Effects of Cysteamine* and Cysteine on Cardiac Output and Oxygen Content of Venous Blood. (21075)

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Considerable attention has been recently focussed on the protection against X-rays afforded in animals by both cysteine and cysteamine (= β-mercaptoethylamine = Becaptan Labaz). The radioprotective action of cysteamine has been demonstrated by Bacq and his associates(1,2) to be about 8 times as potent as that of cysteine† in C57 black mice.

Recently, Salerno and Friedell[(3,4); and discussed by Alexander Hollaender at Aarhus Conference, 1953] reported that cysteine causes tissular anoxia in dogs when given in the large amounts necessary to obtain a marked radioprotection and, in their opinion, the radioprotective effect of cysteine would be due at least partially to the induced anoxia. Thus it seemed pertinent to determine if cysteamine also causes tissular anoxia and to determine experimentally if large amounts of cysteine reduced the oxygen content of the *mixed* venous blood, as they do for the *peripheral* blood, according to Salerno and Friedell. Since the experimental procedures used for this research involve the collection of arterial and *mixed* venous blood samples, there was opportunity to study the changes in cardiac and systolic outputs and the respiratory exchanges which follow administration of cysteamine and cysteine.

Methods. Six dogs were anesthetized with chloralose. The blood pressure in the femoral artery was recorded; the heart rate could be obtained accurately at any moment. Calculations of the cardiac output were based on the well-known Fick's principle. Blood samples were collected with the usual care to avoid air contamination. Mixed venous blood was obtained directly from the right ventricle by right heart catheterization according to Cournand's technic(5), the catheter being passed along the right jugular vein. Arterial blood was taken from the femoral artery. Oxygen consumption was determined by analysis of expired air collected through a tracheal cannula in a Douglas bag; ventilation was measured in a spirometer and the gas analyses (oxygen and carbon dioxide) were carried out in Haldane's classical apparatus. Measurements were made before and after administration of the drugs, usually 5, 15, 30, and 45 minutes following injection. For each determination of the cardiac output, mixed venous blood and expired air were collected simultaneously. Since the heart rate is known at any moment, the systolic output can also be determined. Both cysteamine and cysteine were injected very slowly (in about 5 minutes) by venous route, cysteine hydrochloride having been neutralized just before injection with a normal solution of sodium hydroxide. All injections were made at one-hour intervals; cysteamine (10, 20, and 40 mg/kg) was injected first in dogs 8, 9, 10, and 11, and cysteine (20, 80, 160, and 320 mg/kg) was given first in dogs 12 and 13. Results obtained for cardiac output and systolic output are reported in Table I in which figures are calculated in percentage of the control values.

Results. 1. *Cysteamine.* Cysteamine did not significantly reduce the cardiac output. In dogs 8 and 9 there was a very slight fall of cardiac output after 45 minutes; in others, the cardiac output did not change at all (dog 10 after 5 minutes and dog 13 after 5 and 15 minutes). In 4 dogs, cysteamine produced an increase in cardiac output, ranging from 10 to 75% (dog 10 after 15 minutes). Heart rate was not affected. The changes in systolic output were similar in direction and degree to those of cardiac output. Variations in pul-

* Bacq, Baddiley, Lipmann, Lynen, and Eldjarn have agreed to use in biological discussions the term *cysteamine* for β-mercaptoethylamine, the amine obtained by decarboxylation of cysteine (*Science*, 1954, v119, 163).

† In weight, cysteamine base (M.W.77), against cysteine HCl (M.W.158).

TABLE I. Variations in Cardiac Output and Systolic Output following Intravenous Injection of Cysteamine and Cysteine in Dogs.

Dog No.	Dog Wt (kg)	Dose (mg/kg) Cysteamine	Dose (mg/kg) Cysteine	Control values of output (ml) Cardiac	Control values of output (ml) Systolic
8	25	10	20	3475	24
9	20	10	80	1188	6.3
10	31	20	160	2592	16.6
11	28	20	320	1602	8.6
12	23	40	320	1872	12.3
13	24	40	320	1575	9.7

Cysteamine

Dog No.	Cardiac output (%) in indicated time* Min. 0	5	15	45	Systolic output (%) in indicated time* Min. 0	5	15	45
8	100	—	82.5	87.4	100	—	78	67.5
9	100	—	143.5	85.5	100	—	132	90.5
10	100	96	174	—	100	114	190	—
11	100	165	142	—	100	181	148	—
12	118	129	134	—	118	128	138	—
13	116	122	97	—	95	113	102	—

Cysteine

Dog No.	Cardiac output (%) in indicated time* Min. 0	5	15	30	45	Systolic output (%) in indicated time* Min. 0	5	15	30	45
8	87.4	—	84.3	77	80	67.5	—	75	57.5	62
9	85.5	—	87.8	94.9	84.3	90.5	—	93.6	100	88.8
10	174	121	126	100	—	190	112	117	100	—
11	142	56	105	165	—	148	56	105	153	—
12	100	79.9	118	—	—	100	84.6	118	—	—
13	100	94.6	116	—	—	100	95	95	—	—

* Time 0 is time of injection.
All figures are in percentage of control values (100%).

monary ventilation were as follows: an increase averaging 10-15% but never exceeding 30% occurred in all cases but one (dog 9). Oxygen consumption decreased slightly (10%) in dogs 10 and 13 and showed an average increase of 15% in the other 4 dogs. No appreciable change was observed in the oxygen content of mixed venous blood except in dog 10, where an increase of 16% was noted. In no case was a significant decrease noted; the observed slight variations of the oxygen content in the mixed venous blood are within physiological variations and accuracy of the method. No change in blood pressure was seen after cysteamine.

