Effect on Urinary Nitrogen Excretion of Rate of Administration of Solution of Amino Acids in Man. (19387)

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A protein hydrolysate has been prepared for intravenous use in man which is virtually free of the dicarboxylic amino acids, aspartic and glutamic acids(1). The significant reduction in anorexia, nausea, and vomiting from this solution compared to preparations containing these amino acids has been accompanied by an increase in possible rate of infusion without reaction, thus broadening the clinical usefulness and patient comfort in parenteral feeding(2). With this solution, rapid rates of infusion are possible, in fact up to 10 mg of nitrogen/kg/minute intravenously, representing an infusion time of just over 10 minutes for 500 cc of a 10% solution. Such rapid rates of infusion raise the possibility of increased urinary excretion of the infused amino acids or increased conversion to urea. Previously rapid rates of infusion induced greater urinary excretion of amino acids; nevertheless even at very rapid rates only about 10% of the 50 g infused was excreted(3). The urinary excretion of amino acids correlated more closely with size of infusion than with rate of administration. There was no selective excretion of any one of the 10 essential amino acids determined microbiologically.

The data presented in this communication were collected to determine whether rapid rates of infusion of the amino acid solution resulted in increased deamination of amino acids and hence increased excretion of non-protein nitrogen in the urine.

Materials and methods. The amino acid mixture† was made by the complete acid hydrolysis of casein, contained no peptides, was essentially devoid of the dicarboxylic amino acids (glutamic and aspartic), and was supplemented with dl-tryptophane and glycine so that it contained approximately 10% amino acids including the 8 essential for man. Seven subjects were selected. Two were normal medical students, 3 had liver disease (alcoholic cirrhosis), mild in 2 and severe in one, one patient had severe undernutrition from prolonged obstruction due to carcinoma of the larynx, and one was a chronic alcoholic essentially normal metabolically at time of study. The 24-hour urine was collected in glacial acetic acid and toluol and the total nitrogen content determined by micro-Kjeldahl digestion and Keyes' distillation. All urines were examined for protein and analyzed for alpha amino nitrogen by the gasometric ninhydrin method as described by Van Slyke, MacFadyen, and Hamilton(4). The patients were maintained on the ward with nurses and dietitians in attendance trained in metabolic methods. The food consumed daily was calculated from standard tables.

Results. Fig. 1 and 2 show the intake of protein by mouth and of amino acids intravenously, the total nitrogen excreted in the urine, and the rate of administration of the 10% solution of amino acids in terms of mg of nitrogen per kg per minute. Although nitro-

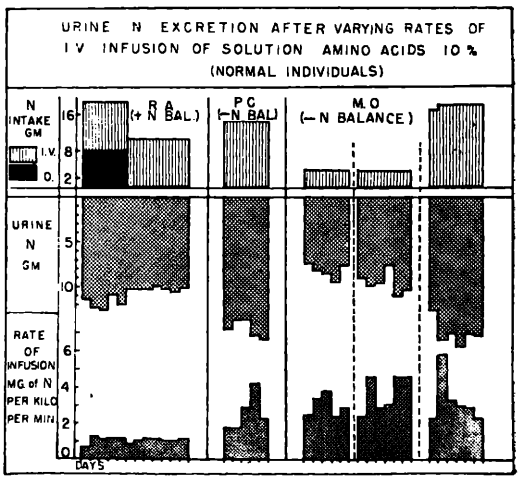

FIG. 1.

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† Furnished by Merck & Co., Rahway, N. J.

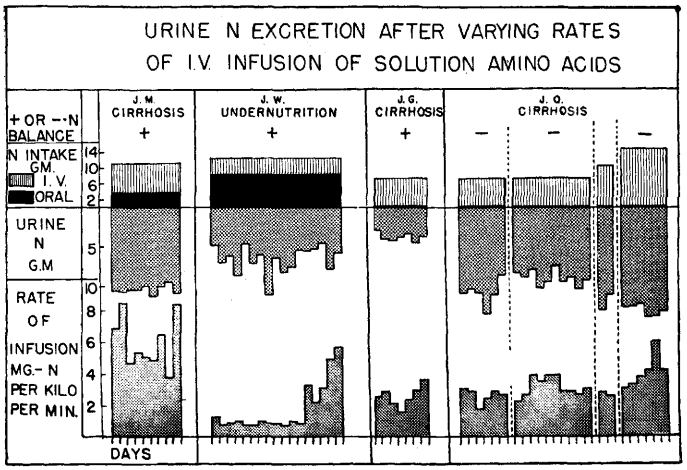

FIG. 2.

gen balance was performed on these patients, it is indicated in the chart only by the + (positive) or — (negative) sign. In four patients nitrogen balance was positive throughout, while in 3 negative balance obtained since for concurrent studies the total nitrogen intake was maintained below the minimum requirement.

