Total external ophthalmoplegia induced by phenytoin

A case report

R. SANDYK

Summary

Total external ophthalmoplegia was observed in a patient following oral administration of phenytoin, although the state of consciousness was relatively unimpaired and the plasma phenytoin level was within the recommended therapeutic range. This report demonstrates the potency of phenytoin to act selectively on the vestibulo-ocular system. Recognition of such association may be important as regards further investigations aimed at excluding structural brainstem lesions.

Case report

A 34-year-old man had a history of grand mal seizures since 1978. Two weeks before presentation he was given phenytoin 300 mg daily and folic acid 5 mg daily.

On examination he was drowsy but fully co-operative. Examination of the cranial nerves revealed bilateral miotic pupils that reacted both directly and consensually to light. However, the eyes were in midposition, and optokinetic, oculocephalic and caloric stimulation were all unsuccessful in eliciting eye movements. In addition the patient was unable to move his eyes on command or to follow a moving object. Corneal reflexes were present bilaterally, and voluntary eye movements in a 20-year-old woman who had developed a total external ophthalmoplegia out of proportion to involvement of pupillary responses, other reflexes and level of consciousness.

Phenytoin was discontinued for 6 days and then reintroduced at a dosage of 200 mg daily. Within 48 hours of admission the patient's mental state had gradually improved; he became more alert and could answer questions correctly. However, the caloric and oculocephalic responses remained absent for the following 3 days. On the 5th day after admission caloric testing produced tonic conjugate deviation of the eyes towards the irrigated ear, but no nystagmus. On the 6th day after admission the patient was fully alert and co-operative and a normal caloric response could be elicited on the 8th day when the plasma phenytoin level was 37 mmol/l. The patient was discharged 10 days after admission, awake, alert, and able to tolerate the dosage of 200 mg daily.

Discussion

Total external ophthalmoplegia with impaired ocular movements in response to head rotation or flexion (oculocephalic reflex) or to ice-water stimulation of the ears (caloric response) has traditionally been used as an accurate indicator both of the depth of unconsciousness and of the absence or presence of structural brainstem lesions. Full conjugate excursion of the eyes elicited by either of these two stimuli in a comatose person generally indicates an intact brainstem at or below the level of the third nerve nucleus. The converse is also generally believed, i.e. lack of eye movement means that the cause of the unconsciousness is a primary or secondary parenchymal brainstem lesion. A remarkable feature of this case was the profound involvement of the oculomotor reflex function, out of proportion to the effects on other reflexes, such as the corneal and pupillary responses, and on the level of consciousness. It seems that phenytoin, even in normal dosages, can alter reflex eye movements so as to suggest a structural brainstem lesion. This effect of phenytoin has received scant attention in the literature. Orth et al. reported total external ophthalmoplegia in four patients who had been taking phenytoin in combination with primidone, alcohol and barbiturates, and Rosenberg et al. reported two patients with supratentorial lesions who had received phenytoin and experienced a reversible loss of calorically induced eye movements. Blair et al. described divergent strabismus and a gross deficiency of reflex and voluntary eye movements in a 20-year-old woman who had intentionally taken 12 g phenytoin and 15 g primidone. In all these cases, phenytoin was taken with other central nervous system depressants and it was therefore difficult to ascertain whether phenytoin alone was responsible. The patient in this report was taking only phenytoin, the blood level of which was within the accepted therapeutic range. Although oculomotor functions were severely impaired, the patient was conscious and relatively well oriented. With a fall in the blood phenytoin level, the restoration of vestibulo-ocular responsiveness lagged behind the return of mental responses which was surprising because patients with toxic and metabolic central nervous system depression usually retain oculo-vestibular reflex functions even when the brainstem is severely depressed.

It seems therefore that when phenytoin has been administered, oculomotor responses cannot serve as reliable indicators of the patient's level of consciousness, although this highly selective
action of phenytoin is not well understood. There is evidence to suggest that the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) participates in the control of the oculovestibular system. Phenytoin has been shown to act on GABA in the cerebral cortex and the spinal cord, and it seems possible that it may act selectively on GABA action on the oculomotor and vestibular system causing a severe suppression of this system out of proportion to inhibition of other reflexes and mental functions. Recognition of this association may save a great amount of unnecessary investigations aimed at excluding structural brain-stem lesions.

REFERENCES

Nuus en Kommentaar/News and Comment

Propranolol as a spermicide

The use of 80 mg propranolol tablets as a vaginal spermicide may seem odd at first, but it has in fact been known for 10 years that propranolol, like other membrane-stabilizing drugs, inhibits sperm motility in vitro. Moreover, this effect is independent of the β-blocking activity, since the dextro form which is almost devoid of β-blocking properties is as effective a spermicide as the commonly used racemic form.

After animal studies had shown that propranolol applied topically to the vagina prevented conception, Zipper et al. (Br Med J 1983; 287: 1245) carried out a study on 198 fertile women in Santiago de Chile who wished to change from an intra-uterine contraceptive device to some other form of contraception. The women inserted a commercially available 80 mg tablet of racemic propranolol into the vagina each evening between menstrual periods over a period of 11 months. There were only 5 pregnancies instead of an expected 170 or so (the cumulative rate of conception 12 months after removal of an intra-uterine contraceptive device is 88,2/100 women as against 3,4/100 for the propranolol trial). The authors consider that this failure rate compares favourably with that of other methods of contraception.

In the same issue of the BMJ (p. 1247) Patel et al., a London group, report a study in 6 women of plasma levels of propranolol after intravaginal insertion of tablets. The study demonstrated that systemic bio-availability of the drug was even greater from the vagina than from the gastro-intestinal tract, probably because of lack of a first-pass effect through the liver. Systemic side-effects (reduction in blood pressure, heart rate, and forced expiratory volume), although significant, did not cause symptoms, and could be avoided by using the dextro form.

However, vaginal itching and discomfort were noted by some women in the Chilean trial, and the above reports can only be regarded as preliminary but very interesting.

Fundamental therapy

Clostridium difficile enterocolitis can pose considerable problems in treatment and management, particularly when it becomes recurrent. However, a new treatment just described by Schwan et al. from Sweden (Lancet 1983; ii: 845) may need some selling to prospective patients but at the same time restores faith in human nature by confirming that marriages still exist in which love, devotion and self-sacrifice are, even in this materialistic age, of paramount importance. Now read on.

A 65-year-old woman who had a long history of irritable colon also had diverticulosis and diverticulitis for which a partial colectomy was performed. A pre-operative course of neomycin and metronidazole was given, and 1 week postoperatively she was given co-trimoxazole for a chest infection. Shortly after this, she developed Cl. difficile enterocolitis which was treated successfully with vancomycin. However, when the vancomycin was stopped, her enterocolitis recurred, and this pattern went on for 4 months. As she could not carry on with vancomycin indefinitely, it was decided that the most hopeful line of treatment would be to try and restore a normal bowel flora, and it was also decided (the letter does not say by whom) that the best way of achieving this would be by infusing homologous faeces into the large bowel. At this stage the husband's help was enlisted, and he duly obliged by providing the fresh faeces which were processed into the form of enemas in an anaerobic cabinet, and subsequently infused into the patient rectally. This resulted in prompt and complete normalization of bowel function, and 9 months later the patient is still well.

The implications of this form of therapy will doubtless repay further investigation, but one advantage which stands out clearly is that the raw material used is considerably cheaper and more plentiful than vancomycin.