

CASE REPORT

Doxycycline and suicidality

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SUMMARY

A case series outlining three young individuals with no history of mental disorder who were treated for skin conditions with doxycycline, but developed suicidal ideation with an outcome of suicide in two of the cases. One of these individuals had CYP2C19*2 heterozygote genotype associated with a diminished cytochrome p450 enzyme activity and two of his siblings had developed severe anxiety previously while on doxycycline. Another had previously developed mood difficulties on a lower dose of doxycycline which resolved after discontinuation. In the third individual, a discontinuation of doxycycline has led to the resolution of symptoms without the need for psychotropic medications.

BACKGROUND

Doxycycline is a tetracycline antibiotic that has been in use since 1967. It is used to treat urinary and respiratory tract infections, periodontitis, pelvic inflammatory disease, acne and other inflammatory skin conditions and as a prophylaxis against malaria.^{1 2}

The common adverse effects of doxycycline affect the gastrointestinal tract. Rarely side effects include hepatotoxicity, pancreatitis, blood disorders, photosensitivity, hypersensitivity reactions, headache and visual disturbances. Apart from anxiety no other psychiatric symptoms are listed as side effects in the British National Formulary.³ However, in the recent years, there are increasing reports of psychiatric adverse events including cases of suicide.⁴

The cases we report highlighted three individuals with no history of mental disorders who developed suicidality, with two completed suicides soon after the start of doxycycline.

CASE PRESENTATION**Case A**

This is the case of a 19-year-old man, the youngest of four siblings from a happy home, with a stable social life. He was easy-going and intelligent. Patient A had no history of mental disorder and no history of alcohol or substance misuse. He had an early childhood history of mild asthma, allergic rhinitis, giardiasis, hives and allergic reactions with a resultant swelling of his fingers and toes. The only family medical or mental history of note is that the patient A's eldest brother had reported severe anxiety symptoms after being started on doxycycline for malaria prophylaxis and another brother had developed similar symptoms on doxycycline for dermatitis which resolved after discontinuation of the medication.

Patient A developed perioral dermatitis and was started on doxycycline 50 mg twice daily 6 days prior to his death. He was not on any other medication. Four days after this, he went out socialising with friends and nothing unusual was noticed in his behaviour. On the night before his death, he engaged in sports with his friends.

Later in the evening, he had a discussion with his parents about his future and they indicated and thought he was spending too much time on Facebook and socialising. He accepted this and indicated he would limit his facebook usage in the next academic year to a set amount of time per day. His parents also had similar conversations with his brothers in relation to their academic courses. Patient may have been a little bit more quiet than usual but nothing untoward was noticed.

On the day of his death, he had a normal morning at home with his family and exchanged innocuous text messages with his friends. He sent a text 17 min before his death to his friend to bring some whites for him to the cricket match. He then sent a text to the girl he liked, which read 'wake up it's nearly midday'. Within 5 min of this text, he jumped off a building at his former school, which is located close to his family home. Neither his family nor his friends had noticed any warning signs, and no letter of intent to the possibility of a suicide has been discovered.

Following the death of patient A, the family came to an understanding that the medication prescribed in the cases of his older brothers aforementioned was possibly doxycycline.

In the autopsy report there was no alcohol or illicit substances detected in patient A's blood or vitreous humour. Genetic testing of patient A revealed CYP2C19*2 heterozygote genotype associated with diminished cytochrome p450 enzyme activity. However, there was no method available in the laboratory for the analysis of doxycycline in the body.

Case B

This is the case of a 33-year-old health professional in a stable relationship with her family including her sisters and mother. She had no history of mental disorder, alcohol or substance misuse. She has a history of mild acne for the last 9 years. She has no other medical history of note.

Following a recurrence of her acne, she was started on doxycycline 200 mg stat and then 100 mg once daily. The tablet gave effective relief for the acne. However, she developed nausea and headache on the second day of the treatment. There was a feeling of disinhibition in her interaction with others, which she found liberating.



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This quickly developed into instability in her mood, fluctuating rapidly between irritability, anxiety and low mood. She became withdrawn, detached and began to ruminate over minor occurrences. By the third day, she privately began to consider suicide as a solution to end her perceived problems.

Patient B continued taking doxycycline for the next few days and the suicidal ideation, including thoughts of crashing her car got worse. She stopped the treatment; she later attributed her stopping to luck. Ten days after discontinuation of doxycycline, her mental state had returned to normal without any treatment with psychotropic medication. She remains well 3 months after discontinuation of the medication.

