brief communications

Slow saccades and hypometria in anticonvulsant toxicity

Article abstract—We report a patient with abnormal saccades in association with anticonvulsant toxicity (phenytoin 27.5 μg/ml, phenobarbital 18.8 μg/ml). The patient looked toward visual targets either with multiple, small, hypometric saccades or with single slow saccades. These abnormalities resolved when anticonvulsant levels returned to therapeutic range. Thus, slow saccades may be clinical evidence of anticonvulsant toxicity.

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Phenytoin toxicity has been reported to cause a variety of ocular motor disorders: gaze-evoked nystagmus,[1-3] loss of oculocephalic and caloric responses,[4-8] impaired optokinetic responses,[9] total external ophthalmoplegia,[4-6] downbeat nystagmus,[10] and limited abduction.[11] Most of these reports were based on clinical observations, and accurate eye movement recordings were not made. Here, we document slow and hypometric saccades due to anticonvulsant intoxication.

Case report. A 55-year-old man with a history of chronic ethanol abuse was seen for evaluation of a cough. He took phenytoin, 300 mg daily, and phenobarbital, 90 mg daily, for a post-traumatic seizure disorder. Routine blood chemistries, including liver enzymes, protein, albumin, and magnesium, were normal. CT and EEG were normal. Because of phenytoin and phenobarbital blood levels of 2.6 and 5.2 μg/ml, respectively, drug doses were doubled to 600 mg of phenytoin daily and 180 mg of phenobarbital daily (figure 1, day 1). On day 5, he was started on isoniazid, 300 mg daily, and pyridoxine, 50 mg daily, because of a positive PPD skin test; sputum culture grew an acid-fast bacillus, subsequently identified as *Mycobacterium fortuitum*. Chest films were normal. On day 14, he was admitted because of alcohol intoxication (ethanol level, 46 mg/dl on admission), and the anticonvulsants were continued.

By day 19, he was ataxic and complained of blurred vision. He was mildly lethargic, but cooperative. Visual acuity was 20/30 OD and 20/40 OS without correction. He had a small exotropia that was long-standing. He also had difficulty initiating any voluntary eye movements in the horizontal or vertical planes to command. When given a target to look at, he would make a slow saccade after a prolonged latency. Saccadic hypometria was not evident at the bedside. Pursuit and vergence eye movements were absent; there was no nystagmus. Oculocephalic reflexes and responses to optokinetic tape were absent; caloric testing was not performed. Gait was wide-based and ataxic; there was mild dysmetria in the extremities. Sensation was decreased to all modalities in a distal distribution, and the ankle jerks were hypoactive. Neurologic examination was otherwise normal. Phenytoin and phenobarbital levels

