CASE REPORT

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Death as a Result of an Adverse Reaction from Nalidixic Acid

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ABSTRACT: This article reports a death occurring in an apparently healthy, 27-year-old male as a consequence of an adverse reaction to a common urinary tract antibiotic (nalidixic acid). The deceased had cardiac enlargement at autopsy. The clinical presentation before his sudden death coincides with the occurrence of seizures and psychotic reaction as an adverse reaction to the injection of the drug, rather than merely a result of cardiac symptoms.

KEYWORDS: toxicology, nalidixic acid, death

Nalidixic acid (NegGram®) is an oral antibacterial agent used to treat urinary tract infections. Uncommonly, various adverse reactions such as dermatosis, hematological alterations, and nervous system changes have been reported [*1*]. These reactions are usually reversible when the drug administration is terminated. The following case report involves unsupervised ingestion of nalidixic acid in an adult with a subsequent fatal central nervous system reaction.

Case Report

A 27-year-old white male was found dead on the ground outside his trailer. According to a witness, he had been yelling for several hours. Later, he was observed lying on the ground outside, moaning, foaming at the mouth, and waving his arms. The furniture and belongings inside the trailer were in disarray. Blood was noted in the trailer in several places. The porch rail was broken. The man was divorced, unemployed, and had no known medical history. A drug-related death was anticipated based on the scene evidence and the preterminal behavior of the victim observed by witnesses. The possibility that the observed preterminal activity of the victim was a seizure was considered.

At autopsy, the deceased was observed to be a muscular, white male, measuring 188 cm (6 ft, 2 in.) and weighing 93 kg (205 lbs). Multiple insignificant abrasions and contusions

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were noted over the pretibial surfaces and arms. A 12.7- by 12.7-mm (1/2- by 1/2-in.) contusion was noted in the left frontoparietal scalp. An abrasion was noted over the left eyebrow. The injuries were considered insufficient to cause death.

On internal examination, there was diffuse, nonspecific organ congestion. The brain showed mild swelling with a dusky appearance and weighed 1550 g. The heart was enlarged and weighed 420 g. The cardiac ventricles were widely dilated and there was hypertrophy of the left ventricle with the free wall measuring up to 1.5 cm. The myocardial muscle appeared firm in consistency and red-brown in color. The gastric contents included 200 mL of tan-white liquid including a very fine sedimentary material, and food solids resembling kidney beans. No capsular material was present. There were no other significant gross findings.

Microscopic examination revealed diffuse congestion. Chronic portal inflammation was noted in the liver. Sections of the myocardium, including the conduction system, revealed intramuscular arteriolarsclerosis and eosinophillic changes in the myocardial fibers. Vacuolization of the fibers was also noted. No inflammatory cells were noted in the myocardium.

Toxicologic examination of the blood, urine, and gastric contents was negative for alcohol, organic bases, organic neutrals, opiates, cocaine, amphetamines, and barbituates. With these unexpected negative findings, the sedimentary material from the stomach was examined further. After repeated centrifugation and resuspension in water, the material was examined under a microscope. The material, definitely not of food origin, displayed a finely needled crystalline structure that was not identifiable but may have been a medicinal filler. With a clear indication of a foreign substance present, chemical analysis was continued.

Screening of the gastric contents for organic acids revealed a positive ultraviolet absorption in 0.45*N* sodium hydroxide at 258 and 335 nm. Analysis of this fraction by gas chromatography-mass spectroscopy (GC/MS) indicated a single component having poor gas chromatographic properties with a molecular weight of 232 *m/e*.

A search of mass spectral tables proved unrewarding, but a likely candidate was found in a table of ultraviolet absorbances. Nalidixic acid, $C_{12}H_{12}N_2O_3$, molecular weight (MW) 232, ultraviolet (UV) maxima 259, 338 nm (Fig. 1) would be likely to fragment via loss of carbon dioxide (*m/e* 44) to yield a mass spectral value of *m/e* 188 consistent with the most intense fragment of the unknown.

