Suppression of craving and withdrawal in humans addicted to narcotics or amphetamines by administration of alpha-methyl-para-tyrosine (AMPT) and 5-butylpicolinic acid (fusaric acid)

Treatment of narcotic and amphetamine addiction in humans; preliminary report

Jose Pozuelo, M.D.

Department of Psychiatry, Division of Research

Accepted for publication April 21, 1976.

Drug addiction is a worldwide problem and its solution depends on the efforts of many disciplines. Two aspects of the treatment of the individual addict relate to prevention of the craving and dependence, be they psychological or physical, and to the prevention of the withdrawal or abstinence syndrome. Attempts to accomplish these objectives in a pharmacological manner can be considered in two major categories: the replacement of the offending drug with one more acceptable, although still addictive, and the use of compounds that may alter the biochemical basis of addiction and withdrawal symptoms.

Previous experimental work by Pozuelo and

Kerr[1] in morphine addicted monkeys demonstrated that treatment with alpha-methyl-paratyrosine (AMPT) abolished the craving for morphine and diminished or abolished the manifestations of the abstinence syndrome. When the results of this investigation were presented at the First International Congress on Alcoholism and Addiction (June 5 to 10, 1972, Seville, Spain) it was suggested that AMPT could be used ". . . in the treatment of narcotic and amphetamine addictions and other mental conditions where the catecholamines were known to play a fundamental role." Later, Davis and Smith[2] demonstrated that AMPT prevented the self-administration of morphine and amphetamines in addicted rats.

The encouraging results of these experiments led, in 1972, to the trial of AMPT in four patients addicted to morphine. They all developed AMPT crystalluria, as in retrospect, had the monkeys, and treatment was discontinued.

It was my impression that alkalinization of the urine to pH 8 or above could prevent crystalluria. However, a search for a more soluble compound that might have effects similar to AMPT led to the consideration of fusaric acid.[3-5]

This preliminary communication presents the initial results obtained in treating six addicted patients with AMPT or fusaric acid.

Methods and procedure

Six patients (two men and four women) with well documented histories of addiction and dependence on narcotics and amphetamines submitted voluntarily to this preliminary study. Two of the patients had severe, chronic amphetamine addiction. Three patients (two men and one woman) were chronic heroin addicts, and another patient was a severe methadone and pentazocine addict as a consequence of chronic postoperative pain.

The heroin dependent patients were transferred from the irregular doses of heroin or other substitutes they could obtain to satisfy their craving and prevent the manifestations of abstinence to regular doses of morphine given every 3 to 4 hours during the day and spaced every 4 to 6 hours at night. The patient dependent on methadone was transferred to a maintenance dose of morphine. A baseline of the daily requirement of morphine for each patient, as measured by the amount of morphine needed to satisfy the craving and to prevent the manifestations of abstinence was established. A period of a week was used for each patient, not only to confirm the morphine requirement, but also to study catecholamine levels, urinary pH, and other constants. During this initial week, the patients assigned to be treated with AMPT were carefully studied to determine the requirements to obtain a urinary pH close to 8.

Doses of AMPT or fusaric acid were started after the baseline was determined, and increased gradually until either a therapeutic level was reached, as measured by the lack of desire of the patient to have narcotics or amphetamines, or previously established maximum serum levels of AMPT and fusaric acid were reached. Having established the tentative doses of the alkalinizer Polycitra to obtain a urinary pH close to 8,

the patients to be treated with AMPT were started on a dose of 50 mg/kg of body weight per day which was increased gradually at the rate of 25 mg/kg of body weight every 2 days. The starting dose of fusaric acid was 5 mg/kg of body weight per day given in four divided doses.

Urine specimens were checked four times daily on patients receiving AMPT to determine the urinary pH and to look for crystals of AMPT in the sediment. The urine specimens of the patients receiving fusaric acid were also checked daily in a similar way, but we did not expect to find any crystals because fusaric acid is highly soluble.

The morphine addicted patients were maintained on regular doses of morphine, and amphetamine dependent patients on 40 to 50 mg amphetamine per day to prevent a rebound of amphetamine depression.

When the dosage of AMPT administered orally was close to 80 mg/kg of body weight or dosage of fusaric acid administered orally was close to 10 mg/kg of body weight per day for the narcotic group of patients, the regular dosage of morphine was discontinued and given only at the patient's request. For the amphetamine dependent patients, amphetamines were discontinued after reaching a dose of 100 mg AMPT/kg or 15 mg fusaric acid/kg. The patients were told that the amphetamines or morphine would be given if they still craved them.

Case reports

Case 1. A 35-year-old, married woman had a chronic history of amphetamine addiction that had started at age 18 to curb her appetite and to overcome feelings of depression. She had reached the point of consuming 200 mg dextroamphetamine a day, and other addicting compounds for headaches and general aching. She had needed as much as 40 to 50 mg of dextroamphetamine to start work in the morning and continued taking 20 to 30 mg of amphetamines every 2 to 3 hours to "keep going" during the day. To sleep at night she resorted to various barbiturates.