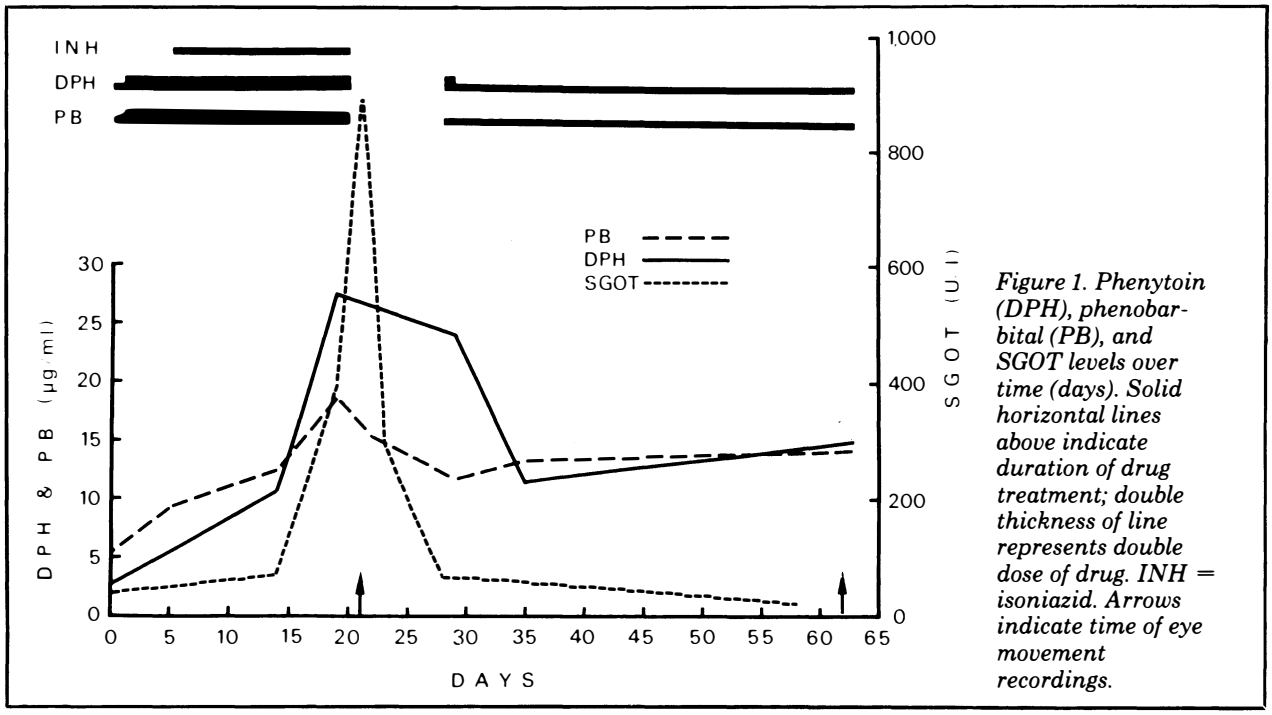

Figure 1. Phenytoin (DPH), phenobarbital (PB), and SGOT levels over time (days). Solid horizontal lines above indicate duration of drug treatment; double thickness of line represents double dose of drug. INH = isoniazid. Arrows indicate time of eye movement recordings.

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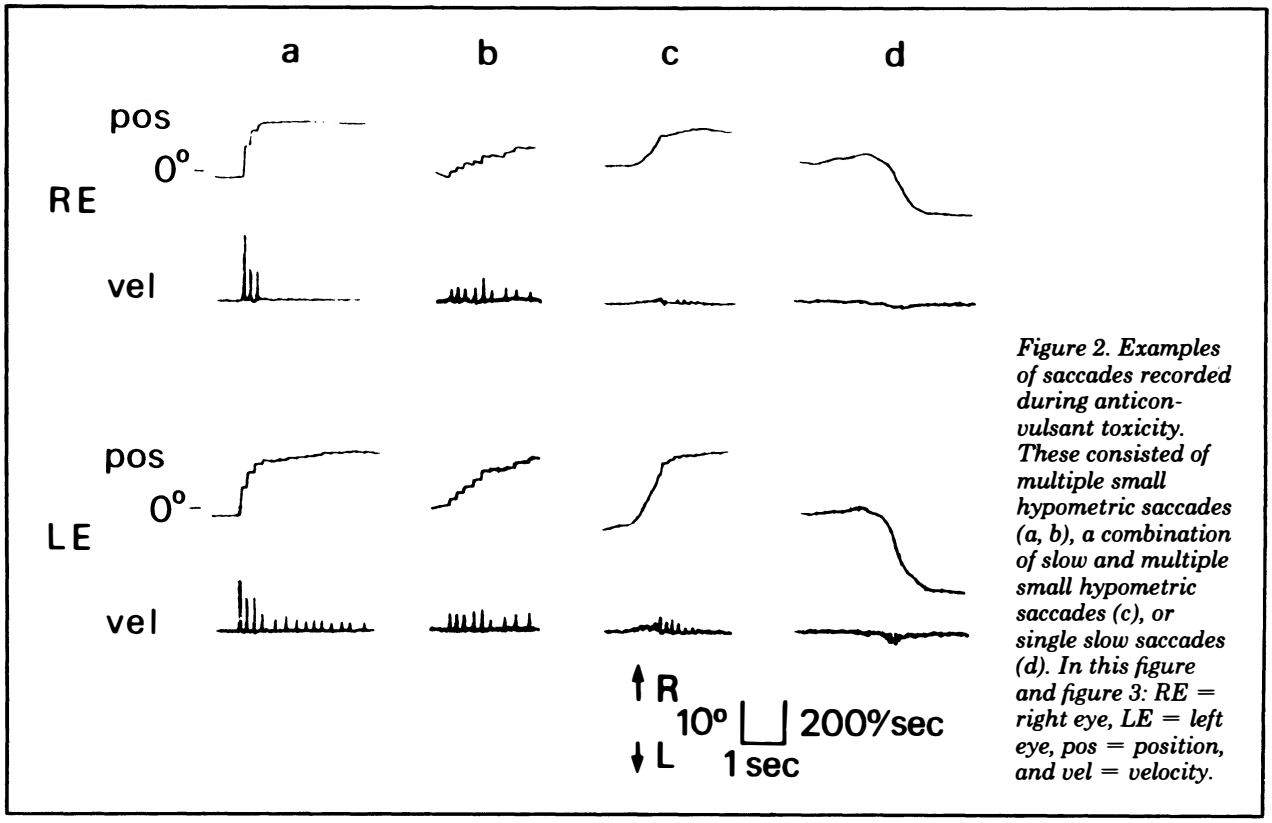

