Cognitive and Neuropsychiatric Side Effects of Mefloquine

SIR: Mefloquine hydrochloride is often used as a prophylaxis for malaria. Rare cases of neuropsychiatric side effects have been reported with its use.[1–3]

Case Report

We document the neuropsychological functioning of a 52-year-old master's-educated woman with no psychiatric history who used mefloquine prophylactically once a week for 3 weeks (250 mg) prior to and during a trip to Africa and who acutely developed anxiety, paranoia, visual hallucinations, confusion, and depressive symptoms during her return flight. She was initially treated as an outpatient with olanzapine, lorazepam, fluoxetine, and trazodone. When she continued to show suicidal ideation, other neuropsychiatric symptoms, and cognitive disturbances 3 months after her last dose of mefloquine, she was hospitalized for inpatient psychiatric treatment. Laboratory and infectious disease workup showed mildly elevated TSH (7.04 μU/ml) with normal free T_3 and T_4, and was positive for past exposure to hepatitis A. Brain MRI showed no abnormalities. Medical history was noncontributory. She had previously used mefloquine as a prophylaxis intermittently for about 4 years with no adverse reactions. While hospitalized, she was treated with risperidone and paroxetine and showed improvement in mood symptoms and cognition over 4 days. After initially living with her daughter following discharge, she has returned to independent functioning.

During a brief neuropsychological evaluation on day 2 of her admission, she was alert and partially oriented, misstating her age and the city, time, date, and day of the week. Her affect was sad. She reported feeling depressed, afraid, confused, and tense. Test results revealed impaired attention and mental control difficulties, with slowed performance on overlearned tasks, inaccuracies in mentally manipulating information, and inability to alternate between counting by sixes and reciting the days of the week. Psychomotor speed was slowed. Performance on several tasks of executive functioning indicated difficulty with response set main tenance, verbal fluency, and judgment/problem solving. Her copy of a complex design showed significantly impaired visuospatial and constructional skills. On a verbal list learning test, she learned 10 of 12 words, but recalled only 3 of them after a 20-minute delay. Although she correctly endorsed 11 of the words with a recognition format, she made 7 false-positive errors.

Comment

This case is the first to carefully document the neuropsychological functioning of an individual with severe mefloquine side effects and demonstrates that mefloquine may produce deficits in orientation, attention, psychomotor speed, and executive, visuospatial, and verbal memory functioning, as well as mood and psychotic symptoms. The potential mechanism of the drug in causing these deficits is not entirely clear, although there is evidence that the neuropsychiatric side effects of mefloquine are a result of a central cholinergic syndrome,[3] which may also explain cognitive changes seen in the present case. Our patient's cognitive impairments were well beyond what would be expected based solely on her psychiatric symptoms and possible subclinical hypothyroidism. Although multiple factors may have contributed to her cognitive impairment, the temporal relationship between onset of her symptoms and mefloquine use suggests a high likelihood that mefloquine was the causal factor.

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Clonic Seizure Associated With High Clozapine Plasma Level

SIR: We report a case of clonic seizure accompanying clozapine treatment for schizophrenia.

Case Report

A 26-year-old Caucasian man (weight: 59 kg), treated for refractory schizophrenia (DSM-IV criteria) with clozapine (dosage: 600 mg/day) over a 6-week period, lost consciousness in the street and developed a clonic seizure (heart rate: 60 B/min, systolic blood pressure: 110 mm Hg). The EEG showed a postcritical profile, and the scan was normal. This patient did not suffer from other medical antecedents, such as previous convulsive episode, but had neonatal anoxia. However, he had been previously treated for aggressive behavior with valpromide, a prodrug of valproic acid, for 16 weeks; the dosage had been reduced gradually over 22 days and stopped 7 days before the convulsive episode. Clozapine and norclozapine levels, obtained just a few hours after the event, were 2,115 ng/ml and 630 ng/ml, respectively. The daily dose of clozapine was reduced to 300 mg, and to date (at 10-month follow-up) no more seizures have occurred. Clozapine and norclozapine levels, obtained at steady-state condition, were lowered to 820 ng/ml and 300 ng/ml, respectively.

