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Medical Histories: A Case Report of Pharmacovigilance in Supporting Dentists and Participation in a Drug-Safety Program

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Abstract

Introduction—Antibiotics are a class of medications widely used by dentists. The class of agents has a number of listed side effects. This case report details an unusual adverse effect of tetracycline-induced psychosis recognized due to the diligence of a practitioner. To our knowledge, this is the first reported case by a dentist.

Case Presentation—A 44-year-old patient was started on tetracycline therapy for prophylaxis before a periodontal procedure. The patient began having paranoid and psychotic experiences. The patient sought psychiatric medical care and was diagnosed with tetracycline-induced psychosis. He was treated with an antipsychotic drug, which resolved his symptoms.

Conclusion—Dental medical histories are a resource that is underused and can often be of value in the continual assessment of drug safety and pharmacovigilance.

Keywords

Drug toxicity; pharmacovigilance; psychotic disorders; safety; tetracycline

Background

The Food and Drug Administration (FDA) constantly tries to balance the promotion of greater drug safety with a quicker drug-review process. The director of the Center for Drug Evaluation and Research, which now includes the Center for Biologics Evaluation and Research, oversees the balance of drug safety versus innovation through science. Dentists have traditionally not been included in this process. Drug utilization by dentists has not been determined by the pharmaceutical industry. However, the recent FDA opioid drug-safety initiative program¹ has shown that dentists contribute to the overprescribing of opioids, which led to stricter prescription patterns already in place in some states. The majority of dentists are not aware, nor do they participate in the FDA's MedWatch program² directed at drug safety. As more targeted drugs aimed at reducing drug-adverse effects are developed, the US drug safety net would require the participation of all prescribers, especially for the

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completeness of all electronic medical records. One example of dentists participating in this process was the reporting of osteonecrosis of the jaw.³ The medical histories dentists take are, for the most part, isolated and remain in their offices. Electronic dental records as part of the patient's electronic health record or electronic medical record under the broader banner of the electronic medical home will forever change how dentists record medical histories. An electronic dental record will be integrated into the patient's record and therefore require oversight or some level of quality assurance, much like a hospital record. This case report describes a dentist's (EHK) initiative to substantiate a medical finding before and during periodontal treatment.

Pharmacotherapy is playing an increasing role in the treatment and therapy for the management of oral conditions, notably periodontal disease. Although the dental pharmaceutical armamentarium is increasing, there is a concomitant wider use of conventional drugs, such as tetracycline. The tetracycline family of drugs consists of a number of altered chemical modifications to increase efficacy, distribution, and substantivity. As newer chemically-modified drugs become more specific for targeted therapy, the adverse effects become more subtle and more difficult to recognize unless further training in pharmacology is required.³ The current case report documents a case of tetracycline-induced psychosis observed by a periodontist during treatment of a patient and as followed using drug-safety procedures of pharmacovigilance. The patient was receiving routine treatment for chronic periodontal disease.

It is well documented that several classes of antibiotics have psychiatric adverse effects that range from minor confusion to psychosis.⁴ These classes include antibacterials, antimycobacterials, and antifungals. The term Hoigne syndrome⁵ is used to describe an acute non-allergic reaction to procaine penicillin, with predominant acute psychiatric symptomatology. The onset of symptoms in this syndrome can be abrupt. Typical disturbances of perception are auditory, visual, olfactory, gustatory, and/or somatosensory pseudohallucinations recognized by the patient as being unreal perceptions.⁶ The experience of anxiety parallels the onset of perceptual disturbances or may be conceived as a reaction to their extraordinary and dreadful nature.⁶ Perceptual disturbances and anxiety are accompanied by tachycardia, increase in blood pressure, feeling of breathlessness, numbness in the extremities, and psychomotor agitation.⁶ Occasionally, these symptoms may progress into a full-blown psychosis or delirium, with disorientation, true hallucinations (mostly visual), and, in rare cases, delusions.⁶

Tetracyclines have the ability to distribute widely throughout the body and into tissues and secretions.⁵ Inflammation of the meninges is not required for the passage of tetracyclines into the cerebrospinal fluid. Tetracyclines have also been reported to cause neuropsychiatric toxicity. The intent of this case report is to describe an actual delusion or psychotic event of a patient who was diagnosed with tetracycline-induced psychosis by a hospital known for its professional expertise in mental illness.