Figure 2. Examples of saccades recorded during anticonvulsant toxicity. These consisted of multiple small hypometric saccades (a, b), a combination of slow and multiple small hypometric saccades (c), or single slow saccades (d). In this figure and figure 3: RE = right eye, LE = left eye, pos = position, and vel = velocity.

were 27.5 and 18.8 μg/ml, respectively. The SGOT was 397 U/l. All medications were discontinued on day 20, and eye movements were recorded the next morning. Phenytoin and phenobarbital were restarted on day 28 at 300 mg and 90 mg daily, respectively; on day 62, with blood levels of phenytoin, 14.9 μg/ml, and phenobarbital, 14.1 μg/ml, eye movements were again recorded. At that time, the patient was asymptomatic, and his cerebellar findings had resolved. Clinically, his eye movement abnormalities had resolved except for minimal saccadic dysmetria and gaze-evoked nystagmus in the extremes of horizontal gaze.

Methods. Horizontal eye movements were recorded on days 21 and 62 (figure 1) using infrared oculography with a system bandwidth (position and velocity) of DC to 100 Hz and linearity of ±20° (Biometric Model 200 and rectilinear Beckman R612 Dynograph, both modified to achieve the above bandwidths). The patient was seated in a chair with head and chin stabilized at the center of a 1.5-m arc that contained red, light-emitting diodes as targets, and against which a hand-held pursuit target was moved. Vertical optokinetic stripes were rear-projected onto a screen placed immediately in front of the patient, filling his entire visual field. The vestibulo-ocular reflex (VOR) was tested by chair rotation.

Results. During eye movement recording on day 21, the patient showed a number of deficits of voluntary saccades (figure 2). These included slow saccades that were uniocularly orthometric and normal-velocity saccades that were hypometric. Most of the recorded saccades were very slow for their amplitude (figures 2 and 4). Some refixations, however, consisted of a "staircase" of many small hypometric saccades. The peak velocity-amplitude relationships of these small, hypometric saccades were normal (figure 4). Occasionally, in what appeared to be single slow refixational eye movements, a sequence of these very small hypometric saccades could be discerned with the aid of the velocity channel. Pursuit was absent, as was optokinetic nystagmus, although the patient described a sense of circular vection during the latter stimulation.

Eye-movement recording on day 62 revealed varied saccadic metrics including hypometria, orthometria, and hypermetria (figure 3). Peak velocity-amplitude relationships, however, had become normal (figure 4). Frequent square wave jerks (SWJ) and square wave oscillations (SWO)[13] were noted. Smooth pursuit was improved, but was disconjugate. With full-field stimulation, horizontal optokinetic nystagmus was present when the patient was asked to "follow the stripes," but not when he was asked to "look straight ahead." The gain of the VOR, evaluated with sinusoidal rotation at 0.25 Hz, was approximately 0.7 and symmetric. VOR suppression was normal.