Comment

Seizure is a dose-related side effect of clozapine treatment and is well documented. During low-dosage treatment (<300 mg/day) the risk is similar to that of other classic antipsychotic drugs (1%), but it increases significantly (to 4.4%) with higher doses (>600 mg/day).[1] EEG alterations have been observed in a retrospective study of 283 patients and revealed abnormalities in 61.5%.[2] Although reports exist of patients with extremely high clozapine or norclozapine plasma levels (up to 3,300 ng/ml over several months) who have not presented convulsions, concentrations above 1,300 ng/ml have correlated with higher risk of seizures.[3] Simpson et al.[4] have reported the occurrence of grand mal seizure in 2 patients related to high clozapine plasma levels, 1,313 ng/ml and 2,194 ng/ml, respectively. Seizures have been described after initiation of drugs like erythromycin, occurring probably by means of cytochrome c_1a_2 inhibition.[5]

This case report confirms the importance of clozapine drug monitoring to prevent side effects related to elevated concentrations.

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Intravenous Valproic Acid in the Treatment of Severe Catatonia

SIR: Catatonia is a neuropsychiatric syndrome, characterized by motor and behavioral symptoms, that occurs in many psychiatric and medical disorders. Lorazepam and ECT therapy are considered the treatments of first choice for catatonia; however, about 30% of patients do not respond to these interventions. The use of neuroleptics in patients with catatonia should be restricted because they bear an increased risk of inducing neuroleptic malignant syndrome in these patients and may worsen some catatonic symptoms.[1,2] Carbamazepine has been reported to resolve catatonic stupor in a single case study.[3]

In this letter, we report the successful treatment of a catatonic schizophrenic patient with intravenous valproate.

Case Report

M.T. is a 38-year-old man who had been diagnosed with catatonic schizophrenia at age 18. He required, on average, 10 admissions per year. The acute phases were characterized by motor excitement; impulsive aggression; groping; stereotypies; iterations; impulsive behaviors such as binge eating, pica, and public nudity and masturbation; grimacing; vocal utterances (screaming); negativism; and gegenhalten. Neurological and medical disorders had been excluded. In the short intervals between acute phases, he exhibited severe negative symptoms accompanied by mannerisms and bizarre behaviors. The patient had been treated unsuccessfully with typical and atypical neuroleptics during previous hospitalizations and had shown minimal sedation on up to 12 mg/day of lorazepam both orally and intravenously. His legal representative had not agreed to ECT treatment.

During the index admission, oral administration of medication had not been possible because the patient was unable to open his mouth or to swallow due to extreme rigidity, negativism, and gegenhalten. Because of the previous treatment

failures, we started a regimen of high-dose intravenous valproic acid monotherapy. On day 1, the patient received 4,000 mg/day of valproic acid, followed by a reduction of catatonic symptoms of 30% (measured by a systematic rating scale for catatonia[4]). On day 2, the patient received 3,000 mg/day of lorazepam followed by an additional 20% symptom reduction. On day 3, the dose was reduced to 2,500 mg/day, and on day 4, 1,800 mg/day were administered, resulting in a symptom reduction of 90%. The patient tolerated the treatment well and was finally able to take medication orally. He was maintained on 900 mg/day of valproate (plasma level 60 μg/l) and has not required any admissions for acute catatonic symptoms for 6 months.

Comment

This is the first report of successful intravenous valproic acid monotherapy in severe catatonic schizophrenia. We have since successfully treated 3 more cases with a similar regimen.

Although the etiology of the complex catatonic syndrome is not known, some symptoms have been associated with deficiency of gamma-aminobutyric acid (GABA).[5] Valproic acid increases central GABAergic transmission by inhibiting GABA catabolism, stimulation of GABA synthesis, and potentiation of postsynaptic GABAergic effects[6] and may thus lead to amelioration of catatonic symptoms. It would certainly be worthwhile to investigate the use of valproic acid in the acute and even prophylactic treatment of catatonia more systematically, as this agent may provide an effective and safe alternative in treatment nonresponders with a severe catatonic syndrome.

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5-Lipoxygenase (5-LOX) Promoter Polymorphism in Patients With Early-Onset and Late-Onset Alzheimer's Disease

SIR: Anti-inflammatory drugs are currently being considered for treatment of Alzheimer's disease; it is believed that although they may not cure the disease they could slow the progression or delay the onset of this devastating disorder.[1] The inflammatory enzyme 5-lipoxygenase (5-LOX), which is implicated in the pathobiology of asthma,[2] may also participate in the pathology of Alzheimer's disease.[3] It has been proposed that an overexpressed 5-LOX gene could significantly increase the brain's vulnerability to neurodegeneration.[4] The expression of this gene is diminished in individuals with a mutation in the core promoter of the gene 5-LOX (on chromosome 10q11.2); if such an individual suffers from asthma, the asthma will not respond well to the treatment with a 5-LOX-specific inhibitor.[2] Hence, we hypothesized[5] that 5-LOX promoter polymorphism could affect the onset of Alzheimer's disease and/or influence the response of Alzheimer's patients to treatment with anti-inflammatory 5-LOX inhibitors. To test this hypothesis, 5-LOX genotyping should be performed in a population of well-characterized Alzheimer's patients. The feasibility of such a study is demonstrated by results of the pilot study summarized below.