Clinical Presentation

A 44-year-old male patient presented to a private practice (EK), in Glastonbury, Connecticut, and was started on a tetracycline antibiotic for prophylaxis before a periodontal procedure. The patient had been on the tetracycline for ≈ 1 or 2 weeks before periodontal surgery. The patient did not have any previous documented psychiatric episodes. The case as described by the patient and recorded in his psychiatrist's medical record (psychiatrist unknown, The Institute of Living, West Hartford, Connecticut) was provided to the periodontist (EK). This is similar to a previously reported medical case⁵ in which a patient was being treated with amoxicillin.

Case Management

The psychiatrist reported that, before the event, the patient had been removing snow with a plow until $\approx 1:00$ am. The patient reported to the psychiatrist that the next day, when he was driving his car, he began to have experiences that were paranoid and psychotic in nature. The patient reported that he thought his wife was "standing on a corner with another guy," which was unexpected. He never had a thought like this previously and had a very visceral emotional reaction to it. He felt as though "his heart dropped into his stomach." The psychiatrist's medical record reports that, while still driving home, the patient heard a voice that he thought might be that of God telling him that he should move to Arizona, that there would be a spin out on an exit ramp, and that there was a dead animal below an underpass. He had irrational thoughts, such as thinking of the number three, which was confirmed by the configuration of certain light posts. These thoughts continued until he arrived home, at which time he saw that his wife was there. He tried to "fight the thoughts" but could not resist asking his wife about his suspicions. His wife became quite concerned and felt as if he were a "different person," and, although he was not overtly threatening to her, she felt concerned for her safety. He did not utter or speak any spontaneous noises. However, he did hear a voice telling him that, if his suspicions turned out to be true, he should hit himself in the head with a hammer. He did not act on any of these thoughts.

Clinical Outcomes

The patient reported to the psychiatrist that he reconciled with his wife that night. The next day he and his wife sought professional help. A counselor immediately said the patient should go to the hospital, where he was admitted for 2 days at a local institution (The Institute of Living, West Hartford, Connecticut), and was evaluated, diagnosed, and treated by a psychiatrist with the antipsychotic drug risperidone. His symptoms then resolved. He was diagnosed with a tetracycline-induced psychosis.

Discussion

Antibiotics, from penicillin to tetracycline, have been associated with neuropsychiatric toxicity ranging from 1% to 5%.⁵ Depression, insomnia, and irritability may emerge at higher doses of tetracycline, but the frequency of sudden events in the adult population taking any tetracycline is likely to be $\leq 1\%$.⁷ Minocycline is most often implicated in the genesis of tetracycline-induced neuro-psychiatric toxicity. Tetracyclines have been reported

to produce a neuromuscular blockade as a result of postsynaptic antagonism of acetylcholine.⁷ Because the symptoms can be abrupt, it has been suggested that the phenomenon of “kindling” may be the basis of the mechanism. Kindling has been defined as the appearance of physiologic and behavioral responses to repetition over time of a stimulus initially without effect.⁶ The administration of some pharmacologic agents may serve as a stimulus for the development of pharmacologic-induced kindling.⁸ Neurotransmitter processes associated with the mechanism of kindling may include the facilitation of excitatory *N*-methyl-D-aspartate receptors and a reduction in the inhibitory activity of γ -aminobutyric acid transmission.⁹

Drug safety is an ongoing concern for as long as the drug is on the market. The responses to a drug range from the complexity of pharmacogenetics to a simple food–effect response. The difficulty may be in identifying the cause of a side effect. That is the basis for pharmacovigilance of a drug, and it is the responsibility of every prescriber to note and report any unusual drug response. This case report is an example of post-marketing drug surveillance and pharmacovigilance of a widely used antibiotic through which the drug-safety database can be updated to educate and alert subsequent prescribers as to the potential effect. Patient histories can be viewed as vital statistics and, when incorporated into the electronic health record, can be cost effective as the nation struggles to contain health care costs. Dentists are a national resource to expand the drug safety net to monitor and report drug side effects.

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Summary

Why is this case new information?

- To the best of our knowledge, this is the first reported case by a dentist of unusual side effects of an antibiotic.
- Demonstration of a dentist's awareness of psychiatric conditions
- Demonstrates that dentists can participate in pharmacovigilance and/ or drug-safety programs

What are the keys to successful management of this case?

- Comprehensive patient medical history
- Dentists' knowledge of their patients' medical history
- Dentists' follow-up on patients' medication history

What are the primary limitations to success in this case?

- Lack of patient follow-up
- Lack of patient motivation and compliance
- Lack of financial resources