Discussion. Slow saccades are a well-documented feature of several neurologic disorders,[14] including olivopontocerebellar atrophy, Huntington's disease,

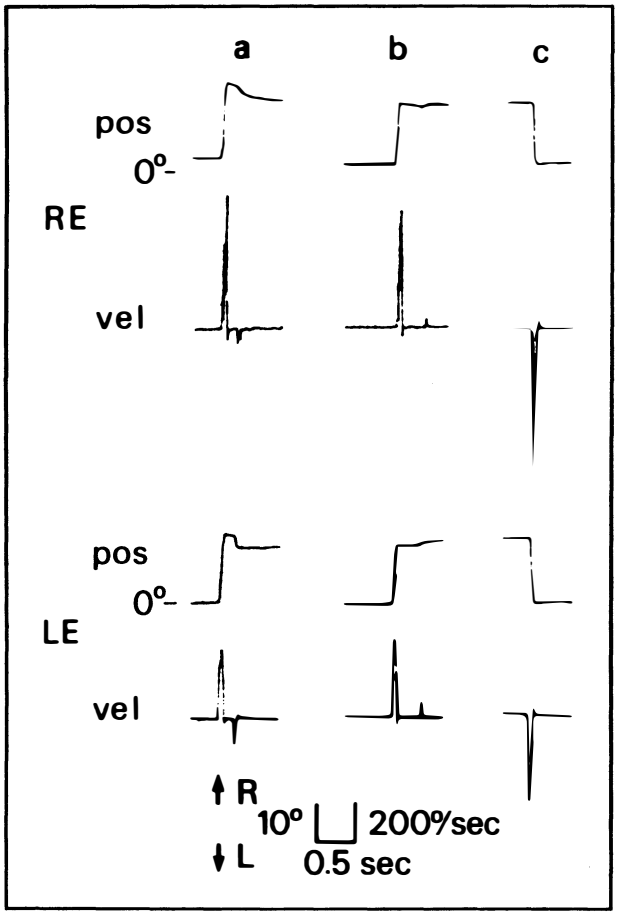

Figure 3. Example of saccades recorded while anticonvulsant levels were in therapeutic range. There was some hypermetria (a), as well as rare hypometria (b), but most saccades were orthometric (c). All saccades had normal peak velocities. Note different time scale.

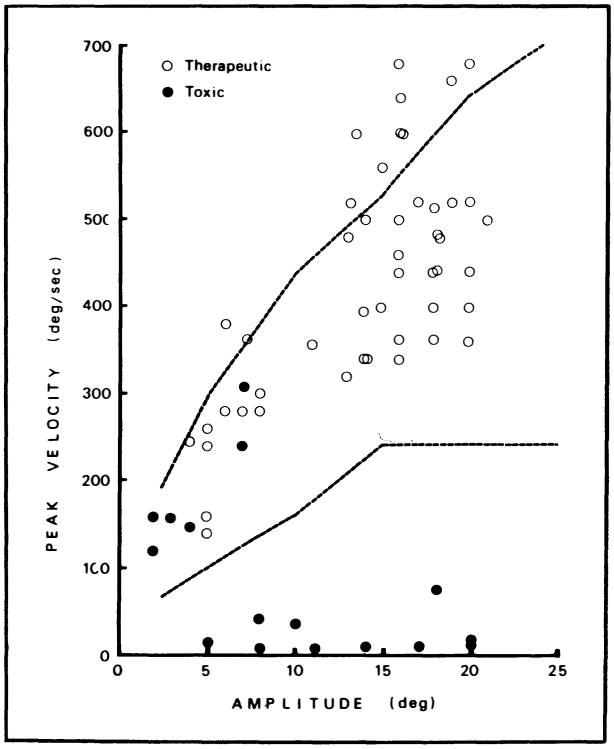

Figure 4. Peak velocity-amplitude relations of saccades recorded during anticonvulsant toxicity (filled circles) and while anticonvulsant levels were in therapeutic range (open circles). Dotted lines denote normal range (±2 SD) of an elderly population (age 59 to 87 years).[12] All filled circles falling within the normal range were hypometric. The remaining filled circles were orthometric, but slow.