The nitrogen excretion varied greatly from individual to individual depending upon nitrogen intake, nutritional status, and other factors. There was also day to day variation in nitrogen excretion in individual patients. There was a wide variation in the rate of administration of the solution from below 1 mg/kg body weight/minute to almost 9. In spite of this wide variation, there was no correlation between rate of administration and quantity of nitrogen excreted in the urine during each 24-hour period, either from patient to patient or in the individual patients. This is well illustrated by patient J.W. (Fig. 2) in whom there was little variation in nitrogen excretion although the rate of administration varied from 1 to almost 6 mg nitrogen/kg/minute.

The urinary excretion of alpha amino nitrogen was determined daily and formed only a small portion of the total urinary nitrogen. This fraction did not exceed 10% of the total nitrogen excreted, and, as previously observed (3), did not increase strikingly with marked increases in the rate of administration of the solution. Proteinuria did not occur. The variations in the excretion values for urinary total nitrogen shown in Fig. 1 and 2, therefore, reflect primarily changes in the urinary excretion of non-protein, non-amino acid nitrogen.

Discussion. The advantages of the 10% solution of amino acids used in this investigation are chiefly those of the low incidence of anorexia following infusion and the possibility of rapid rates of administration without nausea and vomiting. Although it was previously shown that even rapid rates of infusion did not increase the excretion of amino acids sufficiently to limit the nutritional value of the material for intravenous protein feeding(2), the possibility that increased deamination might occur, thus limiting its biological value, had to be considered. This was especially true since Silber and Porter(5), using the same or a similar preparation in dogs, observed that a 4-fold increase in the rate of infusion caused a decrease of approximately 60% in nitrogen retention, not, however, due to an increased loss of amino acids but rather to non-amino acid, non-protein nitrogen. The rates of infusion used by Silber and Porter usually were greater per kg in their dogs than in the individuals reported here. However, even in the few instances in which a similar rate was used in our patients, for example in patient J.M., no increase in nitrogen excretion occurred so that there was no change in nitrogen retention

or biological value. In fact, there appeared to be no influence of rate of infusion on nitrogen retention whether the amino acid mixture was given as a sole source of nitrogen or as a supplement to small or large protein intakes by mouth.

Summary. 1. Seven subjects (including normal individuals and patients) were given daily intravenous infusions of a 10% solution of amino acids at widely varying rates of infusion. 2. There was no correlation between the daily non-protein nitrogen excretion and the rate of infusion. Very rapid rates of infusion did not increase the nitrogen excretion and thus did not reduce the biological value of the amino acid solution.

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Protective Effect of Pitressin and of Epinephrine Against Total Body X-Irradiation. (19388)

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Pendergrass and his associates(1) have demonstrated a protective effect of pitressin and epinephrine against local x-irradiation injury of the leg of the rat. It was assumed by the authors that local tissue anoxia, produced by these principles, was involved in the protective mechanism. It became of interest, therefore, to investigate the possible effect of these agents on the aerobic and anaerobic metabolic cycles, as well as to study the effect of these agents on the survival rate after total body x-irradiation.

Methods. "Labile phosphate" (ATP*) content and cytochrome oxidase activity of muscle of rats as influenced by pitressin and epinephrine administration or by limb occlusion. Phosphate content and cytochrome oxidase activity determinations were done on gastrocnemius muscle samples from normal male Sprague-Dawley rats weighing 220-300 g. The rats were starved for 24 hours with water *ad libitum*, and were sacrificed 15 or 30 minutes following intraperitoneal injection of pitressin (Parke, Davis) or epinephrine (Abbott). Control animals received equivalent volumes of 0.9% saline or no treatment prior to sacrifice. Treated and untreated controls showed no significant difference and were grouped in the calculations. Phosphate determinations on lyophilized tissue were carried out according to the method described by Umbreit(2). Cytochrome oxidase activity was determined according to the method of Schneider and Potter(3). In the occluded limb experiments the rats were anesthetized with sodium pentobarbital (45 mg/kg) and a tourniquet consisting of 5 turns of a rubber band (Eberhard Faber No. 30) was applied to the right hind leg as high as possible. The teeth were clipped to prevent tourniquet removal or self-laceration. Control animals were anesthetized and the teeth were clipped. All animals were sacrificed without tourniquet release at ½ hour or 4½ hours after tourniquet application. Gastrocnemius muscle samples were taken from the occluded limb as well as from the opposite hind limb of the tourniquet animal and from a hind limb of the control animal. The effect of pitressin or epinephrine administration against total body x-irradiation: Male Sprague-Dawley rats weighing 220-300 g were irradiated in pairs,

* Adenosinetriphosphate.