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Effect of Intravenously Administered Amino Acids on Blood Ammonia.* (22543)

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In a study of the metabolism of parenterally administered glycine Handler, Kamin and Harris(1) reported that glycine infused into dogs at rates exceeding 1 mg amino N/kg/min. was invariably found to be lethal, although after varying periods of time. These findings were interpreted by Handler *et al.* as a manifestation of the toxicity of glycine. Doolan *et al.*(2) in studies on renal clearance of amino acids in humans observed a severe reaction in a subject receiving a 5% solution of glycine injected intravenously at a mean rate of 0.67 mg amino N/kg/min. Because of the symptoms associated with the reaction to glycine these authors suggested that an elevation in blood ammonia might be responsible for the toxicity otherwise attributed to the amino acid itself. To investigate this possibility the effect in dogs of intravenous administration of amino acids on the levels of ammonia in the blood was studied.

Procedure. One liter of an amino acid solution was infused intravenously over a 2-hour period to adult male mongrel dogs under sodium pentobarbital anesthesia. Blood samples were drawn prior to the infusion and at 30-minute intervals thereafter. Heparin was used as the anticoagulant. Each sample was analyzed for ammonia, urea and amino acid nitrogen. Ammonia nitrogen was determined by the method of Conway(3); urea nitrogen by the method of Van Slyke and Kugel(4), and amino acid nitrogen by the method of Hamilton and Van Slyke(5).

In the first series of experiments glycine was infused in doses ranging from one to 7 mg amino N/kg/min. In a similar study DL-alanine was infused at a rate of 3.5 mg amino N/kg/min. To compare the blood ammonia levels that follow the infusion of a mixture of amino acids with those after infusion of a single amino acid, an acid hydrolysate of casein fortified with DL-tryptophan† was infused at rates of 3.5 or 0.58 mg amino N/kg/min.

Results. In Table I the concentrations in blood or plasma of ammonia, urea and amino acid nitrogen after the infusion of the various amino acids are given. The data were derived from individual experiments under the conditions described. It is apparent that significant increases in blood ammonia occurred after the infusions of glycine at levels above one mg amino N/kg/min. At the maximum infusion rate used (7 mg amino N/kg/min) the dog expired in respiratory failure immediately after the 2-hour infusion. At lower rates of administration no symptoms were elicited. The elevations of ammonia in the blood were directly related to the amounts of amino acid administered, indicating an immediate relationship between the dose of amino acid and the occurrence of ammonia intoxication. The amino nitrogen levels reflect the concentration in the blood of glycine that was being infused. Conversion to urea of the nitrogen derived from the infused amino acid was responsible for the rise in blood urea nitrogen since it was proportional

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† Courtesy, Winthrop Laboratories.

TABLE I. Ammonia, Urea and Amino Nitrogen in Blood at Intervals after Intravenous Infusions of Amino Acids in Dogs.

	Interval (min.) 0	30	60	90	120
			Glycine (1 mg N/kg/min.)		
Ammonia N*	.18	.52	.25	.72	.38
Urea N†	17.1	17.2 (.1)	20.4 (3.3)	21.9 (4.8)	22.4 (5.3)
Amino N‡	6.2	9.	9.5	7.1	7.6
			Glycine (1.75 mg N/kg/min.)		
Ammonia N*	.37	1.88	1.69	.63	1.55
Urea N†	25.	29. (4.)	30. (5.)	33. (8.)	33. (8.)
Amino N‡	5.1	11.7	10.6	9.7	8.1
			Glycine (3.5 mg N/kg/min.)		
Ammonia N*	.12	3.67	10.77	14.43	17.4
Urea N†	34.	36. (2.)	38. (4.)	42. (8.)	44. (10.)
Amino N‡	4.9	15.2	32.	33.7	36.7
			Glycine (7.0 mg N/kg/min.)		
Ammonia N*	.27	7.	14.9	26.3	>35.
Urea N†	16.8	19.4 (2.6)	23. (6.2)	27.9 (11.1)	32.1 (15.3)
Amino N‡	3.1	38.1	58.2	70.8	89.2
			DL-Alanine (3.5 mg N/kg/min.)		
Ammonia N*	.74	.59	1.66	1.91	1.7
Urea N†	15.7	17.6 (1.9)	22.6 (6.9)	25.6 (9.9)	27.6 (11.9)
Amino N‡	4.1	34.7	41.3	43.6	43.9
			Casein hydrolysate (3.5 mg amino N/kg/min.)		
Ammonia N*	.16	5.89	5.2	4.41	5.1
Urea N†	14.9	21.9 (7.)	26. (11.1)	31.1 (16.2)	37.8 (22.9)
Amino N‡	4.1	23.2	24.8	31.9	40.9
			Casein hydrolysate (0.58 mg amino N/kg/min.)		
Ammonia N*	.13	.55	.87	.82	.13
Urea N†	19.8	19.4 (-.4)	21. (1.2)	22.3 (2.5)	22.3 (2.5)
Amino N‡	4.6	4.6	5.5	4.4	4.6