We obtained 34 DNA samples from the National Institute of Mental Health (NIMH) Center for Genetic Studies. These samples were from Alzheimer's patients with a known age of onset of the disease: early onset (before 62 years of age) and late onset (80 years and older); 17 samples were chosen randomly from each onset group. The samples were analyzed for tandem repeats of the Sp1-binding motif GGGCGG by using described techniques;[2] the wild type (+/+) and the mutations (–/+, heterozygous; –/–, homozygous) were assigned as suggested.[2]

There were 12/17 wild type individuals in the early-onset group and 10/17 wild type individuals in the late onset group (71% and 59%, respectively). The only homozygous mutation (44)[2] was found in the late-onset group. The sample size in this pilot study was too small to derive any statistical significance. However, the trend to a lower frequency of wild type 5-LOX in late-onset Alzheimer's is in line with the previously published hypothesis[5] proposing that the onset of Alzheimer's disease will be delayed in subjects with 5-LOX promoter mutations. Further studies are needed to test this hypothesis. This pilot study has established that about 35% of Alzheimer's patients have a

mutation in the 5-LOX promoter. Prompted by this observation and by previously identified pharmacogenetic association between 5-LOX promoter genotype and the response to anti-inflammatory treatment of asthma,[2] we now propose that 5-LOX polymorphism should be taken into consideration when the efficacy of anti-inflammatory drugs is tested for possible therapeutic benefits to Alzheimer's patients.

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Celecoxib- and Rofecoxib-Induced Delirium

SIR: Nonsteroidal anti-inflammatory drugs (NSAIDs) are well known to cause significant side effects, including delirium, particularly in older adults. The new cyclooxygenase-2 (COX-2) selective agents are generally considered to cause fewer gastrointestinal side effects and perhaps less renal dysfunction. We report delirium induced by both celecoxib and rofecoxib.

Case Report

An 81-year-old woman was prescribed celecoxib 100 mg/day. Over the next 2 weeks she developed confusion, disorientation, and auditory and visual hallucinations. She was seen in the emergency room where delirium was diagnosed, metabolic causes were ruled out, and the celecoxib was stopped. The symptoms resolved over several days. Six months later she was prescribed rofecoxib 12.5 mg but took only a few doses. After another 2 months she was encouraged to take rofecoxib regularly and began doing so. One month later, she was taken to the emergency room agitated, with visual hallucinations, and disoriented to person, place, and time. She was unable to complete a Mini-Mental State Examination and did not recognize her children. She was placed in restraints in the emergency room.

She suffered from several chronic conditions, including atrial fibrillation (for which she was prescribed sotalol, cilazapril, and furosemide) and hypothyroidism (levothyroxine), and she also took conjugated estrogen tablets (Premarin) and nizatidine.

Physical examination suggested no cause of the delirium other than rofecoxib. Chest X-ray, electrocardiogram, and basic laboratory data were normal. A CT scan of the head showed mild atrophy and periventricular leukoaraiosis. The only abnormal laboratory result was a TSH level of 25 μU/ml, which was confirmed by repeat testing. Her pharmacy reported that her thyroid supplement was dispensed at appropriate intervals for the number of tablets.

The rofecoxib was stopped, and over the next 2 days her delirium resolved. It is difficult to know if the hypothyroidism made her more vulnerable to delirium. Although her levothyroxine dose was increased on the second hospital day, this would not have cleared her delirium.

On follow-up 3 months later she was cognitively intact, with an MMSE of 27/30 and normal clock drawing.

Comment

This report demonstrates delirium induced by two COX-2 inhibitors. Delirium caused by nonselective NSAIDs has been documented.[1] In some cases, the putative mechanism was a link to the indolic moiety in certain NSAIDs.[1] Consistent with the serotonin hypothesis of delirium, the similarity of this moiety to serotonin was proposed as the reason why certain NSAIDs can cause delirium. Neither celecoxib nor rofecoxib has such moieties, leaving the mechanism in this case open to speculation. The role of COX-2 in the brain remains unknown, as does the effect of selective COX-2 inhibitors.[2] Interestingly, some studies have documented that nonselective NSAIDs worsen cognitive function in elderly people.[3,4]

This case illustrates the importance of several prescribing principles in geriatrics, including "Any drug can cause any side effect" and "Any new symptom should be considered to be due to a drug until proven otherwise."

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