Some Effects of N-Nitrosodimethylamine on Rabbit Kidney Function. (23082)

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N-nitrosodimethylamine (NNDMA) has become of interest as an intermediate in the manufacture of asymmetrical dimethyl hydrazine, used as a component of rocket fuels. One of 2 laboratory workers exposed accidentally to this compound died of "acute terminal passive congestion" of the kidneys(1). Other cases have shown toxic effects on the liver(2,3,4). Animal experiments have shown degenerative and malignantly proliferative changes in liver(3,5). Because fatally poisoned animals may die within a few hours and because hepatectomized animals may be expected to survive for up to 40 hours(6), work was undertaken to see whether NNDMA has other significant toxic effects. The early report implicating the kidney in NNDMA toxic effects(1), and our own observation that the material caused variations in urine output in dogs, suggested that kidney effects might be a part of the toxic mechanism of this compound.

Materials and methods. Rabbits of mixed breed and sex were used for kidney function studies in which inulin and p-aminohippuric acid (PAH) clearances were measured(7). The animals were lightly anesthetized with pentobarbital and infused continuously with physiological saline solution containing inulin 2.5 mg/ml and PAH 14.3 mg/ml, at 1 ml/min. Blood samples were taken from a deep femoral artery, and urine flowed through polyethylene catheters in the ureters. Urine was collected at 30-minute intervals and corresponding blood samples were taken at midpoints of the intervals. Urine and blood were analyzed for inulin(8) and PAH(9).

Rabbits which had been injected intravenously with NNDMA (10 mg/kg or ⅔ approximate LD_{50}) 18, 45 and 65 hours previously were anesthetized and prepared as described above. Two or 3 animals were studied at each time, yielding 6 experimental periods each. Values obtained from poisoned animals were compared with those from 7 animals which received no NNDMA, using the "t" test(10,11).

Results. Preliminary experiments on short-term effects of 60 mg/kg of NNDMA on renal function showed no significant changes from control values, with the possible exception of a decrease in fPAH(7) 2 hours after NNDMA was given.

Longer term studies of kidney function are presented in Table I. It is apparent that 18 hours after injection of NNDMA, urine flow was significantly decreased. There was also a significant decrease in clearance of PAH. While it is questionable that the simultaneous decrease in mean glomerular filtration rate (inulin clearance) is real, there is little doubt that the tubular epithelium transfers less PAH into the tubular lumina at 18 and 45 hour intervals.

The net result of the kidney studies, then, is that NNDMA (60 mg/kg) until 2 hours after injection has no clearly adverse effects upon renal function, but that there may be decrease in tubular function beginning at this time. Loss of tubular function is definite 18 hours after administration of smaller doses of NNDMA (10 mg/kg), and continues through the 45 hour period. Some recovery from the impairment is evident by 65 hours. Filtration is not significantly impaired, but a minimal decrease in filtration rate may be present also.

Urine flow decreased significantly at 18 (by 67%) and 45 (by 76%) hours, and this was simultaneous with depressed tubular excretion of PAH. Since filtration had decreased by only 47% and 58%, respectively, at these 2 times, the rest of the decrease in urine flow must occur by increased passage of water from the tubular lumina into the peritubular capillaries. We observed that capsules of kidneys of poisoned animals are usually tense. This observation suggests that oliguria in NNDMA poisoning may result in part from increased intracapsular pressure

TABLE I. Long Term Effects of NNDMA on Rabbit Kidney Function, Dose 10 mg/kg, I.V.

Hr after NNDMA	N	Urine flow	Inulin clearance	PAH clearance	fPAH
		ml/min. ± S.E. and (P)*			± S.E. and (P)*
0	42	.76 ± .067	3.64 ± .714	18.39 ± 2.450	9.61 ± 2.645
18	18	.25 ± .063 (.001)*	1.92 ± .602 (.1)	4.60 ± .421 (.001)	2.09 ± .425 (.05)
45	12	.18 ± .024 (.001)	1.52 ± .248 (.1)	2.19 ± .611 (.001)	2.75 ± .803 (.1)
65	12	.79 ± .137 (.8)	3.22 ± .475 (.1)	13.33 ± 1.660 (.2)	4.01 ± .645 (.2)

* P = Probability of chance difference from controls.

N refers to No. of 30-min. clearances measured. Value fPAH(7) represents tubular excretion rate of PAH in terms of glomerular filtration rate, and was calculated independently for each clearance measurement.

with increased back-diffusion of water across the tubular epithelium. Also, when kidneys of animals used in long-term studies were sectioned, stained and examined microscopically, vascular congestion, particularly in the area of the collecting tubules, was evident in poisoned animals as compared with controls. Such congestion could contribute to increased intracapsular pressure and oliguria(12), and appeared correlated in degree with functional changes. Livers of experimental animals showed central zone damage as reported by other investigators(3,4).

Preliminary experiments indicated that circulatory, respiratory, and autonomic nervous systems are not implicated to any important extent in acute death resulting from administration of NNDMA. The principal causal factor in such deaths has been recognized generally as liver damage(2,3,4).

Summary. 1. The present studies have shown that, in addition, significant loss of kidney function can result from exposure to this material. Such kidney debilitation could be of considerable consequence if it occurred together with severe liver damage. The time of occurrence of maximal kidney effects correlates well with time of death after NNDMA, as well as with that of rise of blood NPN in rabbits and in dogs. 2. No histologically demonstrable changes in functional kidney cells were evident in these animals nor in those examined by other investigators(3,4). However, other investigators found local vascular congestions in liver, lungs and intestine. The present experiments indicate this to be true in kidneys which show significant loss of function. The suggestion(3) that an outstanding property of NNDMA is its affinity for vasculatures of liver, lung and intestine may also apply to vasculature of kidney.

The authors acknowledge the valuable analytical work of Aurora Bransford in the clearance studies.

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Received February 8, 1957. P.S.E.B.M., 1957, v94.