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Effects of Sodium Nitrite and Certain Organic "Nitrates" on Blood Pressures of the Cat.*

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Herrman *et al.*[1] reported that in the etherized dog mannityl hexanitrate produced a greater lowering of carotid blood pressure than glyceryl trinitrate. Krantz *et al.*[2] concluded that isomannide dinitrate caused a more prolonged lowering of the carotid blood pressure of the etherized dog than glyceryl trinitrate, erythrityl tetranitrate or mannityl hexanitrate. In both experiments cited above the drugs were given by intravenous injection. In the paper by Krantz *et al.* there appear to have been no direct comparisons of isomannide dinitrate and glyceryl trinitrate or mannityl hexanitrate, the conclusions about the latter drugs being drawn from the literature. In neither paper is there data to allow one to assess the variability of the experimental results and the validity of the authors' conclusions.

The present experiment was undertaken to examine the effects of sodium nitrite and a number of organic "nitrates" on the carotid and right atrial pressures in such a way as to yield comparable results. The substances used were sodium nitrite ($NaNO_2$), isomannide dinitrate (I2N), glyceryl trinitrate (G3N), erythrityl tetranitrate (E4N) and mannityl hexanitrate (M6N).

Experimental. Cats were anesthetised by intraperitoneal injection of sodium pentobarbital, the doses being calculated from a curve similar to that of Bazett and Erb.[3] They were prepared then for recording respiration by lateral pressure, carotid blood pressure and right atrial pressure. The blood of the animal was rendered noncoagulating by intravenous injection of 1 ml/kg of an 8% solution of chlorazol fast pink. Drug solutions were washed into a saphenous vein with saline.

The compounds studied, except $NaNO_2$, were dissolved in a solvent consisting of 80 g of urethane in sufficient 95% alcohol to make 100 ml of solution. $NaNO_2$ was dissolved in a similar solvent containing water in place of alcohol. The aqueous and alcoholic solvents had identical effects. Solutions of the drugs were made to contain 4 mg of drug per ml, a dose of 0.25 ml of solution per kg of cat being used in all experiments.

The various solutions, including the solvent, were injected serially into each cat, at least one-half hour elapsing between successive injections. The order of administration of the 6 solutions was varied in a cyclic manner through the series of 12 cats, so that there were 2 such cycles.

Table I shows the actions of the solvent and the 5 drug solutions on the mean carotid pressure and the right atrial pressure. It is evident that while the mean effects on carotid pressure show differences which agree in some respects with those reported previously in the etherized dog,[1,2] the variations in the present experiment were so great as to force the conclusion that equal doses of the 5 drugs used here have roughly identical effects on mean carotid pressure. There is no evidence that the same thing is not true of the previous experiments.

When the atrial pressures are considered, it is apparent that $NaNO_2$ and E4N differ from the other drugs and from each other. Both of these drugs produced a lowering of

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1 Herrman, R. F., Leake, C. D., Loevenhart, A. S., and Muehlberger, C. W., *J. Pharm. Exp. Therap.*, 1926, **27**, 259P.

2 Krantz, J. C., Jr., Carr, C. J., Forman, S. E., and Ellis, F. W., *J. Pharm. Exp. Therap.*, 1939, **67**, 191.

3 Bazett, H. C., and Erb, W. H., *J. Pharm. Exp. Therap.*, 1933, **49**, 352.

TABLE I.

Effect of Sodium Nitrite and Organic Nitrates on the Mean Carotid Pressure and Right Atrial Pressure of the Cat Anesthetized with Nembutal.

Drug	Mean carotid pressure				Right atrial pressure			
	Mean*	Maximal† drug effect	Mins. to max. effect	Mins. to recovery	Mean‡	Maximal§ drug effect	Mins. to max. effect	Drug effect‖ at 8 mins.
Solvent	141	—13 ± 35	3.7	7.7	—11.2	+1.0 ± 1.4	0.4	+0.1 ± 0.1
M6N	134	—81 ± 36	0.9	6.1	—16.2	+1.2 ± 0.9	1.7	+1.1 ± 0.7
E4N	129	—65 ± 23	0.7	8.6	—13.3	+2.2 ± 1.8	1.2	—2.0 ± 1.6
G3N	153	—92 ± 29	0.8	5.5	—15.5	+4.5 ± 1.2	1.6	+2.5 ± 0.8
I2N	135	—59 ± 26	1.0	6.0	—13.5	+2.5 ± 2.1	1.6	+0.3 ± 0.3
$NaNO_2$	141	—46 ± 35	0.5	8.0	—11.5	—3.7 ± 1.4	0.4	—1.5 ± 0.7

* Mm of mercury pressure.
† Mean maximal change in mm of mercury ± standard deviation of mean.
‡ Mm of water pressure.
§ Mean maximal change in mm of water ± standard deviation of mean.
‖ Mean change in mm of water ± standard deviation of mean.

right atrial pressure at a time (8 minutes after the injection) when the other substances caused or permitted increases in this pressure. $NaNO_2$ differs from E4N in that it produced an immediate fall in atrial pressure while the fall after injection of E4N was a delayed reaction.