Afterwards she analysed her circumstance with the help of family and friends to determine whether any occupational, family or social stressors could have precipitated or maintained the change in her mental state. None were identified.

Case C

Patient C was initially put on doxycycline for mild acne at the age of 18 years. He had no personal history of a mental disorder, and was on no other medication. His sister was being treated for social anxiety. He had completed mechanics pre-apprenticeship and was employed part time.

Patient C took doxycycline 50 mg/day over a period of a year. He felt unwell on it, and appeared 'down' at times, and walked out of a job he appeared to be enjoying. This led his mother to talk things through with him but without making a connection between his mood and his medication. He stopped the treatment in August 2011. His mood brightened. He resumed work and began saving for a holiday.

The patient restarted doxycycline in February 2012 as his acne had returned. At this point, he was apparently dispensed 100 mg medication in 50 mg packaging. He again began to have intermittent periods of low mood in the absence of any identifiable psychosocial stressors, which he reported to his mother. He again left his job. Eight weeks after restarting doxycycline and 2 days after leaving work he committed suicide by hanging.

OUTCOME AND FOLLOW-UP

Case A and C's outcome was death by suicide. Case B's mental state became stable 10 days after discontinuation of doxycycline and remained so 3 months afterwards.

DISCUSSION

The mechanism by which any drug may lead to suicide as an adverse event is unclear. Drugs that are associated with increased suicidal ideations are also associated with increased suicidal attempts or completions.⁵

Reviewing our cases using the Bradford Hill criteria for causation,⁶ there are a number of factors that point to a link between doxycycline and suicidality.

First, there was a temporal relationship between starting doxycycline and the onset of suicidal ideation/completed suicide. Buttressing this relationship, discontinuation of doxycycline led to symptom resolution in cases B and C and rechallenged led to a reoccurrence of symptoms in case C.

Second, there is also evidence for a biological gradient in case C, with suicide occurring on a higher dose than that which caused anxiety.

Third, there were no other identifiable factors that could have led to suicidality in the three cases.

Fourth is the evidence for biological plausibility in case A, given the family history of anxiety while on doxycycline. It was also revealed that case A had the CYP2C19*2 heterozygote

Table 1 Food and Drug Administration psychiatric adverse drug reporting for doxycycline

Symptom	Number of reports	Symptom	Number of reports
Aggression	003	Feeling of despair	003
Agitation	018	Inappropriate affect	001
Anger	002	Irritability	016
Anhedonia	001	Mood altered	004
Anxiety	043	Mood swings	006
Anxiety disorder	001	Nervousness	010
Apathy	004	Obsessive thoughts	001
Crying	003	Panic attacks	011
Depersonalisation	006	Panic disorder	001
Depressed mood	013	Panic reaction	002
Depression	047	Paranoia	001
Depressed symptoms	001	Personality change	001
Derealisation	006	Psychotic disorder	004
Dysthymic disorder	001	Self-injurious behaviour	015
Fatigue	067	Suicide attempt	016
Fear	004	Thinking abnormal	002
Feeling jittery	003	Total reports indicating a change in mental state	317

genotype associated with diminished cytochrome P450 enzyme activity. Whether this had a role in the outcome of patient A is not clear, given that it was not possible to analyse for doxycycline at the autopsy. Genetic testing for polymorphisms in CYP2C19 is increasingly available particularly for evaluating the metabolic process of clopidogrel prior to coronary arterial stenting, with a London Hospital becoming the UK's first hospital to launch bedside testing to identify polymorphism of the CYP2C19 gene in May 2012.⁷

Fifth, there is a consistency between these reports and adverse events reported to Food and Drug Administration (FDA). There have been 317 adverse reports indicating a change in mental state on the US FDA database⁴ (see table 1). Although only 16 of the 317 FDA reports are suicide attempts, the possibility of any of the other symptoms such as agitation, anxiety, depression, abnormal thinking and self-injurious behaviours leading to suicidality cannot be overlooked.

Learning points

- ▶ These cases highlight the need for further research into the biochemical basis underlying suicidality, so as to identify potential biochemical triggers.
- ▶ There may be need for monitoring the mental state in individuals on doxycycline who have a family history of adverse psychiatric reactions to doxycycline.
- ▶ In cases of the new-onset suicidality without other likely precipitants while on doxycycline, it may be advisable to withhold doxycycline and reassess as part of management.

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