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# Effect of Insulin, Insulin-Dextrose, and Water Diuresis on Metabolism of Isopropyl Alcohol.*†

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Since it is a reasonable assumption that the important toxic effect of isopropyl alcohol is on the central nervous system,[1] it follows that any therapeutic measure which may limit access of the alcohol to the nervous tissue could be effective in the prevention and treatment of isopropyl alcohol poisoning. Any procedure which is aimed at removal of the agent from the blood could achieve this objective. The present investigation deals with the influence of insulin, insulin plus dextrose, and water diuresis on the post-absorptive blood levels of isopropyl alcohol and acetone as observed in dogs.

*Procedure.* Isopropyl alcohol was administered intravenously to 3 female dogs in doses of 1 g per kg diluted to a 20% concentration in 0.9% sodium chloride solution. The rate of injection was kept constant at 0.25 cc per kg per minute so that the administration time was 25 minutes for each injection. One hour was allowed for equilibration and complete urine specimens, obtained by catheterization, and blood samples were taken hourly thereafter for 6 hours. Analysis for isopropyl alcohol was carried out by a colorimetric method adapted from a procedure described for ethyl alcohol.[2] Acetone was determined by the method of Greenberg and Lester.[3] All animal work was conducted in air-conditioned laboratories, hence environmental conditions were the same throughout.

After the control values were established for the 3 animals, the test dose of alcohol was repeated with one of the following combinations: 1 unit of insulin per kg, 1 unit of insulin per kg plus 2 g of dextrose for each unit of insulin, and 10 cc of water per kg. The insulin was administered subcutaneously, and the dextrose and water were given orally by stomach tube at the time the alcohol injections were completed. The water administrations were repeated hourly for 5 hours, making a total of 60 cc per kg for each animal.

*Results.* An inspection of Fig. 1 shows that all of the procedures tried actually interfered with the metabolic processes concerned with the removal of isopropyl alcohol from the blood stream. The greatest change in the slope of the blood alcohol curve was effected by insulin in combination with dextrose. The rate of decline of blood alcohol was only about one-half as fast with this combination as with alcohol alone. In the case of water diuresis and insulin, the rate of decline was three-fourths and five-sixths, respectively, that of the control. Acetone, an intermediate metabolite of isopropyl alcohol, showed a gradual increase in the blood from an average of 30 mg % to about 72 mg % from the first to the sixth hour. This fairly uniform rise in the 4 series of experiments indicated that the appearance of acetone in the blood was of no significance in detecting any acceleration in the rate of isopropyl alcohol metabolism. Urine acetone concentrations, except for a slight lag during the first hour, were about the same as those found in the blood. Isopropyl alcohol was excreted to some degree in the urine. Al-

* This report is part of a project which involves a complete pharmacologic investigation of isopropyl alcohol and is supported by the Standard Alcohol Company of New York, through the courtesy of Mr. James Park.

† Preliminary report appeared in *Fed. Proc.*, 1946, **5**, 189.

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[2] Newman, H., and Abramson, M., *J. Pharm. Exp. Therap.*, 1942, **74**, 369.

[3] Greenberg, L. A., and Lester, D., *J. Biol. Chem.*, 1944, **154**, 77.

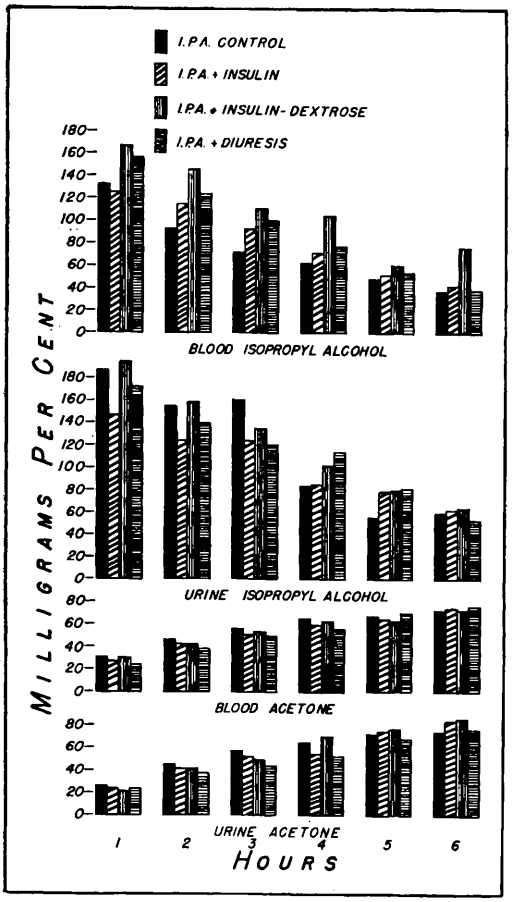


FIG. 1.

Blood and urine isopropyl alcohol and acetone concentrations after intravenous injection of 1.0 g per kilo of isopropyl alcohol (I.P.A.) in dogs, alone and in combination with insulin, insulin plus dextrose, and water diuresis. Each column represents the average of 3 observations.

though it is excreted more rapidly in diuresis, the blood alcohol concentrations remained higher than in the controls. It should be pointed out that the total excretion is a minor factor in regulating blood levels.[4] The effect of variations in the rate of excretion is obscured by the much larger variation in rate of metabolism. These results support the work of Pohl,[5] who tried a number of agents such as epinephrine, an extract of pituitary, histamine, etc., none of which appeared to have any effect on the rate of combustion of isopropyl alcohol.

