

Effects of Propranolol on Epinephrine-induced Arrhythmias during Halothane Anesthesia in Man and Cats. ETSUTARO IKEZONO, M.D., KATSUHISSA YASUDA, M.D., and YOSHIO HATTORI, M.D., *Department of Anesthesia, School of Medicine, Tokyo Medical and Dental University, 1-5-47, Yushima, Bunkyo-Ku, Tokyo, Japan.* The successful treatment of ventricular arrhythmias with propranolol during anesthesia has been reported. The injection of epinephrine in man and animals may elicit cardiac arrhythmias in the presence of halothane. This study was done to determine the effects of propranolol in preventing cardiac arrhythmias which might occur when epinephrine is used during halothane anesthesia in man and cats. *Method: Clinical Cases:* The ECG was monitored during halothane anesthesia in 120 E.N.T. cases in which epinephrine was locally injected or topically applied to nasopharyngeal mucosa for hemostasis. Respiration was assisted to maintain end-tidal CO_2 at 4-5 per cent throughout the operation. The patients were classified in two groups. Group A: 50 $\mu\text{g./kg.}$ of propranolol was given prophylactically to 52 patients in whom epinephrine was injected (0.15-4.6 $\mu\text{g./kg./hr.}$) or topically applied (35.7-1,254.8 $\mu\text{g./kg./hr.}$). Group B: No propranolol was used in 62 patients in whom epinephrine was injected (0.54-10.7 $\mu\text{g./kg./hr.}$) or topically applied (15.0-279.0 $\mu\text{g./kg./hr.}$) during halothane anesthesia. *Results:* In Group A no ventricular arrhythmias were observed even though excessive amounts of epinephrine were used. In Group B 13 patients developed ventricular arrhythmias during halothane anesthesia. These arrhythmias were controlled easily by injection of 50 $\mu\text{g./kg.}$ of propranolol. There were no complications which can be attributed to propranolol. *Animal Experiments: method:* In 35 cats anesthesia was induced and maintained with 1 per cent halothane in oxygen. End-tidal CO_2 was measured by Capnograph. The animals were divided into two groups. In group A, ventilation was adjusted to maintain 4-5 per cent of end-tidal CO_2 , and a dose of epinephrine which would produce ventricular arrhythmias up to at least 10 P.V.C. in one minute was determined. Fifty $\mu\text{g./kg.}$ of propranolol was given and

changes in the arrhythmic doses of epinephrine were measured. In group B CO_2 was administered to elevate end-tidal CO_2 to 8 per cent, an arrhythmic dose of epinephrine was determined, and the effects of propranolol were studied using the same technique as in group A. *Results:* In group A the arrhythmic dose of epinephrine was found to be 5.9 $\mu\text{g./kg.}$ This increased to 21 $\mu\text{g./kg.}$ after the administration of propranolol. In group B half of the animals developed P.V.C. without injection of epinephrine. The arrhythmic dose in this group was 0.68 $\mu\text{g./kg.}$ It increased to 3.75 $\mu\text{g./kg.}$ after the use of propranolol. *Summary:* In 52 patients, receiving 50 $\mu\text{g./kg.}$ of propranolol no ventricular arrhythmias occurred during halothane anesthesia with epinephrine injections. Without the prophylactic use of propranolol, epinephrine produced ventricular arrhythmias in 13 of 68 patients during halothane anesthesia. These were abolished by using 50 $\mu\text{g./kg.}$ of propranolol. In animal experiments the average arrhythmic dosage of epinephrine during halothane anesthesia was increased 3.5-5.5 times over control values after the injection of propranolol. *Conclusions:* The results of this study appear to justify the use of propranolol for both prophylaxis and treatment of epinephrine-induced arrhythmias during halothane anesthesia.

