Unexpected outcome (positive or negative) including adverse drug reactions

Quinacrine induced mood disturbance – the unmasking of bipolar affective disorder

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Summary

The authors report the case of a 20-year-old man who presented with a de novo episode of hypomania subsequent to the initiation of quinacrine for treatment resistant giardiasis. The hypomanic episode commenced some 20 days after the successful completion of a week long course of quinacrine 100 mg three times daily. The hypomanic episode was treated with olanzapine 10 mg daily. Two months subsequent to this, the patient developed a moderate depressive episode which was treated with escitalopram and olanzapine. One month after the resolution of the depressive episode, he once again presented with a hypomanic episode. The recurring episodes of discrete mood disturbance all occurred within 5 months of the commencement of quinacrine in an individual with no personal history of affective disorders.

BACKGROUND

Quinacrine was associated with the onset of recurrent discrete mood episodes in an individual with no prior history of mental illness. The pattern of episodes was consistent with diagnosis of bipolar affective disorder.

The case highlights this risk and acts as an important clinical reminder to ascertain a personal or family history of affective disorders before commencing quinacrine. It also highlights the need to be vigilant regarding any further episodes of mood disturbance which may occur in close temporal proximity to quinacrine ingestion.

CASE PRESENTATION

We report the case of a 20-year-old man who presented with a de novo episode of hypomania subsequent to the initiation of quinacrine for treatment resistant giardiasis. The patient presented initially to his general practitioner (GP) with a 7 day history of persistent loose stools and steatorrhea following his return from an 8 week holiday to Nepal. He described an increasing frequency of loose, foul-smelling stools with associated abdominal cramps and discomfort, bloating, mild nausea and a decreased appetite. He did not notice passing blood per rectum. His symptoms were associated with a 4 kg loss of weight since onset.

A stool sample identified the presence of giardia cysts enabling a diagnosis of giardiasis to be made.

He was treated with repeating courses of metronidazole at higher dosages and increasing duration but failed to demonstrate a therapeutic response. At this point he was commenced on quinacrine 100 mg three times a day for 1 week. He demonstrated a good therapeutic response to quinacrine and over the next 3 weeks had three negative stool samples for giardia cysts.

He was previously well with no medical or psychiatric history of note. He was not on any other medications and had no history of psychotropic medication use. He had

no history of illicit drug use or an alcohol or drug-related disorder. He drank approximately eight units of alcohol per sitting on four occasions per month. The family history was significant only for bipolar affective disorder in a paternal cousin.

He was currently an undergraduate university student who on his return from a working holiday in Nepal planned to recommence his undergraduate degree. He was described premorbidly as a pleasant and outgoing man who was diligent with regard to his work responsibilities and was well liked by friends and family.

Twenty days after the completion of the course of quinacrine he attended the GP accompanied, by his mother, and reported a change in his behaviour over the previous 5 days. He described sleep disturbance (only going to sleep for one hour in every 24 hours) with a pervasive level of overactivity and restlessness. This was accompanied by an alteration in his mood which he described as been 'as good as I have ever felt'. His mother reported that he was making contact with old school friends and making plans for a new business venture. His GP found him to be mildly dishevelled in appearance and was distractible and restless during the interview. He was disinhibited and somewhat overfamiliar. His speech was loquacious and pressured, though no flight of ideas were evident. His mood was subjectively described as 'brilliant' and objectively appeared to be hypomanic. There was evidence of heightened affective intensity, with hyper-arousal evident. He displayed over-optimistic ideation, exaggerated self-importance and grandiosity though this was not of delusional intensity. There were no overt psychotic features identified. His insight was preserved as he was able to attribute the symptoms to a change in himself which may have been related to a mental illness.

He was oriented to time, place and person. He was distractible but there was no deterioration in his level of consciousness.

INVESTIGATIONS

Physical examination was normal. Before treatment with quinacrine, he had six consecutive faecal stool cultures which were positive for *Giardia intestinalis*. Subsequent to treatment with quinacrine there were three faecal stool cultures which were negative for giardia cysts. Stool cultures were negative for *Shigella* species, *Salmonella* species and *Cryptosporidium* cysts.

The GP took bloods including full blood count, full blood chemistry profile and thyroid function tests which were all subsequently reported as normal.

The GP referred him urgently to the Crisis Resolution and Home Treatment team (CRHT) and he was seen and assessed later that day.

When seen by the CRHT, a urine toxicology screen was arranged and was negative for cannabinoids, benzodiazepines, opiates, amphetamines and cocaine.

Concurrent to the hypomanic episode he scored 23 on the Young Mania Rating Scale.¹ The Naranjo algorithm² which was constructed at the time of his presentation scored 6, indicating that the hypomanic event was a probable adverse drug event.

Concurrent to the depressive episode, he scored 28 on the Beck Depression Inventory-II,³ indicating an episode of depression of moderate intensity.

