ELSEVIER

European Journal of Pharmacology 387 (2000) R15–R16

ejp

www.elsevier.nl/locate/ejphar

Rapid communication

Lethal seizures predicted after aminophylline therapy in cocaine abusers

Maciej Gasior *, Jesse T. Ungard, Jeffrey M. Witkin

Drug Development Group, Behavioral Neuroscience Research Branch, National Institute on Drug Abuse, NIH, 5500 Nathan Shock Drive, Baltimore, MD 21224, USA

Received 4 November 1999; accepted 16 November 1999

Abstract

Mice with a history of chronic (10 days), but not acute, treatment with a non-convulsant dose of cocaine showed increased sensitivity ($P < 0.001$) to the toxic effects of aminophylline (seizures, lethality) relative to controls even days after the cessation of cocaine treatment. The present finding suggests that individuals with a history of cocaine use may be at increased risk for convulsive and lethal complications associated with the therapeutic use of aminophylline.

Keywords: Seizure; Lethality; Sensitization

Aminophylline continues to be a mainstay therapy of asthma, neonatal apnea and chronic obstructive pulmonary disease despite potential cardiac and neurological complications (Serafin, 1995). As plasma levels of aminophylline are not always predictive of toxicity, the recognition of other risk factors becomes imperative (Shannon, 1999). We now report data that predict an increased risk of lethal seizures in cocaine abusing patients.

Male Swiss–Webster mice were given a single injection (group A) or repeated injections (group B, group C) of 40 mg/kg (−)-cocaine HCl (Sigma, St. Louis, MO, USA) (Fig. 1, top plot). The incidence of clonic seizures was monitored for 30 min after each cocaine treatment. Mice were then challenged with 250 mg/kg aminophylline (theophylline ethylenediamine, Sigma) 24 h after the last cocaine treatment (group A, group B) or after a 6-day drug-free period (group C). The occurrence of clonic seizures (brief episodes of clonic movements of the limbs with loss of the righting response), tonic seizures (tonic extension of the hind limbs), status epilepticus (clonic–tonic seizures continuously lasting for at least 5 min) and lethality were recorded for 120 min after aminophylline injection. Control groups were given saline instead of cocaine. All injections were intraperitoneal in a volume of 0.01 ml/g.

A 10-day treatment regimen of 40 mg/kg cocaine did not affect the health of the mice, produced no visible behavioral changes and engendered less than a 0.5% cumulative incidence of clonic seizures (Fig. 1, middle plot). A history of chronic cocaine treatment (group B) significantly ($P < 0.001$) increased the percentage of aminophylline-treated mice exhibiting clonic seizures, tonic seizures, status epilepticus and death relative to controls (Fig. 1, bottom plot). This increased sensitivity remained unchanged after a 6-day washout period (group C), indicating durable changes. In contrast, acute cocaine treatment (group A) did not increase the toxicity of aminophylline.

Cocaine abusers without a history of seizures can develop seizures and become increasingly more sensitive to the convulsant effects of cocaine with continued exposure (Dhuna et al., 1991). The present study provides the first experimental evidence implicating chronic cocaine use with the development of a profound sensitivity to the toxic effects of aminophylline. Status epilepticus after theophylline was recently reported in a cocaine abuser (Krieger and Takeyasu, 1999) and our findings implicate cocaine use as a causative factor.

A short half-life of cocaine (~ 30 min) and the lack of accumulation of cocaine and its metabolites after an 18-day treatment with 20 mg/kg cocaine in mice (Reith et al., 1987), imply the involvement of pharmacodynamic over pharmacokinetic factors in the enhanced toxicity. Although the mechanisms responsible for this phenomenon are not known, adenosine receptors may play a role. The convulsant effects of aminophylline have been attributed to the

* Corresponding author. Tel.: +1-410-550-3399; fax: +1-410-550-1648.

E-mail address: mgasior@intra.nida.nih.gov (M. Gasior)

