditioned MEP was determined for each ISI.

The drug adverse events profile was assessed using 19 common side effects including unsteadiness, tiredness, headache, double/blurred vision, difficulty in concentration, shaky hands, dizziness, sleepiness, memory problem, disturbed sleep, restlessness, aggression, nervousness/agitation, depression, hair loss, skin reaction, upset stomach, trouble with mouth or gums, weight gain with scales from 1 to 4 for each. The drug adverse events profile and Beck depression inventory were measured at each visit.

Differences from baseline TMS measurements were compared to plasma drug levels (total, free and epoxide levels for CBZ, and total plasma level for LTG, respectively). Other clinical variables (adverse events profile and Beck depression inventory) were also compared to the TMS indices and plasma drug levels.

The protocol was approved by the Institutional Review Board of the National Institute of Neurological Disorders and Stroke, and informed consent was obtained. Subjects participating in this study were all healthy volunteers without a history of seizures and with normal EEG. To our knowledge, acute withdrawal of non-sedating AEDs does not increase the risk of seizures in non-epileptic normal subjects.

2.1. Statistical analysis

Repeated measures ANOVA (ANOVA RM) was used to compare the mean of TMS indices in each visit from each subject. Regression analysis was used to determine correlations between TMS indices and AED blood levels. Differences in MEP indices and clinical variables (drug adverse events profile and Beck depression inventory) from baseline at peak level and during withdrawal were also compared within each drug group using an analysis of variance with repeated measurements (ANOVARM). When the effects were significant, post-hoc comparisons of the mean values for each visit were made with the two-tailed Bonferroni-Dunn test. The significance level was set at $P < 0.05$ to allow a 5% risk of type I error.

3. Results

All subjects on CBZ completed the experiment at the full dose. Two subjects on LTG only reached 150 mg/day, one due to a drug rash and the other due to nonspecific CNS side effects. Peak total CBZ levels varied from 3.7 to 13.7 mg/dL (9.97 ± 3.23 mg/dL), free CBZ 0.9 to 3.6 mg/dL (2.34 ± 0.84 mg/dL), and epoxide level between 0.6 and 7.0 mg/dL (2.22 ± 1.83 mg/dL) during the drug intake. Peak LTG levels were between 2.0 and 6.3 mg/dL (3.57 ± 1.21 mg/dL).

3.1. Effects of chronic administration of CBZ

R-MT increased with increasing drug levels of total, free CBZ and epoxide ($P < 0.0001$). After acute drug withdrawal, r-MT remained elevated, slowly returning to baseline over several days, while drug levels dropped abruptly becoming undetectable (Fig. 2a). Total CBZ level
showed a positive linear relationship with elevation of r-MT during drug intake ($P < 0.0001$, $\hat{y} = 1.702 + 0.817x$, identified in 8/10 subjects), but not after drug withdrawal ($P = 0.095$). Free CBZ levels showed a similar linear relationship with r-MT elevation ($P < 0.0001$, $\hat{y} = 2.357 + 3.011x$), and epoxide levels showed borderline significance ($P = 0.051$, $\hat{y} = 5.352 + 1.361x$) during drug intake.

ICI correlated with increasing total CBZ level ($P = 0.042$, $\hat{y} = 0.566 - 0.016x$). ICF decreased with increasing CBZ dose, showing a similar negative relationship with total CBZ level ($P = 0.022$, $\hat{y} = 1.623 - 0.031x$). Inhibition showed a non-significant trend to increase with r-MT elevation ($P = 0.084$) (Fig. 2b), but there was no significant relationship between ICF and r-MT changes ($P = 0.223$).

### 3.2. Effects of chronic administration of LTG

R-MT increased with increasing LTG levels ($P < 0.0001$) (Fig. 3a) and showed a positive linear relationship during drug administration ($P < 0.0001$, $\hat{y} = 0.548 + 1.646x$,
detected in 8/10 subjects), but not after acute drug withdrawal ($P = 0.095$). In contrast to CBZ, r-MT returned to baseline abruptly after LTG levels became undetectable ($P < 0.05$). In contrast to CBZ, r-MT returned to baseline abruptly after LTG levels became undetectable (Fig. 3a). ICI increased with increasing LTG levels showing a negative relationship between ICI and LTG ($P = 0.017$, $\beta = 0.597 - 0.041x$), but there was no correlation between ICF and LTG levels ($P = 0.585$). Inhibition showed a non-significant trend to increase with r-MT elevation ($P = 0.060$) (Fig. 3b), but there was no significant relationship between ICF and r-MT changes ($P = 0.818$). MEP amplitudes were not affected by chronic administration of either drug.