A known sample of nalidixic acid was obtained. The drug produced ultraviolet, gas chromatographic, and mass spectra identical to the unknown gastric content. Quantitative analysis of blood, urine, and gastric content was done by ultraviolet spectroscopy. The analytical equipment was a Beckman Model 35 UV-VIS spectrometer and a Hewlett Packard HP-5996 GC/MS computer system with a 50-mm SE-30 capillary column. The results for nalidixic acid were: blood, 0.50 mg/100 mL; urine, 44.5 mg/100 mL; and gastric, 1.05 g. The ultraviolet, gas, and mass spectra of nalidixic acid are in Figs. 2, 3, and 4.

After consideration of the autopsy and toxicologic findings in the context of the scene history, the immediate cause of death was determined to be adverse drug reaction to nalidixic acid. Cardiomyopathy was determined to be another significant condition.

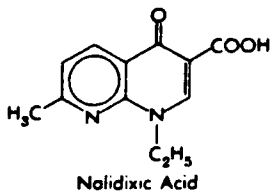

FIG. 1—*Nalidixic acid.*

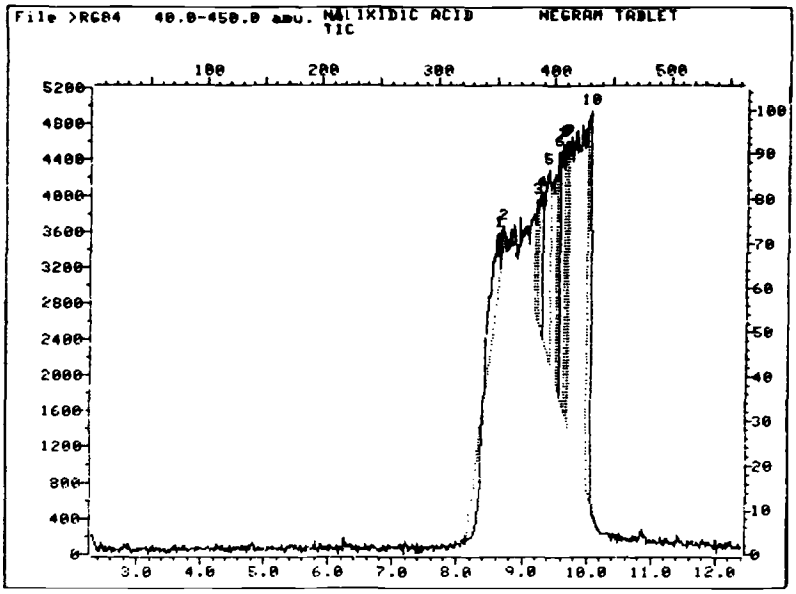

FIG. 2—*Ultraviolet spectrum of nalidixic acid.*

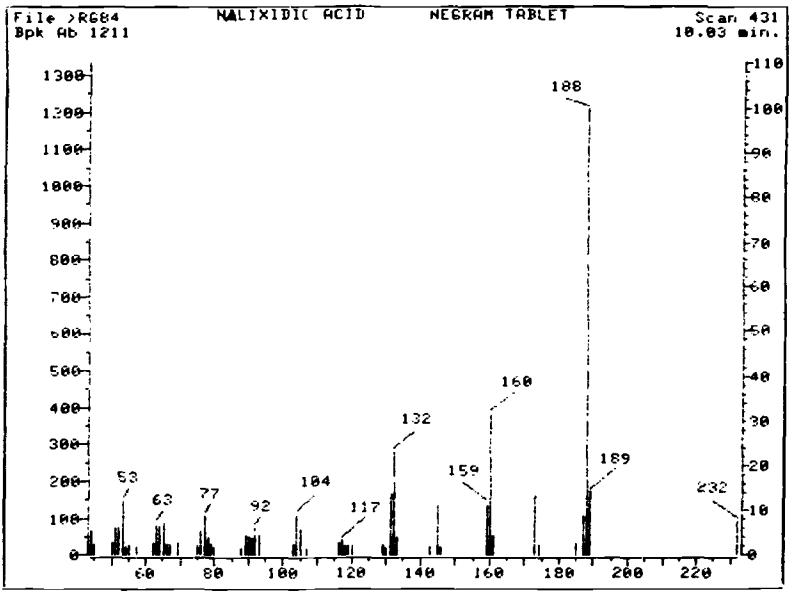

FIG. 3—*Gas chromatographic spectrum of nalidixic acid.*

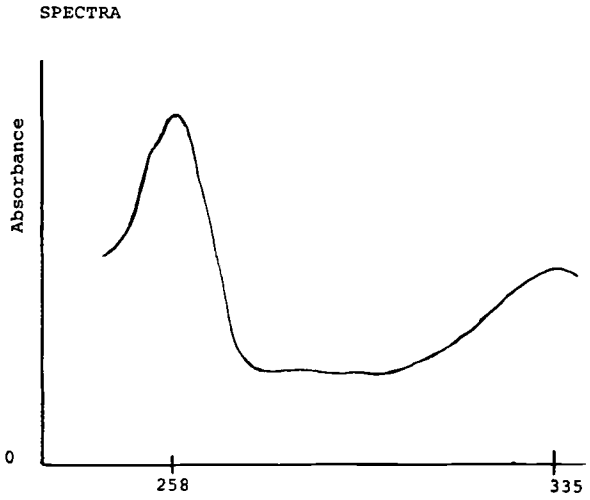

FIG. 4—*Mass spectrum of nalidixic acid.*

Discussion

Nalidixic acid (NegGram) is a carboxylic acid introduced in the 1960s for treatment of urinary tract infections. Since its introduction, there have been numerous reports of nonfatal central nervous system reactions including tremulousness, confusion, drowsiness, headache, and dizziness. Toxic psychosis with confusion and hallucinations have also been reported, but no clear predisposing factors are evident. Convulsions, with and without hyperglycemia, have been reported in patients with underlying seizure disorder or an overdose of the drug [*1*].

Gedroyc and Sharvon [*2*] emphasized the association of these central nervous system reactions with benign increases in intracranial pressure (pseudotumor cerebri). Most of the patients noted with these adverse reactions were children; however, Fraser and Harrower reported convulsions in a 31-year-old woman, who had no predisposing conditions, after initiation of nalidixic acid therapy. Their patient ceased seizure activity when the drug was withdrawn [*3*]. They concluded that even normal nonepileptic patients may show convulsions after administration of this drug, probably as an idiosyncratic reaction.

