17170. Sympatholytic Effects of Diethylaminoethanol in Man.*

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(Introduced by Robert W. Wilkins.)

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A recent report by Rosenberg and his coworkers[1] indicates that diethylaminoethanol, an *in vivo* decomposition product of procaine, may revert ventricular tachycardia to normal rhythm, suppress ventricular premature contractions, and induce transient hypotension. Since the mechanism of these effects was not determined the present investigation was instituted to inquire into the hemodynamic properties of the drug in man.

Methods and results. Both hypertensive and normotensive subjects were given diethylaminoethanol in doses of 2 to 5 g either by slow intravenous drip in 0.5% solution at a rate of 0.02 g per minute or by rapid intravenous injection of a 10% solution at a rate of 1.0 g per minute. Sympathetic vasopressor and digital vasoconstrictor reflexes were determined before and at various intervals after the drug according to methods previously described.[2] Doses of 5 g of diethylaminoethanol injected intravenously at a rate of 1 g per minute were followed by a reduction of basal arterial pressure and marked postural hypotension. Heart rate either did not change significantly or increased moderately. Accompanying the hypotensive response there was an inhibition of sympathetic vasopressor responses (Valsalva and tilt-back overshoots), as well as a reduction in reflex vasoconstrictor responses to "noxious stimuli" in the digits. In addition, a sudden increase in digital volume and pulse volume was observed. These hypotensive and sympatholytic effects were transient, the arterial pressure and sympathetic reflexes returning to normal within ½ to 1 hour after the drug was administered. Slow rates of administration of the drug and low dosage were not followed by such cardiovascular or sympathetic reflex changes. No serious toxic effects were noted.

Discussion. The observed sympatholytic properties of diethylaminoethanol in man probably are the basis for its hypotensive action as well as its effect on ventricular tachycardias. In the latter respect the drug is similar to certain other sympatholytic agents such as dibenamine,[3] ergotamine,[4] and dihydroergokryptine.[5] This correlation between adrenergic inhibition and the prevention or cessation of attacks of ventricular tachycardia seems to be limited to drugs which suppress the sympathetic system only; since in dogs under cyclopropane anesthesia the drug tetraethylammonium, which inhibits transmission through all autonomic ganglia, intensifies rather than prevents epinephrine induced ventricular tachycardia.[6]

Rosenberg and his co-workers demonstrated that high blood levels of diethylaminoethanol are not maintained due to rapid diffusion of the drug out of the blood stream.[1] The results of the present study suggest that the sympa-

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tholytic and hypotensive effects are dependent upon a high blood level of the drug since slow rates of infusion at low dosage did not result in sympathetic inhibition. Even with large doses rapidly injected adrenergic inhibition was transient and disappeared at a rate similar to the observed disappearance of high concentrations of diethylaminoethanol from the blood. It was not possible to determine from the present experiments whether the site of sympathetic inhibition was central or peripheral.

Summary and conclusions. Doses of diethylaminoethanol sufficient to produce high blood concentrations resulted in a temporary inhibition of sympathetic vasoconstrictor reflexes in man. It is suggested that the effects of the drug on arterial pressure and ventricular tachycardias are secondary to its sympatholytic action.

Since preparation of this paper, Clark and Helpern (*Fed. Proc.*, 1949, **8**, 282) have reported on the ganglionic blocking action of diethylaminoethanol in dogs and cats. Their observations on the sympatholytic effects of the drug in animals are in essential agreement with the results of the present investigation in man.

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17171. Action of 1-Methyl-4-(3-Hydroxyphenyl)-4-Piperidyl Ethyl Ketone on the Gastrointestinal Tract.*

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One of the most active analgesic compounds reported by Kleiderer, Rice *et al.*[1] was 1-methyl-4-(3-hydroxyphenyl)-4-piperidyl ethyl ketone which will be referred to in this report as WIN 1539. This compound has the same basic phenyl-piperidine nucleus as Demerol (brand of isonipecaine), but contains a meta-hydroxy group on the phenyl ring and has a propionyl group in place of the carbethoxy substituent of Demerol. The analgesic activity of WIN 1539 is 5-10 times greater than that of Demerol.[1-4] Because of its high analgesic activity and its close chemical relationship to Demerol, the actions of WIN 1539 on the gastrointestinal tract have been investigated.

Results. A. *Effect on excised intestinal segments.* WIN 1539 and Demerol were compared for their activity against barium chloride and acetylcholine induced spasms of the rabbit ileum and against histamine induced spasms of the guinea pig ileum by the procedure described by Miller, Becker and Tainter.[5] The results are given in Table I. These data indicate that the spasmolytic activity of WIN 1539 is considerably greater than Demerol against all three spasmogenic agents.

B. *Effect on intestine in situ.* Kymographic recordings were made of a segment of the intact ileum of anesthetized dogs by a modification of the Barbour method as described by Jackson.[6] Aqueous solutions of the drugs

* This work is part of an investigation carried out under the supervision of Dr. M. H. Seevers and submitted in a dissertation to the Graduate School of the University of Michigan in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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