DIFFERENTIAL DIAGNOSIS

- Bipolar affective disorder (NOS)
- Bipolar affective disorder
- Substance induced hypomanic episode
- Bipolar affective disorder, current moderate depressive episode.

TREATMENT

The de novo episode of hypomania was treated with olanzapine 10 mg daily. The moderate depressive episode was treated with escitalopram 10 mg daily in combination with olanzapine 10 mg daily. The second episode of hypomania was treated with olanzapine 15 mg daily and escitalopram was discontinued. He was subsequently switched to quetiapine xr 300 mg daily and has been well maintained on this.

OUTCOME AND FOLLOW-UP

The patient has been well maintained on quetiapine xr 300 mg daily for 6 months with no recurrence of discrete mood episodes. He has tolerated quetiapine with no adverse effects evident and has remained physically well.

He continues to be followed up by the community mental health team with which he is in receipt of a continuing care program. He has received psychotherapeutic input in the form of cognitive behavioural therapy which has been focused on maintaining the patient's wellness.

The physical health and well being of the patient is monitored by his GP. He is screened with 4 monthly fasting glucose and lipid levels and regular monitoring of his weight and blood pressure. This frequency of monitoring is required as he is maintained on quetiapine which is an atypical antipsychotic.

DISCUSSION

Quinacrine is an effective antiprotozoal agent used in refractory cases of giardiasis, with most patients responding to a

single course of treatment.⁴ Studies have established that it has a clinical efficacy over 5–10 days of 95%⁵ in the treatment of giardiasis. It has also been used in the treatment of malaria and rheumatoid arthritis. There has been recent increased interest in quinacrine as a treatment in human prion disease. Although well tolerated in one observational study, quinacrine did not significantly alter the course of the disease.⁶

Quinacrine is known to be rapidly absorbed, to have extensive tissue distribution and an extended pharmacological half-life.⁷ There is documented evidence of quinacrine demonstrating extensive brain tissue penetration in animal studies⁸ and a previous case report which reported a case of toxic psychosis secondary to quinacrine use, hypothesised that it was due to quinacrine acting as a cortical stimulant.⁹

This case highlights the onset of de novo mood disturbance in an individual following the administration of quinacrine. It demonstrates the onset of an acute episode of hypomania and a subsequent pattern of recurring mood episodes in keeping with a diagnosis of bipolar affective disorder. There was a clear temporal relationship between the onset of the episode of hypomania and the use of quinacrine. The episode responded to treatment with olanzapine with a complete resolution of symptoms at 14 days. The patient met the criteria for a substance induced hypomanic episode. The symptom onset was within 21 days of the commencement of quinacrine in an individual with no history of an affective disorder. The symptoms did not precede the initiation of the quinacrine and abated some 2 weeks after the initiation of antipsychotic treatment. The occurrence of an episode of mania within 2 weeks of the commencement of quinacrine has been reported in one case study,¹⁰ but there is more extensive literature documenting the occurrence of acute quinacrine induced psychosis.

Quinacrine induced psychosis was found to have an incidence rate of 0.4% in one large study involving over 7500 patients with malaria.¹¹ A case series reported three cases of acute psychosis subsequent to quinacrine therapy and emphasised the broad clinical spectrum of neuropsychiatric manifestations associated with quinacrine. All cases had their onset within 8 days of therapy initiation and displayed a broad range of neuropsychiatric disturbances, from irritability, restlessness and insomnia to frank psychosis with disorganised thinking and perceptual abnormalities reported. All the patients in this case series had a rapid resolution of symptoms and there were no permanent sequelae noted.¹² A case of quinacrine induced psychosis has also been reported in a paediatric patient with common immune deficiency who presented with chronic giardiasis.¹³

There is a much more extensive literature on the neurotoxic side effects of the quinacrine related medication mefloquine. Mefloquine, though still prescribed today for the prophylaxis and treatment of malaria, has been consistently shown to have neuropsychiatric adverse effects.¹⁴ It has been shown to be associated with disabling neuropsychiatric side effects in 1:140 travelers taking mefloquine as prophylaxis.¹⁵ A Dutch case control study found a threefold increase in the incidence of psychiatric events with mefloquine use in over 500 travelers¹⁶ and a literature survey found that mefloquine use was causally associated

with three suicides.¹⁷ Mefloquine has been demonstrated to have an association with episodes of manic relapse in individuals with a history of bipolar disorder¹⁸ and has been associated in one case series with six episodes of acute psychosis.¹⁹

Learning points

- ▶ This case serves as a clinical reminder that quinacrine can be associated with episodes of hypomania, in addition to the more commonly described psychotic episodes.
- ▶ It highlights the risk of quinacrine triggering a discrete mood episode which precipitates recurring mood episodes consistent with a bipolar affective disorder pattern of mood disturbance.
- ▶ There is a need for physicians to be vigilant in ascertaining a personal or family history of affective disorders in individuals when prescribing quinacrine.

Competing interests None.

Patient consent Obtained.

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