Disposition of acebutolol following intravenous administration. *P. J. Meffin, Ph.D.*, R. A. Winkle, M.D., F. A. Peters, R.N., S. R. Harapat, B. S., Y. G. Yee, B.S., and D. C. Harrision, M.D., Division of Cardiology, Stanford University School of Medicine, Stanford, Calif.

Acebutolol (±-[2-acetyl-4-butyramidophenoxy]-2-hydroxy-3-isopropylamine hydrochloride), a new cardioselective beta adrenergic antagonist, was administered to nine normal volunteers (mean age 22.4 ± −1.9 (SD) yr, weight 75.7 ± 12.3 kg) by constant intravenous infusion over 15 min at a dose of 1 mg/kg of body weight. Three of the volunteers also received 15 min infusions of 0.25 and 0.5 mg/kg and in addition infusions over 8 hr designed to rapidly attain and maintain an acebutolol blood concentration of 500 ng/ml. A specific high-pressure liquid-chromatographic method was used to determine acebutolol blood concentrations. Blood concentration time data were fitted to a two-compartmental open model. Mean blood clearance was 437 ± 70 ml/min and the fast and slow half-life 6.8 ± 2.4 and 187.3 ± 19.0 min, respectively. Area under the acebutolol concentration time curve was a linear function of dose ($p < 0.0001$). Acebutolol blood concentrations during and subsequent to the 8 hr infusion were in close agreement with those predicted by data obtained from the 15 min infusion studies. The mean fraction of acebutolol unbound to plasma proteins was 0.735 < 0.031 and the mean ratio of acebutolol plasma to blood concentrations was 0.62 ± 0.02 (mean hematocrit 43.4 ± 3.3). Both relationships were independent of concentration in the range of 50-500 ng/ml.

Dopamine, the psyche, and extrapyramidal disorders.* *F. S. Messiha, Ph.D.*, Departments of Pharmacology and Therapeutics and Psychiatry, Texas Tech University School of Medicine, Lubbock, Texas.

Indirect evidence suggests the involvement of dopaminergic mechanism(s) in certain neurological disorders of the extrapyramidal system as well as in the motor disturbances associated with drug-produced psychoses in man. Accordingly, the urinary excretion of dopamine (DA) and some of its major metabolites were determined in patients with drug-induced Parkinson-like syndrome, motor hyperkinesias, and dyskinesias, as well as in healthy volunteers prior to and during administration of the psychotomimetics lysergic acid diethylamide (LSD) and *Cannabis sativa* (CS). The urinary outputs of DA and homovanillic acid were markedly decreased from normal values in patients with drug-induced parkinsonism compared to a marked rise in DA excretion in cases with motor hyperkinesias and dyskinesias. Similarly, the results derived from animal models for chlorpromazine-induced dyskinesias in monkeys show an increase in the concentrations of DA and homovanillic acid in urine and cerebrospinal fluid, respectively. Administration of LSD to normal volunteers resulted in a significant decrease in DA excretion during periods of altered behavior compared to administration of CS, which exerted little change on the psychic behavior and the urinary output of DA. The results will be discussed in the context of the role of DA in neurologic disease of the extrapyramidal system causing psychiatric symptoms.

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Evaluation of lithium carbonate (Li_2CO_3) in the management of Gilles de la Tourette's syndrome.* *F. S. Messiha, Ph.D.*, H. M. Erickson, Jr., M.D., and J. E. Goggin, Ph.D., Departments of Pharmacology and Therapeutics, Psychiatry, and Pediatrics, Texas Tech University School of Medicine, Lubbock, Texas.

Indirect evidence suggests a dopaminergic dysfunction in Tourette's disease (TD) as indicated by unfavorable response to levodopa therapy and elevated urinary dopamine (DA) excretion (Messiha, F., and Knopp, W.: Dis. Nerv. Sys., in press). The management of stereotyped hyperkinetic behavior as seen in TD by DA-receptor blocker drugs, coupled with the favorable response of dyskinesias to lithium therapy, prompted the evaluation of Li_2CO_3 in TD. A longitudinal study of the efficacy of Li_2CO_3 was conducted in two male patients suffering from severe TD syndrome. Li_2CO_3 was administered orally in a gradual dose buildup over 3-4 wk to obtain plasma Li^+ levels of 0.8-0.9 mEq/L after 7 days drug-free. Serial 24-hr urine collections and blood specimens were obtained on the days clinical ratings and objective behavioral assessments were made. Improvements were noted in coprolalia and tics at plasma Li^+ concentration of 0.5-0.6 mEq/L. This was followed by complete remission of symptoms in one patient and a marked improvement in the second patient at plasma Li^+ levels of 0.8 and 0.9 mEq/L, respectively. Data obtained on DA excretion and changes in plasma and urinary electrolyte levels indicate an interrelationship between these systems and the observed clinical response. The results suggest a hypersensitivity of DA receptors in TD and the clinical efficacy of Li_2CO_3 in this disorder.

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Bioavailability and pharmacokinetics of orally administered triazolam in normal subjects. *C. M. Metzler, Ph.D.*, H. Ko, Ph.D., M. E. Royer, M.S., W. Veldkamp, M.S., and O. I. Linet, M.D., The Upjohn Company, Kalamazoo, Mich.

Triazolam has proved to be an effective hypnotic in extensive clinical trials. To characterize its bioavailability and pharmacokinetic properties, two trials were done in normal volunteers: (1) a single-dose crossover study comparing the compressed tablets and a liquid formulation and (2) a