Wilson's disease, ataxia-telangiectasia, lipid storage diseases, progressive supranuclear palsy, lesions of the pontine or mesencephalic reticular formation, internuclear ophthalmoplegia, peripheral nerve or ocular muscle lesions, and myasthenia gravis. Although a variety of disturbances of ocular motility have been described with anticonvulsant intoxications, slow saccades have not. Other drugs (eg, benzodiazepines) may produce mild slowing of saccades evident in quantitative eye movement recordings,[15-18] but clinically apparent slowing has not been reported.

Our patient developed symptoms and signs of slow eye movements in association with rising anticonvulsant levels and, in particular, with toxic phenytoin levels that were due to increased dose, better compliance in the hospital, and impaired hepatic function attributed to isoniazid. Free anticonvulsant levels were not measured. Although only the phenytoin level was toxic, phenobarbital may have contributed. Isoniazid, given with pyridoxine, and mild hepatic dysfunction are unlikely causes of abnormal ocular motility. When the phenytoin level returned to therapeutic range, saccadic velocity became normal and hypometria rare. However, hypermetria, SWJ, and SWO were then manifest, consistent with mild underlying cerebellar disease probably due to chronic alcohol exposure.

This case allows observation of the effect of anticonvulsant toxicity on several aspects of eye movement control. The trajectory of horizontal saccades reflects a tight relationship between saccadic amplitude and peak velocity that is determined by the burst cells in the pons.[19-21] Slow saccades in our patient suggest an anticonvulsant toxic effect on the burst cells or, perhaps, their inputs. The metrics (accuracy) of saccades are largely determined by the dorsal vermis of the cerebellum, lesions of which produce dysmetria, especially hypermetria.[22,23] Persistent hypometria is less well localized and may depend on the brainstem reticular formation or the cerebellum.

Jürgens et al[18] postulated that drug effects on the brainstem saccadic pulse generator might help resolve the issue of closed-loop versus open-loop saccadic control. An open-loop saccadic controller produces ballistic eye movements from motor commands that, once initiated, cannot be modified. This concept predicts that impaired burst cell dis-

charge would result in a hypometric saccade. On the other hand, a closed-loop saccadic controller continuously compares eye position during the saccade with desired final eye position. Only when the eye reaches the desired position would the burst cells stop discharging. A closed-loop concept would predict that even if burst cell discharge were impaired, the cells would continue to discharge until the eye was on target, producing a slow orthometric saccade. Our patient demonstrated abnormalities of both saccadic trajectory and metrics, suggesting that the question of closed-loop versus open-loop control of saccades cannot be settled by studying the effects of anticonvulsant drugs on eye movements.

The literature documents a variety of ocular motor effects of phenytoin (see above) and a variety of blood levels at which they occur. In one study of patients on therapeutic doses of phenytoin, there was no difference in saccadic peak velocity from normals.[24] However, complete external ophthalmoplegia of voluntary and reflex eye movements with levels as low as 36 μg/ml[6] and absent vestibular eye movements with levels as low as 25 μg/ml[7] have been reported. In our patient, saccadic abnormalities; absence of vestibular, pursuit, and vergence eye movements; and suppression of saccadic intrusions (SWJ) and oscillations (SWO) occurred with a phenytoin level of 27.5 μg/ml. There are two possible sites of these effects: central and peripheral. Spector et al[6] suggested a possible central role of phenytoin, either in the cerebellar system or in presumed GABA-mediated connections in the vestibulo-ocular system. Phenytoin has adverse effects on peripheral nerve and the neuromuscular junction,[25] but the possibility of peripheral ocular motor toxicity has not been explored. Although the pathophysiology of drug effects on saccadic eye movements is unknown and warrants further investigation, the fact that slow saccades may result from anticonvulsant toxicity is important information for the clinician.

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