* μg/ml.
† mg/100 ml. Increase over fasting level shown in parentheses.
‡ mg/100 ml (plasma).

to the amounts of glycine infused as well as to the blood ammonia levels.

In order to compare the effects on blood ammonia of an amino acid closely related to glycine, alanine was infused intravenously. However, because of limitations of solubility it was impractical to administer this amino acid at a rate exceeding 3.5 mg amino N/kg/min. Increases in the blood ammonia were very similar to those to be expected if one-half this dose were used, judging from the results of the glycine experiment. This suggested that the natural (L) isomer was deaminated more promptly than the D form and that the ammonia was contributed almost exclusively by the L isomer. Injections of the casein hydrolysate at a rate of 3.5 mg amino N/kg/min. also produced increases in the blood ammonia but considerably less than predicted from administration of glycine at a comparable rate. At the same time blood urea nitrogen increased over the fasting level to a greater extent than that observed when comparable amounts of amino nitrogen were given as a single amino acid. This indicated that some of the amino acids in the casein mixture exerted an influence to decrease the levels of ammonia in the blood. The concomitant rise in urea may indicate that this was effected by accelerating the rate of removal of ammonia through its conversion to urea. Administration of casein hydrolysate at a rate of 0.58 mg amino N/kg/min. corresponds to that recommended for its use under clinical circumstances. At this rate, no significant elevation of ammonia in the blood occurred.

The results of these studies indicate that

glycine infusions may be used as a means to produce ammonia intoxication for experimental purposes. This method may be more physiological than the use of inorganic compounds of ammonia.

Summary. 1. Glycine, alanine or an acid hydrolysate of casein were intravenously infused in dogs over a 2-hour period, and the concentrations of ammonia, urea and amino acid nitrogen in the blood were determined at 30-minute intervals. 2. At rates of infusion of glycine above 1 mg amino N/kg/min. significant increases in blood ammonia occurred, which were directly related to amounts of glycine infused. At the maximum infusion rate used (7 mg amino N/kg/min.) the dog expired in respiratory failure at the end of the 2-hour infusion. The results of these experiments indicate that the toxicity attributed to rapid rates of infusion of glycine may actually be due to ammonia intoxication. 3. After administration of a casein hydrolysate increases in blood ammonia were less and those of urea were greater than predicted from administration of glycine at comparable rates. This suggests that certain amino acids in the mixture decrease blood ammonia levels by enhancing urea production.

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Comparative Effect of Arginine and Monosodium Glutamate on Blood Ammonia.* (22544)

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In a previous study(1) on the effect of intravenously administered amino acids on ammonia levels in the blood it was noted that after the administration of a mixture of amino acids (casein hydrolysate) increases in blood ammonia were less and those of urea were greater than predicted from the infusion of a single amino acid (glycine) at a comparable rate. These findings suggested that certain amino acids in the mixture effected a decrease in blood ammonia levels by enhancing urea production. The effect of a single amino acid infused together with glycine was therefore studied in order to investigate this hypothesis. For this purpose, arginine was selected because of its role in the urea cycle.

The use of monosodium glutamate has been advocated as a means to reduce high blood ammonia levels in human patients by Walshe (2) and by McDermott(3). The reduction is presumably effected through amidation of L-glutamic acid to form glutamine. It was therefore of interest to compare the effect on blood ammonia of glutamic acid with that of arginine. This would serve to indicate relative efficiency for detoxification of ammonia of amidation of glutamic acid as compared to urea production.

Procedure. Ammonia toxicity was induced in adult male mongrel dogs by intravenous administration of glycine as described by Harper *et al.*(1). Blood samples were drawn before the infusion and at 30-minute intervals thereafter, for a 2-hour period. Heparin was used as the anticoagulant. The blood samples were analyzed for ammonia, urea, and amino acid nitrogen. Ammonia nitrogen was determined by the microdiffusion method of Conway(4), urea nitrogen by the method of Van Slyke and Kugel(5) and amino acid

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