The Use of In-vitro Technique in the Development of New Neuromuscular Blocking Agents. JOANNES H. KARIS, M.D., RICHARD J. KRITZ, M.D., and WILLIAM L. NASTUK, PH.D., *Departments of Anesthesiology and Physiology, College of Physicians and Surgeons, Columbia University, New York, N. Y.* Many currently-used neuromuscular blocking agents produce blocks which endure longer than required, and many have unwanted side effects. A drug that produces a nondepolarizing block of short duration is clearly desirable. Several series of new quaternary ammonium esters which can be hydrolyzed by acetylcholinesterase and/or plasma cholinesterase, recently synthesized by Drs. Kitz and Ginsburg, may have short durations of activity *in vivo*. To evaluate these agents, we chose an *in vitro* technique to collect specific information about potency as well as mode of

action at the neuromuscular junction. Any promising agents found are to be subjected to *in vivo* studies in animals and perhaps, finally, in man. *Methods:* The sciatic nerve-sartorius muscle preparation of the frog was bathed in Ringer's solution containing appropriate concentrations of each drug to be tested. The intracellular resting potential and the action potentials evoked in response to motor nerve stimulation were recorded at the neuromuscular junction at various times. *Results:* Most of the choline analogues tested produced a depolarizing block. In a concentration of 5×10^{-4} M., benzoylcholine depolarized the endplate below -50 mV., the critical membrane potential. (Similar results can be produced by succinylcholine at 10^{-5} M. and acetylcholine at 3×10^{-6} M.) Some compounds in the phenacetylcholine series (formed by introducing a methylene group between the carbonyl carbon atom and the benzene ring in benzoylcholine) produce a similar degree of postjunctional membrane depolarization when applied at a concentration of 10^{-5} M. One of the diquaternary derivatives of phenacetylcholine was an especially potent depolarizing agent. At 10^{-6} M. it reduced the postjunctional membrane potential to below -50 mV. The ethocholine derivatives produced a nondepolarizing neuromuscular block. Phenacetylthocholine blocked transmission at a concentration of 10^{-4} M. (compare *d*-tubocurarine which blocks at 5×10^{-6} M.). Contrary to our expectations, di- and triquaternary analogs were not more potent than the monquaternary phenacetylthocholine. Compounds in the phenoxy-acetylcholine and ethocholine series were more easily hydrolyzed than those mentioned above, but they lacked potent neuromuscular blocking properties. Several derivatives of phenacetylcholine were prepared by quaternizing the nitrogen with different groups. Preliminary data indicate that some of these compounds are especially potent blocking agents. (Supported by NIH Grants GM 09069 and NB-04988.)

The Uptake, Distribution and Elimination of 14 C-labelled Lidocaine in the Dog. JORDAN KATZ, M.D., *Department of Anesthesia, Stanford University, Palo Alto, Calif.* In an at-

tempt to determine the distribution of lidocaine after intravenous injection, initial work in rats indicated that the liver contained about 33 per cent of injected drug by 15 minutes (Katz, J.: *ANESTHESIOLOGY* in press). Muscle also contained significant amounts of drug (24 per cent by 5 minutes, falling to 16 per cent by 15 minutes). In other organs there were rapid decay curves after the initial measurement at one minute postinjection. In order to elucidate further the distribution and subsequent elimination of the drug in a larger species, experiments were undertaken in the dog. *Methods:* Female mongrel dogs anesthetized with I.V. pentobarbital (30 mg./kg.), were intubated and maintained on N_2O/O_2 and intermittent succinylcholine anesthesia. Hydration was accomplished with a 5 per cent dextrose in Ringer's lactate solution. Laparotomy was performed and in two animals the common bile duct was cannulated. The urinary bladder was catheterized. One hour after closure of the laparotomy wound, and when the animals were stable, 14 C-labelled lidocaine was injected rapidly intravenously. Arterial blood, urine and bile samples were collected at intervals for as long as five hours. Biopsies from the quadriceps muscle were taken at intervals. After laparotomy in a second group (eight animals) liver and fat biopsies were taken in addition to muscle, arterial blood and urine collections. Biopsies of kidney and gut were taken from specific animals. *Results:* Blood levels fell rapidly from 16.8 per cent of injected dose in plasma at one minute to 9.1 per cent at five minutes. At one, two and four hours plasma levels were 4.7, 3.4, and 1.9 per cent, respectively. This pattern was essentially similar to that noted in rats with, of course, a different time base. Concentrations in the liver rose rapidly to 24.5 per cent of injected dose by three minutes and remained in that range until 30 minutes after injection, when concentration began to decline. Muscle held as much as 40 per cent of the injected dose from 5 to 30 minutes before levels declined. When counts/minute/mg. of tissue were made, muscle was found to have low affinity for the drug. The maximum counts were 4.6 cts./min./mg. of muscle compared to 35 cts./min./mg. liver. Higher counts were