Quinacrine-Induced Psychosis in a Pediatric Patient

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Quinacrine is considered the drug of choice by some for giardiasis, the most commonly diagnosed protozoal infection in the United States.[1] Quinacrine is associated with a cure rate of between 53% and 92%; the lower cure rate was found in young children who could not tolerate the medication.[1] Adverse effects associated with the use of quinacrine include headache, nausea, vomiting, and abdominal cramps.[2,3] Long-term administration may produce infrequent adverse effects such as central nervous system stimulation (restlessness, confusion, irritability, emotional change), urticaria, blood dyscrasias, and black and blue skin and nail pigmentation.[3] Seizures and transient toxic psychosis have been observed in adults following administration of only 50 to 100 mg of quinacrine three times per day for a few days.[3] We describe a case of transient psychosis in a child following 5 days of therapy with quinacrine, 100 mg three times daily.

Case Report

T.B. was an 11-year-old male patient who was taken to a Canadian hospital when he began having cramps and diarrhea shortly after drinking water from a river while on a family camping trip. *Giardia lamblia* was found in a stool specimen. Accordingly, the pediatrician prescribed quinacrine, 100 mg three times per day.

The patient returned home. Within 5 days, the patient began to display unusual behavior. At that time, the child's school telephoned his parents stating that he was screaming, kicking, and attempting to eat everything, including his milk card and a pin on the teacher's dress. The teacher reported that the child had displayed memory loss and an inability to concentrate. A sudden degeneration of his handwriting was also noted. An hour later the child was taken to the hospital. Although he seemed calmer at that time, he was admitted for observation.

At admission, the patient appeared hyperactive, but friendly and giddy. He began experiencing a hallucination, which he described as a man-sized pink moth attempting to enter his hospital room. He could perform only very simple addition, and his attention span was short. A physical examination of the patient was unremarkable, including that of cranial nerves, deep tendon reflexes, and coordination, which were all within normal limits. An electroencephalogram showed no abnormalities. Serum quinacrine levels were nondetectable. The patient's past medical history proved noncontributory, and psychiatric difficulties had never been encountered. The quinacrine was discontinued at that time.

When evaluated 5 days later, no further hallucinations had been noted. He did, however, seem more active and had difficulty falling asleep. His sleep gradually improved. At a return visit 1 month later, he appeared normal, but had minimal recall of the psychotic event. Psychological testing (including the Wechsler Intelligence Scale for children, the Bender reproduction test, the DAP [Draw a Person] test, and the Goodenough criterion) and interviews revealed average intelligence and some difficulty in hand-eye coordination. Insecurity, lack of self-confidence, restlessness, and hyperactivity had disrupted his school performance. The patient experienced no further elements of psychosis at follow-up and continued at his normal baseline behavior.

Discussion

Psychosis secondary to quinacrine ingestion is uncommon in the adult population and is even more rare in the pediatric population. In two studies of 30,000 and 7604 adult patients with malaria, the incidence of quinacrine-induced psychosis was estimated at 0.1% to 0.4%, respectively.[4,5] Only three pediatric patients with psychotic reactions secondary to administration of quinacrine have been described in the literature to date.[6–8] This case

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resembles other cases in that emotional lability, as well as agitation and hallucinations, was present.

Gaskill and Fitz-Hugh[4] described two types of psychiatric responses following quinacrine use in adults. The first type, affecting two thirds of patients, is characterized by a sudden increase in motor and psychomotor activity accompanied frequently by visual and auditory hallucinations, delusions, ideas of reference, and an affect of euphoria with expansiveness. The second, less common symptom complex begins insidiously with gradual clouding of the sensorium, disorientation, amnesia, withdrawal, bewilderment, and fearfulness. This pediatric patient experienced symptoms found in both types. His symptoms began acutely with visual hallucinations and aggressive behavior, which included screaming and kicking. He also experienced a clouded sensorium and disorientation and an inability to compute simple addition, which is characteristic of the second type of reaction. Pediatric patients apparently do not adhere to adult symptom patterns.

The total amount of quinacrine ingested before the onset of psychosis ranges from 300 mg to 2.1 g.[2,4–12] The lower end of the spectrum has been encountered in a pediatric patient.[8] The psychotic symptoms generally begin within the first week of therapy but may continue for up to 85 days.[2] The typical course, however, is the onset of psychosis by the 3rd to 6th day, with resolution within 6 to 8 days following drug discontinuation.[9,11] This patient's course, with onset by the 5th day of quinacrine administration and complete resolution within 1 month of discontinuing the drug, is consistent with previously published reports.

Pharmacokinetics for quinacrine remain ill defined, but quinacrine has been detectable in urine in significant amounts 2 months following discontinuation of the drug.[13] Children differ physiologically from adults. They have increased gastric and intestinal motility and increased enzyme capacity, which may predispose a child to unpredictable bioavailability and increased clearance, respectively.[14] How these pharmacokinetic properties will affect the incidence of quinacrine-induced psychosis in the pediatric population is unknown. One cannot necessarily predict that the duration of the reaction will be shortened because of increased clearance. Once the dopamine receptor undergoes sufficient stimulation to produce psychosis, effective drug levels may no longer be required. In an analogous fashion, pigmentation secondary to quinacrine ingestion was readily visible in five patients, even though a plasma quinacrine level was not detectable.[9] Like psychosis, this side effect may well be related to dopamine receptor stimulation, since dopamine is a precursor to melanin.

The exact mechanism underlying this psychotic reaction to quinacrine is unknown. Electroencephalographic studies, however, provided conclusive evidence that quinacrine acts as a stimulant to the central nervous system, affecting patients in a manner similar to that observed in those receiving high doses of amphetamines.[9] Amphetamines, too, have been associated with psychosis and may provide clues to the underlying mechanism explaining quinacrine's association with psychosis. Not all patients exposed to quinacrine develop psychosis, suggesting that a subpopulation predisposed to this reaction exists. Three genetic polymorphisms of drug metabolism have been identified that account for interindividual variability of some drugs.[15] A similar yet undefined phenotype may affect quinacrine pharmacokinetics, producing a metabolite with an affinity for dopamine receptors. It has been hypothesized that quinacrine's ability to inhibit cholinesterase and prostaglandin E and to promote liberation of malarial toxins is what underlies quinacrine's association with psychosis.[16–18] The definitive mechanism has not been identified.

Alternative therapy exists for the treatment of giardiasis. The efficacy of metronidazole has been shown to be equal to that of furazolidone and more effective than quinacrine.[19–21] Cure rates with metronidazole have been estimated at 95%.[22] Psychosis secondary to metronidazole has not been reported.

In acute onset of psychosis in a pediatric patient, quinacrine as a precipitating factor should be considered. More study is needed to elicit predisposing factors and mechanisms for this reaction.

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