### 3.3. Effects of acute drug withdrawal

Acute drug withdrawal resulted in different effects across subjects. R-MT remained elevated despite undetectable blood levels in 7/10 subjects taking CBZ (Fig. 4a, and c), but only in two subjects on LTG (Fig. 4b). Surprisingly, r-MT fell to subnormal levels before returning to baseline in 3/10 subjects after CBZ withdrawal (example in Fig. 4d) and 2/10 after stopping LTG. There was no consistent change of ICI or ICF after drug withdrawal.

### 3.4. Side effects

Drug side effects increased with increasing drug levels and with elevation of r-MT both on CBZ (Fig. 5a) and LTG (Fig. 5b). In the CBZ group, drug side effects increased with increasing total and free CBZ levels ($P < 0.0001$ for both, $\hat{y} = 1.250 + 0.609x$ and $\hat{y} = 1.495 + 2.342x$, respectively), but not epoxide level ($P = 0.090$). There was no correlation between side effects and ICI (0.073) or ICF ($P = 0.540$). In the LTG group, drug side effects showed a similar linear relationship with drug level ($P < 0.0001$, $\hat{y} = 0.212 + 1.348x$), ICI ($P = 0.030$, $\hat{y} = 3.563 - 3.041x$), but not with ICF ($P = 0.140$). The Beck depression inventory did not show a significant relation to TMS indices or plasma levels of either drug.

### 4. Discussion

This study found that r-MT was highly correlated with CBZ and LTG levels during chronic intake at therapeutic doses. However, when drugs were discontinued, there was a mismatch between falling AED plasma levels and cortical excitability in some of the subjects. Previous studies evaluated the effects of single oral AED doses on measures of corticmotor excitability in healthy volunteers. However, both pharmacokinetic and pharmacodynamic factors might differ during chronic as opposed to single dose administration, as well as drug withdrawal. This is, to our knowledge, the first report describing effects of acute withdrawal of commonly used AEDs after chronic administration on corticmotor excitability.

### 4.1. Effects of drugs on corticmotor excitability

Motor threshold, measured in each session in this investigation, provides information on cortical excitability, and is influenced by oral doses of drugs that block voltage-gated Na$^+$ channels (Boroojerdi et al., 2001; Mavroudakis et al., 1994; Ziemann et al., 1996). Recruitment curves, showing the sigmoid function of motor evoked potential amplitude to increasing TMS stimulus intensities, are influenced by multiple neurotransmitter systems (Boroojerdi et al., 2001; Devanne et al., 1997). Intracortical inhibition (ICI), the first subthreshold stimulus results in an IPSP in cortical neurons with relatively low threshold, leading to inhibition of EPSPs produced by the second, suprathreshold pulse (Ilic et al., 2002). GABAergic agents (Di Lazzaro et al., 2000; Ilic et al., 2002), dopamine agonists and norepinephrine (NE) antagonists enhance ICI; the GABA reuptake inhibitor tiagabine, dopamine antagonists and NE agonists reduce ICI. Intracortical facilitation (ICF) tests the excitability of neural structures that may differ from those of ICI.

Fig. 5. CBZ (a) and LTG (b)-induced side effects and differences of r-MT from the baseline. The elevation in r-MT increased with high adverse events profile ($P < 0.0001$). Symbols * and # indicate $P < 0.05$ in post-hoc testing for r-MT and adverse events profile. Error bars indicate standard errors of mean. Time axis as in the above figures.
4.2. Effects of administration of CBZ

CBZ and its 10,11-epoxycarbamazepine metabolite limit sustained high-frequency repetitive firing of action potentials by blocking neuronal membrane sodium channels (Macdonald, 1995; McLean and Macdonald, 1986). A single oral dose of CBZ in healthy volunteers increased r-MT without changing ICI or ICF (Ziemann et al., 1996), but 1 week of CBZ treatment in neuropathic pain patients did not change r-MT (Inghilleri et al., 2004). In another study, resting and active MTs increased progressively until the serum CBZ levels reached a steady state in 10 stroke patients with partial seizures (Turazzini et al., 2004). We found that the effects of CBZ on r-MT persisted during chronic administration at therapeutic doses. In addition, enhanced ICI and decreased ICF correlated with plasma levels. In a previous study in focal stroke patients, ICI and ICF showed no significant relationship with CBZ levels, but this was tested in only 3 patients (Turazzini et al., 2004). As intensities of conditioning stimulus (CS) varied across sessions, the observed increase in ICI might have been a consequence of less increase in ICI threshold compared to the increase in r-MT. There has been conflicting evidence about the influence of CS intensities on ICI or ICF. In a previous study, we showed that absolute CS intensities needed to elicit ICI and ICF were not related to MT across tested muscles (Chen et al., 1998). In another study, the values of test MEP area at 3 ms ISI showed U-shaped dependence on CS while the values of test MEP area at 13 ms ISI were augmented with increasing CS (Rollnik et al., 2001). At least for ICI, which followed a U-shape relationship with inhibition most marked in the midrange of stimulus intensities and less inhibition at higher or lower intensities, our finding that inhibition increased at higher plasma levels and at higher CS intensities is most likely a drug effect. It is possible that this effect is related to concentration-dependent NMDA receptor current blocking, accompanied by inhibition of glutamate release (Hasselmo, 1995; Lampe and Bigalke, 1990). Oral intake of NMDA-receptor blockers in healthy subjects also elicits a decrease in ICF and more prominent ICI (Ziemann et al., 1998b).