*Discussion.* It is of interest to compare the urinary excretion of isopropyl alcohol with that of ethyl alcohol. This comparison shows some similarities as well as some differences. Like ethyl alcohol, the amount of isopropyl alcohol eliminated in the urine is not sufficient to influence the blood levels to any extent. From Fig. 1 it is evident that concentration of isopropyl alcohol in the urine does not occur. The alcohol is diffusible into body tissues.[6] After filtering at the glomerulus, it apparently diffuses freely out of the renal tubule as water is reabsorbed, so that the urine comes into concentration equilibrium with the blood. Consequently, it is not possible to hasten alcohol excretion except by increasing the volume of urine. In support of this, it may be pointed out that the control, insulin, and insulin-dextrose series of animals put out an average of 10 cc of urine per hour and excreted 0.49% of the total dose of isopropyl alcohol in 6 hours. The diuretic animals put out 128 cc of urine per hour and excreted 5.49% of the total dose of alcohol in 6 hours. Both urine flow and alcohol excretion increased with diuresis to about the same degree—in this case, approximately 12-fold.

Unlike ethyl alcohol, the concentration of blood isopropyl alcohol bears no fixed relationship to urine isopropyl alcohol. For ethyl alcohol, this is given as 1:1.35 and is independent of the volume of urine excreted. Calculations of this ratio for isopropyl alcohol gave values of 1:0.6 to 1:3.39 and were inconstant, regardless of the time of sojourn of the alcohol in the body or the amount of urine excreted.

No diuretic action attributable to isopropyl alcohol was noted in these experiments. Actually, an inhibition of urinary excretion was noted in the diuretic dogs. The fluid intake of each animal averaged 890 cc, and the volume of urine excreted averaged 769 cc, or a retention of 121 cc of water during the 6-hour period.

*Summary.* 1. Insulin in doses of 1 unit per kg, either with or without dextrose, and water diuresis were ineffective in influencing

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[5] Pohl, J., *Biochem. Z.*, Berlin, 1922, **127**, 66.

[6] Kemal, H., *Z. f. Physiol. Chem.*, 1937, **246**, 59.

the blood isopropyl alcohol curve in dogs given 1.0 g per kg intravenously. The predominant effect was a retardation of the rate of decline, and the use of these substances clinically in acute isopropyl alcoholic intoxication does not appear to be practical.

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## Inhibitory Effect of Thiamine on Vasoconstrictor Action of Nicotine Tested in the Laewen-Trendelenburg Preparation.

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The inhibitory effects of sulfonamides, thiamine and thiazole compounds on the action of nicotine in isolated organs, such as small intestine and striated muscle have been reported previously.[1,2] Recently, investigations have been carried out to determine the effect of thiazole compounds on the blockade action of nicotine on the blood pressure of cats.[3] In view of the probable relationship between tobacco smoking and certain vascular diseases, especially thrombo-angiitis obliterans[4] on the one hand, and the peripheral vasoconstriction induced by nicotine on the other hand, an investigation on the effects of thiamine upon nicotinic vasoconstriction seemed to us of interest. The results reported here deal with such a study.

*Methods.* All the experiments were carried out using the Laewen-Trendelenburg (L-T) preparation in frogs (*Rana pipiens*). This method is highly sensitive for testing vasomotor substances. Male as well as female frogs were used. Frog Tyrode solution was used as a perfusate. Two Mariotte bottles were connected by a Y-piece with the perfusion system, *i.e.* the rubber tubing leading to the aortic cannula. One contained plain Tyrode solution, the other, dissolved in Tyrode, one of the following substances: crystalline thiamine hydrochloride (Merck), thiazole, pyrimidine, sodium sulfathiazole, thiouracil, para-aminobenzoic acid, nicotinamide. These substances were used at various concentrations. Nicotine in the form of nicotine base† or nicotine salicylate in aqueous solution was used. The injections of the different drugs were made through the rubber tubing into the glass cannula inserted into the abdominal aorta of the frog. All due precautions were used during the injection of drugs to avoid mechanical interference with the perfusion. The vasomotor action of the different drugs was measured in terms of the output variations of drops per minute.

*Results.* 1. *Control experiments with nicotine.* The injection of a small amount of nicotine (1-10 γ) in the L-T preparation elicited 2 major reactions: (a) Twitchings of the thigh and leg muscles, lasting as a rule from 30 to 60 seconds. (b) A marked reduction (50%-80%) of the outflow from the abdominal vein, as expressed in terms of drops per minute. The duration of the vasoconstrictor effect varied though the average ranged between 15 to 30 minutes until the output returned to its initial level.[5]

A series of experiments was carried out in which nicotine was tested several times in the same preparation. As a rule, the perfused frog became more sensitive to nicotine as the experiment progressed, *i.e.* a

* Fellows of the Dazian Foundation for Medical Research.

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2 Unna, K., and Pick, E. P., *J. Pharm. and Exp. Therap.*, 1944, **81**, 294.

3 Pick, E. P., and Unna, K., *J. Pharm. and Exp. Therap.*, in press, 1946.

4 Silbert, S., *J. A. M. A.*, 1945, **129**, 5.

† Nicotine Alkaloid Eastman Kodak.

5 Handovski, H., and Pick, E. P., *Arch. f. exp. Path. u. Pharmakol.*, 1913, **71**, 89.