0014-2999/00/$ - see front matter
PII: S0014-2999(99)00801-8

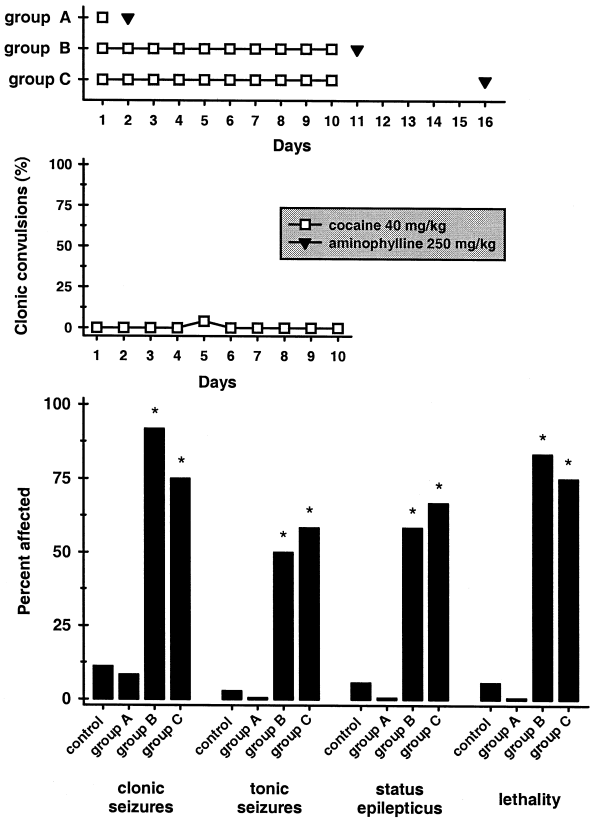

Fig. 1. Top plot: A schematic representation of the treatment protocol. There were three treatment groups ($N = 12$ mice/group): cocaine on day 1 and aminophylline on day 2 (group A); cocaine daily for 10 days and aminophylline on day 11 (group B); cocaine daily for 10 days and aminophylline on day 16 after a 6-day washout period (group C). Doses of cocaine and aminophylline were 40 and 250 mg/kg, respectively. For each of the groups, there was an equivalently-sized control group treated with saline instead of cocaine and subsequently with aminophylline. Middle plot: Expression of clonic seizures over the course of repeated treatment with cocaine. Each data point represents the percentage of mice ($N = 24$) exhibiting clonic seizures within 30 min post-injection with 40 mg/kg cocaine. There was one episode of clonic seizures (day 5) out of 240 total treatments. The cumulative incidence of clonic seizures was less then 0.5%. Bottom plot: Each bar represents the percentage of mice in the control group ($N = 36$) and in experimental groups A, B, and C ($N = 12$/group) exhibiting clonic seizures, tonic seizures, status epilepticus or lethality within 120 min after a single challenge with 250 mg/kg aminophylline. $^{*}P < 0.001$ compared to the control group (Fisher's exact probability test).

blockade of adenosine A_1 receptors (Dragunow, 1990). A role of adenosine in the long-term alterations in synaptic transmission after chronic cocaine treatment has also been reported (Bonci and Williams, 1996).

There are estimates of 1.7 million regular cocaine users, 30 million individuals with a history of cocaine use, and 150,000 cocaine-related emergency room visits annually in the United States (NIDA, 1995). Taken in conjunction with the fact that aminophylline seizures can be refractory to anticonvulsant therapy (Serafin, 1995), the present findings suggest the need for heightened awareness of potential convulsive and lethal complications associated with the therapeutic use of aminophylline in individuals with a history of cocaine use or newborns of cocaine-abusing mothers. The possibility that cocaine abusers may be at increased risk to the toxic effects of other drugs (e.g., caffeine) should not be overlooked.

References

Bonci, A., Williams, J.T., 1996. A common mechanism mediates long-term changes in synaptic transmission after chronic cocaine and morphine. Neuron 16, 631–639.

Dhuna, A., Pascual-Leone, A., Langendorf, F., Anderson, D., 1991. Epileptogenic properties of cocaine in humans. Neurotoxicology 12, 621–626.

Dragunow, M., 1990. Adenosine receptor antagonism accounts for the seizure-prolonging effects of aminophylline. Pharmacol. Biochem. Behav. 36, 751–755.

Krieger, A.C., Takeyasu, M., 1999. Nonconvulsive status epilepticus in theophylline toxicity. J. Toxicol. Clin. Toxicol. 37, 99–101.

National Institute on Drug Abuse, 1995. National Household Survey on Drug Abuse: Population Estimates. U.S. Department of Health and Human Services, Rockville, MD.

Reith, M.E., Benuck, M., Lajtha, A., 1987. Cocaine disposition in the brain after continuous or intermittent treatment and locomotor stimulation in mice. J. Pharmacol. Exp. Ther. 243, 281–287.

Serafin, W.E., 1995. Drugs used in the treatment of asthma. In: Hardman, J.G., Limbird, L.E., Molinoff, P.B., Ruddon, R.W., Gilman, A.G. (Eds.), Goodman and Gilman's The Pharmacological Basis of Therapeutics. McGraw-Hill, New York, pp. 659–682.

Shannon, M., 1999. Life-threatening events after theophylline overdose: a 10-year prospective analysis. Arch. Intern. Med. 159, 989–994.