Direct effects of CBZ on GABAergic transmission are less likely (Inghilleri et al., 2004; Macdonald, 1995). In the withdrawal period, there was a mismatch between plasma levels and cortical excitability, particularly in subjects taking CBZ. It is uncertain why r-MT remained high in some subjects when plasma levels were undetectable, but rebounded below baseline in others. Differences in CBZ metabolism might play a role. CBZ level fell more slowly in a subject with persistent r-MT elevation (although persistent elevation was seen at visits 9 and 10 when CBZ levels were undetectable) than in one with overshoot depression (Fig. 4c and d). Another possible mechanism would be long-term changes in synaptic transmission or neurotransmitter receptors induced by chronic CBZ administration.

The rebound baseline undershoot could represent the neurophysiological correlate of withdrawal seizures during rapid AED taper (Duncan et al., 1988; Malow et al., 1993; Marks et al., 1991; Theodore et al., 1987). Psychiatric manifestations such as anxiety, irritability or even delirium have been reported during AED withdrawal as well (Ketter et al., 1994; Sironi et al., 1979). Our data indicate that in the withdrawal period, plasma levels may not be good indicators of cortical excitability.

4.3. Effects of administration of LTG

LTG, also a use-dependent inhibitor of voltage-gated Na⁺ channels, shows subtle but important differences with CBZ in receptor subunit affinity and electrophysiology (Kwan et al., 2001; Leach et al., 1995; Miller et al., 1986). LTG blocks glutamate-evoked bursts and inhibits sustained repetitive firing (Lees and Leach, 1993). Additionally, it may inhibit glutamate release via effects on Ca²⁺ currents (Kwan et al., 2001). Single oral doses of LTG in healthy volunteers increased r-MT without changing ICI or ICF (Manganotti et al., 1999; Tergau et al., 2003; Ziemann et al., 1996). In our study, chronic LTG administration elevated r-MT and enhanced ICI in correlation with increasing plasma levels. This finding may reflect the influence of chronic LTG administration on GABAergic function, as exemplified by the increased GABA-A receptor beta3 subunit gene expression identified in rat hippocampus (Wang et al., 2002), but there have been conflicting reports as well (Braga et al., 2002; Shiah et al., 2003). An additional consideration is the influence of LTG on Ca²⁺ channels; LTG produces dose-dependent inhibition of high-voltage activation Ca²⁺ currents (Stefani et al., 1996; Wang et al., 1998). In humans, magnetic resonance spectroscopy studies showed that LTG increased brain GABA levels after 4 weeks, but not after a single dose administration (Kuzniecky et al., 2002). Therefore, chronic administration of LTG may influence intracortical circuits through multiple mechanisms including GABAergic and Ca²⁺ channel-dependent modulation. In contrast to CBZ, LTG elicited a more gradual deepening in ICI with accumulating doses (Figs. 2b and 3b), possibly because LTG plasma levels rose steadily during drug administration while CBZ levels experienced a sharper and faster increase, followed by a milder slope in the initial drug induction period.

In a previous single dose study, recruitment curves were significantly depressed by LTG, without changes in ICI and ICF (Boroojerdi et al., 2001). In another study involving 2 months of CBZ treatment, there was no significant relationship between CBZ levels and MEP amplitudes (Turazzini et al., 2004). Our results now show that MEP amplitudes were not correlated with plasma drug levels after chronic CBZ administration. Inter session differences in stimulus intensities (determined relative to r-MT in each session) with chronic administration may explain the difference in results from the single dose study. Our finding
of enhanced ICI is probably due to chronic as opposed to single dose LTG administration.

During LTG withdrawal, persistence of elevated r-MT and rebound undershoot were less prominent compared to CBZ. Clinically, withdrawal seizures have not been reported with LTG.

4.4. Side effects

The finding that side effects increased both with decreased cortical excitability and increasing drug levels is consistent with clinical observations relating AED drug doses and toxicity.

In summary, we demonstrated that CBZ and LTG plasma levels predict changes in cortical excitability during chronic AED intake but not drug withdrawal, when patients are at greatest risk for seizures. In addition, we observed that CBZ and LTG decrease cortical excitability and increase inhibition during chronic AED administration, which implies that those drugs may contribute to therapeutic efficacy by multiple mechanisms. TMS measures may provide more reliable information on changes in cortical excitability during acute AED withdrawal, and help predict potential seizure exacerbation.

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References