The witnesses' description of the decedent's activities before his death were consistent with a toxic psycosis, that of hallucinations and convulsions. The blood concentration of 5 mg/mL would not constitute an overdose as it is far below the reported peak plasma concentrations of 20 to 50 mg/mL [*4*]. Thus, any reactions to the noted level would be classified as idiosyncratic.

The mechanism of death in this case is probably related to the observed seizure or convulsive activity. Sudden death during seizures is a well-recognized medicolegal phenomenon [*5*]. Hirsh and Martin [*6*] concluded that in the absence of anatomic findings, death as a result of epilepsy was related to acute disruption of brain stem, cardiac, or respiratory functions caused by seizure discharge. Jay and Leestema [*5*] emphasized the close interrelationship between wave conduction and cardiac conduction and concluded a cardiac arrhythmia was the essential mechanism of death during a fatal seizure. They concluded that underlying cardiac disease might play a catalytic role in this type of seizure death.

The latter conclusion bears particular relevance to our case. Although the seizure activity

may have been nonfatal in a normal person, it was not in someone with abnormal cardiac findings. Although our subject's heart showed only minimal enlargement and pathology, that was obviously sufficient to cause his death when combined with seizure activity.

It is unclear whether the death would have occurred had the deceased been under medical supervision. Subsequent investigation after performing the autopsy revealed that the drug nalidixic acid had not been prescribed for him by a physician. He had apparently obtained it from a girlfriend, who was being treated by her physician for a urinary tract infection with nalidixic acid. The deceased apparently assumed he could treat himself with his friend's drug, as his symptoms were similar to her's. He evidently did not expect such adverse consequences from an allegedly innocuous drug.

References

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Erratum

In the paper by Robert Gault and Marilee Frazer, "Death as a Result of an Adverse Reaction from Nalidixic Acid," Vol. 31, No. 3, July 1986, pp. 1145-1149, the captions for Figs. 2, 3, and 4 were scrambled.

The correct captions are:

FIG. 2—Total ion chromatogram spectrum of nalidixic acid.

FIG. 3—Mass spectrum of nalidixic acid.

FIG. 4—Ultraviolet spectrum of nalidixic acid.