The patient consulted several psychiatrists and other physicians to obtain relief of her aches and was hospitalized twice in order to treat her dependence. Every attempt to cure her addiction and withdraw the amphetamines had failed.

She was admitted to our study and once the baseline was established she was started on 250 mg fusaric acid per day. Fusaric acid was used in this patient because she was known to have a renal stone and treatment with AMPT and alkalinizer was considered inadvisable.

After a dosage of 1000 mg fusaric acid a day was reached the amphetamines were discontinued and the patient never requested them again. Her generalized aches, fatigue, chronic pain, and headaches disappeared and she was discharged 15 days after the start of fusaric acid therapy. She no longer required amphetamines and had no craving or desire for them. One week after discharge from the hospital she reported that while she was still maintained on 750 mg per day of fusaric acid she had a "nauseous feeling" at the mere thought of amphetamines.

Case 2. A 30-year-old housewife, married 12 years and mother of four children, seemed to be a stable person, free of neurotic traits. She had started to take a combination of dextroamphetamine and dihydrochlorothiazide (dihydrodiuril) 7 years before because of overweight after her second pregnancy and delivery. Increased doses of dextroamphetamine were required to overcome fatigue. When she entered this study, she was taking about 150 mg of dextroampheta-

mine and 200 mg of dihydrochlorothiazide daily in addition to 8 to 10 tablets containing aspirin, codeine, and phenobarbital for relief of severe headaches. Without use of these drugs she could not prepare breakfast nor take her children to school. She would continue taking 30 to 40 mg dextroamphetamine every 3 to 4 hours. Each day she stopped taking amphetamines about 6 pm so that fatigue and exhaustion would allow her to sleep without sedatives. After baseline studies were completed the patient was given AMPT and the urine was alkalinized to a pH close to 8. Doses of 8 g AMPT a day were sufficient to suppress the craving for amphetamines and to abolish the fatigue and withdrawal manifestations.

The patient remained in the hospital for 4 weeks and was discharged 19 days after initiation of AMPT treatment. Amphetamines prescribed at first regularly were withdrawn and given only at the request of the patient after reaching a daily dose of 7 g AMPT. She never requested amphetamines again. As in Case 1, this patient reported no need for amphetamines on discharge and remembered with "nausea and rage" the need for the amphetamines because of the many troubles she had had with them.

At the time of this report the patient continues well without craving for the amphetamines. She is maintained on 6 g AMPT and alkalinization of the urine to a pH of 8.

Case 3. A 24-year-old married man had started to experiment with marijuana and LSD 4 to 5 years before. He started to take cocaine and heroin 3 years ago and had regular periods each month during which he "mainlined" 1 g heroin a day. When heroin was not available or available only in lesser amounts than needed, other substitutes such as trilitrate were used.

To compensate his heroin dependence with morphine, about 300 mg of morphine was needed daily in four to six divided doses to satisfy his craving and prevent the initiation of withdrawal between doses. He was started on AMPT, 3 g per day, and the dosage was increased gradually to a maximum of 11 g per day, in four divided doses. The requirements for morphine, always available to the patient at his request, decreased gradually after the dosage of AMPT reached 8 g per day. Morphine was requested at longer spaced intervals and for lower amounts each time. The pH of the urine was maintained close to 8 by administration of a urinary alkalinizer. The patient stopped requesting morphine on the 8th day of AMPT treatment, when he was receiving 10 g AMPT per day in four divided doses.

When discharged from the hospital after receiving AMPT treatment for 25 days, he stated that he had no craving for heroin nor any manifestations of withdrawal, signs of which were very well known to this knowledgable patient. He is maintained on 6 g AMPT at the time of this report. He neither craves morphine nor has had any manifestations of withdrawal symptoms since he left the hospital.

Case 4. A 58-year-old housewife had a history of severe depression in her 30s after she underwent a hysterectomy. She had a lumbar disc removed 9 years ago and since then has needed various medications for relief of pain. Four years ago she had a spinal fusion because of persistent lumbar pain. However, the operation failed to relieve her pain and two other back operations were performed.

A well documented history of narcotic intake dates back 4 years, to the time of the spinal fusion, when methadone or pentazocine intramuscularly were prescribed. She alternated with whatever substitute was available by using different prescriptions. She was admitted to hospitals several times seeking relief of pain but never was withdrawn from narcotics, because among other things the amount she was taking never was discovered. Recently, she was taking 3 ampules of methadone (50 mg) or pentazocine (120 mg) in a single injection four to six times a day

for relief of pain in her legs.

To compensate for her narcotic dependence on morphine she needed about 250 to 300 mg daily in six to eight divided doses to satisfy her craving and to prevent the initiation of withdrawal between injections.

