Cardiovascular and Respiratory Effects of Harmine (34539)

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Harmine, 7-methoxy-1-methyl-9H-pyrido-(3, 4b) indole, is an alkaloid obtained from the shrub *Banisteria caapi* (1) and several other South American plants. Harmine has a wide variety of pharmacological actions on the cardiovascular system (2), and on the central nervous system (3, 4), and inhibits monoamine oxidase (5). Although the actions of harmine on the cardiovascular system were described in the 1920's and 1930's (6), the mechanisms involved in many of these actions have not been elucidated. In this study, the effects of harmine on the cardiovascular and respiratory systems and the effects on the responses to acetylcholine and epinephrine have been studied.

Materials and Methods. Three male cats were anesthetized with sodium pentobarbital, 38 mg/kg ip. A cannula was inserted into the carotid artery and blood pressure was recorded with a Statham Model P23AC transducer and a Grass Model 5 polygraph. All drugs in aqueous solution were administered via a cannula in the femoral vein and washed in with 0.5 ml of saline. Respiration was recorded by means of a volumetric pressure transducer attached to one neck of a tracheal cannula; the EKG (lead II) was also recorded. Contractions of the nictitating membrane were evoked by preganglionic stimulation (0.7 V for 3 sec at 60 cps at 30-sec intervals).

Three male rats of the Sprague-Dawley strain were anesthetized with sodium pentobarbital (38 mg/kg) and chloral hydrate (160 mg/kg) ip and a cannula was inserted into the femoral vein. Harmine hydrochloride hydrate (5 mg/ml in aqueous solution) was administered in doses of 0.5, 5, and 50 mg/kg iv and the EKG (lead II) was recorded.

Five healthy human volunteers received 0.5 mg/kg harmine hydrochloride hydrate (5 mg/ml in saline) iv over a period of 5-7 min. Blood pressure, pulse rate, and EKG (lead II) were recorded.

Harmine hydrochloride hydrate was obtained from the Aldrich Chemical Co. and sterilized for human use by Millipore filtration.

Results. Cat. Bradycardia and hypotension of about 1-min duration typically followed harmine administration in the cat; the responses were somewhat variable (heart rate decreased by about 10–40%; systolic and diastolic blood pressure decreased by about 30–60%) (Fig. 1). Apnea of 5- to 15-sec duration occurred with doses above 3 mg/kg. The intensity and duration of the responses were dose-dependent. At doses above 3 mg/kg, cardiac arrhythmias occurred after a lag of about 1 min and lasted for several minutes. The EKG indicated ventricular extrasystoles followed by bigeminy; with higher doses, ventricular tachycardia and fibrillation occurred. Bilateral vagotomy eliminated the bradycardia in response to harmine, but did not abolish the hypotension, apnea, or cardiac arrhythmias. Subsequent administration of atropine (1 mg/kg) eliminated the apnea, but did not affect the hypotension or arrhythmias. Evoked contractions of the nictitating membrane were decreased after administration of 5 or 10 mg/kg of harmine, but returned to normal within 1 min.

Harmine in increasing doses potentiated acetylcholine-evoked hypotension (1 μg/kg); arrhythmias were not observed. The response to epinephrine (1 μg/kg) was also potentiated (Fig. 2); hypotensive doses (1 μg/kg or less) of epinephrine gave a pressor

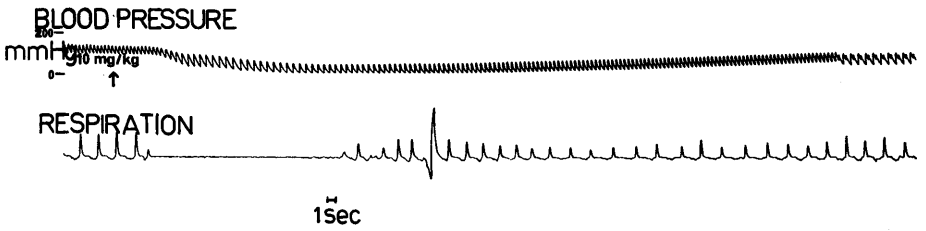

FIG. 1. The effects of 10 mg/kg of harmine iv on blood pressure and respiration in the cat. Harmine was injected at the arrow.

response 2 min after pretreatment with 3 mg/kg of harmine. The pressor response occurred in waves of unknown etiology and was followed by a prolonged period of cardiac arrhythmias.

