Anesthetics I

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PULMONARY MECHANICS DURING GENERAL ANESTHESIA IN NORMAL MAN. M.I. Gold* and M. Helrich* (spon: R. M. Burgison). Univ. of Maryland Sch. of Med. and Hosp., Baltimore, Maryland.

Pulmonary compliance is known to decrease during general anesthesia in spontaneously breathing humans. Change in pulmonary resistance, however, is less clearly defined. Simultaneous measurements of pulmonary compliance and resistance were made in supine, presurgical patients first awake and then continuously during 45-60 minutes of general anesthesia. Halothane was the primary agent while thiopental was used for induction in 75%. Compliance fell 25% after induction but changed little during the remainder of the experiment. Resistance increased more than 100% without oral airway, was still significantly elevated with oral airway and fell to control level with endotracheal intubation. Thiopental induction was associated with a greater decrease in compliance and tidal exchange and a larger increase in resistance than inhalation induction. Changes in compliance and resistance during anesthesia were unrelated. (Supported by a grant from NIH, PHS-HE06429.)

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HYPOTHERMIA, CONSTANT-DEPTH ANESTHESIA, AND VENTILATORY RESPONSE TO HYPERCARBIA AND HYPOXIA. Michael J. Regan* and Edmond I. Eger, II.* (spon: S.C. Cullen), Cardiovascular Research Institute and Dept. of Anesthesia, Univ. of Calif. Med. Center, San Francisco, California.

The influence of hypothermia on ventilatory responses of dogs to hypercarbia and hypoxia was studied at constant-depth halothane anesthesia. Depth was defined in terms of the minimum alveolar halothane concentration (MAC) required to prevent gross movement in response to a standard noxious stimulus. Resting minute ventilation fell from 4.9 L/min at 37°C esophageal temperature to 3.7 L/min at 32° to 2.5 L/min at 28°. Pa_{CO_2} fell concomitantly from 46 mm Hg, to 39 mm Hg, to 38 mm Hg. Ventilatory response to CO_2 fell from .38 L/min/mm Hg rise in Pa_{CO_2} at 37° to .16 L/min/mm Hg at 32° to .10 L/min/mm Hg at 28°. Ventilatory response to hypoxia increased at 37° from a control of 4 L/min (Pa_{O_2} 400 mm Hg) to 15 L/min (Pa_{O_2} 40 mm Hg). At 28° ventilation increased from 2.5 L/min (Pa_{O_2} 400 mm Hg) to only 4 L/min (Pa_{O_2} 30 mm Hg). This change in responsiveness to hypoxia is consistent with the known depression of carotid chemoceptor activity at lower temperatures. Determination of the alveolar halothane concentration which produces apnea indicates little change in the ratio, apneic dose/MAC dose as temperature falls. (Supported in part by USPHS grants 5T1-GM-63; 3-K3-GM-17,685; and 5R01 HE 07946.)

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CARDIAC OUTPUT, ANESTHESIA, AND ACID-BASE CHANGES Richard Schlobohm*, F. Norman Hamilton*, Do Chil Lee*, J. C. Minzel*, & Lucien E. Morris. Anesthesia Research Laboratories, Providence Hospital, Seattle, Washington.

Surgical implantation of an electromagnetic flowmeter probe was done in nine mongrel dogs to examine the effects of various anesthetic situations on cardiac output. Approximately one week later, awake determinations of cardiac output were made, and anesthesia was then induced with a barbiturate. After preparation and catheterization, anesthesia was changed to halothane. Various concentrations of halothane, oxygen, and carbon dioxide were presented in the respired atmosphere at intervals throughout fourteen studies. 146 cardiac outputs were paired with arterial pH, PCO_2, and PO_2. Mild depression of the cardiac output was recorded after the barbiturate induction. During anesthesia, increasing concentration of halothane to three percent progressively decreased the cardiac output to fifty percent of the awake value. Hypoxia in light levels of halothane anesthesia elevated cardiac output above the awake value with base deficit of ±5 mEq. L. bicarbonate. Hypercapnea caused an increase in cardiac output over eucapnea in both light and deep levels of halothane anesthesia. (Supported by grants from N.I.H. #HE 05959-03, and Washington State Heart Association.)