The long period for which the atrial pressure remained lowered after the administration of $NaNO_2$ probably indicates that in the cat the principal prolonged action of this drug is on the venous side of the circulation, as has been found to be the case in man by Weiss *et al.*[4] The eventual fall of atrial pressure after injection of E4N to about the level obtained by giving $NaNO_2$ means possibly that the former drug has a prolonged but weak dilating action on the venous circulation, which is masked at first by the increased return through dilated arterioles.

The effect of E4N on the atrial pressure is of especial interest in that it suggests that E4N is the only one of the 4 organic "nitrates" used here which has a vasodilator action as the result of a mechanism similar to that of $NaNO_2$. Various investigators have found evidences[5-7] that I2N, G3N, E4N and M6N do not act in the body by the release of nitrite ion as postulated by Herrman *et al.*[1] The partial similarity between the actions of E4N and $NaNO_2$ on the atrial pressure certainly does not prove that E4N releases nitrite ion but it does mirror some difference in behavior in the body between E4N and the other organic "nitrates." This difference might involve the slow release of nitrite ions by E4N at such a rate as to produce no significant methemoglobinemia or elevation of the level of nitrite ion in the

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[5] Crandall, L. A., Jr., Leake, C. D., Loevenhart, A. S., and Muehlberger, C. W., *J. Pharm. Exp. Therap.*, 1931, **41**, 103.

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[7] Rath, M., and Krantz, J. C., Jr., *J. Pharm. Exp. Therap.*, 1942, **76**, 33.

general circulation.

Summary. Sodium nitrite ($NaNO_2$), isomannide dinitrate (I2N), glyceryl trinitrate (G3N), erythrityl tetranitrate (E4N) and mannityl hexanitrate (M6N) injected intravenously in doses of 1 mg/kg into the cat anesthetized with pentobarbital had effects on the mean carotid blood pressure which did not differ significantly in magnitude and duration.

$NaNO_2$ appeared to have an immediate and powerful dilating action on the venous system while E4N may have had a similar but weaker action. I2N, G3N and M6N appeared not to affect the venous system significantly.

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Influence of Protein-Binding on the Interpretation of Penicillin Activity *In vivo*.*

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Introduction. In evaluation of the therapeutic use of penicillin and other antibacterial agents, considerable interest was centered on observations of the height and duration of the serum concentrations attained after administration to humans. Studies of this type have been of value in determining the dosage of penicillin, the frequency and route of administration, and the influence of various vehicles and adjuvants on absorption and excretion.

The availability of the individual purified penicillins, X, G, F, K and dihydro F, has stimulated renewed interest in this type of investigation. It has been reported that penicillin X affords higher and more prolonged concentrations in serum than an equal dose of penicillin G.[1,2] Likewise penicillin X has been found to be significantly more effective than penicillin G in the treatment of infections in experimental animals.[3,4]

Of particular interest have been the studies of penicillin K. *In vitro,* penicillin K is distinctly more active than penicillins X, G, F and dihydro F. In the treatment of infections in experimental animals, however, penicillin K has been found to be the least effective of these 5 penicillins.[3,4] It was observed simultaneously in 3 laboratories[5–7] that, following intramuscular injection, penicillin K apparently disappeared rapidly from the circulating blood. It was also observed that the total urinary excretion of penicillin K was low, and it was concluded that the drug was ineffective because of rapid destruction in the body.[5,6]

Eagle[8] has reported a possible explanation of the differences in pharmacologic behavior among the individual penicillins. In a study of penicillins X, G, F and K, he observed that all 4 penicillins were slowly inactivated

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2 Eagle, H., *J. Exp. Med.*, 1947, **85**, 163.

3 Hobby, G. L., Burkhart, B., and Hyman, B., PROC. SOC. EXP. BIOL. AND MED., 1946, **63**, 296.

4 Eagle, H., *J. Exp. Med.*, 1947, **85**, 175.

5 Eagle, H., and Musselman, A., *Science,* 1946, **103**, 618.

6 Coghill, R. D., Osterberg, A. E., and Hazel, G. R., *Science,* 1946, **103**, 709.

7 McDermott, W., and Tompsett, R., cited in *J. A. M. A.*, 1946, **131**, 271.

8 Eagle, H., *J. Exp. Med.*, 1947, **85**, 141.