Fusaric acid was prescribed and after a baseline of morphine requirements was established, the amount of fusaric acid was increased gradually to 1200 mg a day in six divided doses. The requests for morphine gradually decreased and on the 18th day after fusaric acid treatment was initiated she stopped taking morphine and was free of her chronic pain.

Eight days after the patient stopped taking morphine, while receiving a dose of 1000 mg of fusaric acid, she started to manifest symptoms of endogenous depression. It is difficult to say whether this depression was related to her makeup and previous depressive episodes or to the intake of fusaric acid and consequent depletion of norepinephrine. However, neither the craving for morphine nor the manifestation of withdrawal has returned.

Case 5. A 23-year-old married woman had many family conflicts and neurotic traits, being a "nervous child" for as long as she could remember.

She started to smoke marijuana and sniff cocaine about 6 years before. She also took LSD and barbiturates. However, for the past 3 to 4 years she has consumed heroin and cocaine almost exclusively, and had it available most of the time. She used pentazocine when heroin was not available, "mainlining" it to the "rhythm" of 25 to 30 injections per day (750-900 mg). To compensate for her dependence on narcotics she needed about 300 mg morphine a day, in four to six divided doses.

She was given an initial dose of 3 g AMPT per day and the dosage was gradually increased to a maximum of 10 g a day, in four divided doses. Meanwhile, her urine was alkalinized to a pH close to 8; the pH was checked four times daily and the urine specimens were examined for crystalluria. The patient gradually reduced her requests for morphine and stopped taking it on the 15th day of AMPT treatment when the dosage was 10 g daily.

At the time of this report the patient has not had morphine for 9 consecutive days, and denies any craving for it or manifestations of withdrawal symptoms.

Case 6. A 28-year-old, married man, a polyaddict for the last 3 to 4 years, had resorted to the heavy use of cocaine and heroin. Because this patient did not follow the established protocol he was formally excluded from this study. However, before he admitted to violating the protocol, he had stopped taking morphine when receiving 10 g AMPT in four divided doses. He was later returned to the study and again responded to 10 g AMPT and had no desire for morphine and no evidence of withdrawal.

Comment

None of the patients receiving AMPT have had crystals in any daily urine specimen. Except for a slight drowsiness no side effects have been observed and the patients deny any signs of intolerance. Hypotension was observed in two patients but was mild and never caused dizziness nor prevented them from activity.

The two patients receiving fusaric acid manifested a certain degree of nervousness and one patient (Case 4) had significant depression. It is difficult to say at this time if this complication is related to the fusaric acid or to the chronic nervous condition and multiple situational conflicts of the patient.

Conclusion

The results obtained in this study seem to indicate that AMPT and fusaric acid are effective in abolishing the craving for morphine and am-

phetamines, and in preventing manifestations of withdrawal in human addicts. Although the number of cases treated is small, the fact that the morphine and amphetamines were readily available at the patients' requests and that the patients rejected them because the craving had disappeared, and there were no manifestations of withdrawal lends further support to the study.

This report does not claim that the problem of narcotic and amphetamine addictions is solved by the use of AMPT and fusaric acid; extensive laboratory and clinical investigation is mandatory. Furthermore, no biochemical tool alone can resolve the complex psychosocial factors involved in addiction. The pharmacologic approach described here may be a solution for the iatrogenic addict, helping to resolve both the craving for the addictive drug and the painful manifestations of the abstinence syndrome.

Acknowledgment

Although all collaborators in this investigation are not acknowledged in this preliminary report, the indispensable assistance of Professor Louis Revert, Director of the Department of Nephrology, and Dr. F. Freixa, University of Barcelona, deserves special mention; also the collaboration of Dr. L. Bach of the J. Obiols Chair of Psychiatry, University of Barcelona is greatly appreciated.

References

1. Pozuelo J, Kerr FWL: Suppression of craving and other signs of dependence in morphine-addicted monkeys by administration of alpha-methyl-para-tyrosine. Mayo Clin Proc **47:** 621–628, 1972.
2. Davis WM, Smith SG: Alpha-methyltyrosine to prevent self-administration of morphine and amphetamine. Curr Ther Res **14:** 814–819, 1972.
3. Suda H, Takeuchi T, Nagatsu T, et al: Inhibition of dopamine beta-hydroxylase by 5-alkylpicolinic acid and their hypotensive effects. Chem Pharm Bull **17:** 2377–2380, 1969.
4. Hidaka H, Nagatsu T, Takeya K, et al: A hypotensive agent produced by fungi. J Antibiot (Tokyo) **22:** 228–230, 1969.
5. Terasawa F, Kameyama M: The clinical trial of a new hypotensive agent, "fusaric acid (5-butylpicolinic acid)"; the preliminary report. Jap Circ J **35:** 339–357, 1971.