Rat. Harmine (0.5 mg/kg) given to anesthetized rats caused hypotension and decreased the heart rate from about 266 beats/min before administration to 200 beats/min 10 sec after drug administration. After 6 min, the heart rate dropped to 140 beats/min. No changes in P-R or Q-T intervals accompanied the bradycardia; heart rate returned to normal after 15–20 min. Administration of 5 mg/kg of harmine lowered heart rate to 125 beats/min; again, no changes in the P-R or Q-T intervals were noted, but inversion of the P-wave occurred between 1 and 2 min after drug administration. A lethal dose of harmine (50 mg/kg) decreased heart rate progressively (to less than 100 beats/min within 10 sec of drug administration), and caused P-wave inversion and T-wave elevation. Within 30 sec, a progressive heart block developed with conversion to nodal rhythm; after 2 min death ensued from a complete heart block with inverted P-waves and no electrical ventricular systoles.

Man. Administration of 0.5 mg/kg of harmine to five conscious human volunteers slightly decreased heart rates (by less than 10%); occasional periods of tachycardia were recorded in two subjects. Small decreases in blood pressure (by less than 20%) were noted in four subjects. As in rats given 0.5 mg/kg of harmine, no changes in the P-R or Q-T intervals were noted. The duration of the effects in man was variable (5–45 min).

Discussion. Cats, rats, and humans, given intravenous doses of harmine developed hy-

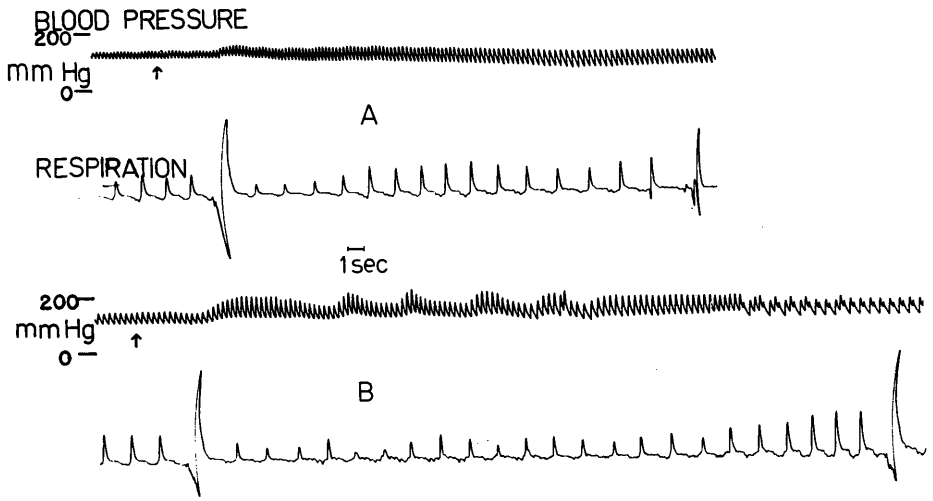

FIG. 2. Potentiation by harmine of the blood pressure response to epinephrine (1 μg/kg iv) in the cat. (A) Control; (B) Pretreated with harmine, 3 mg/kg iv. Epinephrine was given at the arrow. Note the wavelike form of the pressor response to epinephrine and occurrence of cardiac arrhythmias in the harmine-treated animal.

potension and a sinus bradycardia with no alterations in the P-R or Q-T intervals. The bradycardia was eliminated in cats by vagotomy, indicating that this effect of harmine is mediated through the vagus nerve; hence, either a chemoreflex or a direct central mechanism of action for harmine is implicated in the effect on heart rate. The decrement in heart rate was less in conscious human subjects; this diminished effect has also been observed in conscious animals (2). The harmine-induced hypotension was unaffected by vagotomy. Harmine may have a direct effect on the vasomotor center; since harmine is a potent coronary vasodilator (6), the possibility of direct peripheral vasodilation cannot be excluded.

Harmine may potentiate the cardiovascular response to acetylcholine in the cat as a result of its anticholinesterase action, which has been demonstrated *in vitro* (7). Potentiation of the response to epinephrine by harmine may be due to monoamine oxidase inhibition. The inhibition of monoamine oxidase may also account for the predisposition to cardiac arrhythmias produced by harmine or by subsequent doses of epinephrine. Harmine derivatives have been reported to cause ventricular arrhythmias (8).

It has been shown that high doses of harmine can produce ganglionic blockade (9) and that contractions of the isolated nictitating membrane are inhibited by harmine (10). In the light of these studies, transient depression of pre-ganglionically evoked contractions of the nictitating membrane after systemic administration of harmine can be attributed either to ganglionic blockade or to blockade of the effector site. The rapid return to normal may reflect the rapid disappearance of harmine from the blood stream (11).

Summary. Intravenously administered harmine in cats, rats, and humans induced bradycardia and hypotension; cats exhibited apnea and ventricular arrhythmias. In the cat, bradycardia was eliminated by vagotomy and apnea by atropinization. The effects of acetylcholine and epinephrine were potentiated by harmine; possibly this was due to the inhibition of cholinesterase and monoamine oxidase, respectively. Evoked contractions of the nictitating membrane were depressed transiently. High doses of harmine produced third-degree heart block.

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