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GENERAL ANESTHETIC ACTION OF 2-(O-CHLOROPHENYL)-2-METHYLAMINO-CYCLOHEXANONE HCl (CI-581) IN THE RHESUS MONKEY. D. A. McCarthy* and G. M. Chen. Parke, Davis & Co., Ann Arbor, Michigan.

The capacity of CI-581 to anesthetize the Rhesus monkey has been compared with phencyclidine HCl (PCP) and with the general anesthetics, thiamylal (T) and pentobarbital (P). I.V. anesthetic threshold doses (ATD), relative duration, undesirable effect doses (UED) and minimum lethal doses (MLD) were determined following I.V. injections given over a 1 minute period. The MLD/ATD ratios were 16, 26, 3.3 and 6.5 for CI-581, PCP, P and T respectively. The main undesirable drug effects were convulsions with P and respiratory depression with CI-581, P and T. The UED/ATD ratios were 15, 8, 3 and 6 for CI-581, PCP, P and T respectively. While PCP has the most favorable MLD/ATD ratio in monkeys, CI-581 produced a better quality of anesthesia and had a more favorable UED/ATD ratio. Over practical dosage ranges, the order of increasing duration of action is: CI-581, T, PCP, P. Objective measurements of changes in respiratory function produced by CI-581 indicated that this effect is inconsequential at doses producing surgical anesthesia.

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METABOLIC DISPOSITION OF 2-(o-CHLOROPHENYL)-2-METHYLAMINO-CYCLOHEXANONE-HCl (CI-581) IN LABORATORY ANIMALS AND IN MAN. T. Chang*, W. A. Dill* and A. J. Glazko. Research Laboratories, Parke, Davis & Co., Ann Arbor, Michigan.

Blood level assays for CI-581 in laboratory animals by a modified methyl orange procedure indicated rapid absorption following peroral or parenteral doses, and rapid metabolic disposition. Highest concentrations of drug in the rat were found in the body fat (10X plasma levels), with decreasing concentrations occurring in liver, lung, spleen, kidney, brain, heart, skeletal muscle and blood plasma. Only small amounts of free drug were excreted in the urine. Two metabolic products were isolated from monkey urine by counter-current extraction and TLC. These were identified as the demethylated primary amine (I), and the primary amine oxidized to the cyclohexene derivative (II). Good separations of CI-581, I and II were obtained by gas chromatography on columns of 1% ECNSS-M (80/100 GasChrom P) at 170°C. II was the major metabolic product found in urine from man, monkey and dog; I predominated in rat urine, together with a new metabolite (III) which has not been identified. Rat liver homogenates + NADP converted CI-581 → I in vitro; monkey liver homogenates converted CI-581 → I and I → II in vitro. The significance of these species differences in metabolism will be discussed.

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HUMAN PHARMACOLOGY OF CI-581, A NEW INTRAVENOUS AGENT CHEMICALLY RELATED TO PHENCYCLIDINE. E. F. Domino, P. Chodoff*, and G. Corssen*. University of Michigan, Ann Arbor.

The actions of CI-581 [2-(o-chlorophenyl)-2-methylaminocyclohexanone] a derivative of phencyclidine were determined in 20 male prison volunteers. The drug is an effective analgesic in doses of 1.0 to 2.0 mg/kg given i.v. CI-581 is less potent (on a mg basis) but shorter acting than phencyclidine. A 1.0 mg/kg dose produced analgesia and coma in 30 seconds which lasted for 3-10 minutes. No convulsions were noted in doses up to 2 mg/kg, i.v. CI-581 caused psychotomimetic effects similar to phencyclidine but of shorter duration. Full recovery occurred within 1-2 hours. The drug produced transient depression of respiratory rate and tidal volume. A consistent increase in systolic and diastolic blood pressure as well as a tachycardia were noted. CI-581 also produced sweating, lacrimation and hyperactive tendon reflexes. It blocked EEG alpha waves and produced theta activity. During the coma, visually evoked responses were depressed, as during coma by other agents. The early components of somesthetic evoked responses were enhanced, although the subject complained of numbness of extremities. No serious toxicity was noted. CI-581 deserves further clinical trials.