2. *Cysteine.* For small doses (20-80 mg/kg, dogs 8 and 9), there was little change in cardiac output: dog 8 exhibited no variation after 15 minutes and a reduction of 12% after 30 and 45 minutes while an increase of only 12% was noted in dog 9 after 30 minutes; the figures obtained in the same dog after 15 and 45 minutes were normal. The heart rate was unchanged; variations in stroke volume were parallel with those of cardiac output. Pulmonary ventilation was unaffected in dog 8, except after 15 minutes, and moderately increased in dog 9. Small elevation of the oxygen consumption was seen in dog 9, a larger one for dog 8. The figures for the oxygen content of the mixed venous blood (Table II) show that there were only physiological variations (mean value of 4.6%).

Significant decrease in cardiac output was observed when cysteine injection reached 160 mg/kg (dog 10). The fall of cardiac output was about 30% after 5 and 15 minutes following the injection of the drug and more than 40% after 30 minutes. Since there was a concomitant slight tachycardia, the systolic output dropped more than the cardiac output. Pulmonary ventilation increased moderately

TABLE II. Effects of Cysteine on Oxygen Content of the Mixed Venous Blood in Dogs (ml/Liter).

Dog No.	Dose (mg/kg)	Before cysteine	Time after cysteine (min.) 5	15	30	45
8	20	215	—	216	206	206
9	80	198	—	196	196	195
10	160	169	157	160	152	—
11	320	202	150	178	195	—
12	320	139	122	143	—	—
13	320	121	104	114	—	—

but oxygen consumption did not change. The oxygen content of the mixed venous blood decreased by 10% after 30 minutes (Table II).

Doses of 320 mg/kg of cysteine induced large decrease in the cardiac output in 2 dogs: in dog 11, the cardiac output was only 40 and 70% of normal, respectively, 5 and 15 minutes after the injection; dog 12 exhibited a smaller decrease (20% after 5 minutes) which is nevertheless significant. There was no variation in dog 13.

It is worth noting that, when it falls, the cardiac output does not remain long at low level but after some time, returns to 16-17% above the control values (30 minutes in dog 11 and 15 minutes in dogs 12 and 13). The heart rate remained unaffected and the changes in systolic output were identical with those of cardiac output. Both pulmonary ventilation and oxygen consumption increased in the 3 dogs. The blood pressure showed negligible variations except in dog 11 which, 15 minutes after injection of 320 mg/kg of cysteine, had some hypotension. The important point was that after injection of large doses of cysteine there was a significant fall in oxygen content of the mixed venous blood (Table II). This fall exceeded 13% and even reached 25% in dog 11. In all dogs, the fall in oxygen content of the blood was maximum 5 minutes after the injection of cysteine: this fall is transient since the figure for oxygen content in the blood was already rising 15 minutes after injection.

Discussion. Cysteine hydrochloride in large doses regularly induces a significant decrease in the oxygen content of the *mixed* venous blood, as already reported by Salerno and Friedell(3) for *peripheral* venous blood. It is possible that the radioprotective effects of the drug are related to this action since the maximum of desaturation in oxygen occurs just after the injection, when the radioprotective activity of the drug is also maximal. But this tissular anoxia alone cannot completely explain the protection against X-rays by cysteine because, 30 minutes after the injection, the oxygen desaturation of the mixed venous blood has returned to normal, when the radioprotection is still present, although diminished.

Cysteamine does not cause any fall of the oxygen content of the venous blood taken in the right heart; thus its radioprotective effect cannot be due to anoxia. Bacq and Alexander(6) are of the opinion that cysteamine competes with radiosensitive molecules for the oxidizing free radicals (HO_2 mainly) resulting from the ionization of water and protects a factor (or several factors) important for tissue regeneration.

Summary and conclusions. Data are submitted concerning the changes in cardiac output, systolic output, pulmonary ventilation, oxygen consumption, and oxygen content of the mixed venous blood of the right heart following intravenous administration in anesthetized dogs, of 2 radioprotectors, cysteine and cysteamine. 1. Cysteamine (= β-mercaptoethylamine = Becaptan Labaz), for doses of 10-40 mg/kg, generally increases the cardiac output and the systolic output from 10 to 75% of control values. Heart rate and femoral blood pressure are unaffected. No significant change is noted in the oxygen content of the mixed venous blood. 2. The effects of cysteine are as follows: a) For doses of 20-80 mg/kg, the cardiac and systolic outputs do not change significantly; blood pressure, heart rate, and oxygen blood content remain at control values. b) Doses of 320 mg/kg in 2 of 3 dogs induce a large decrease in both cardiac output and stroke volume. In all cases, the oxygen content of the mixed venous blood is reduced, most conspicuously 5 minutes after the injection. 3. Equiprotective doses of cysteamine do not decrease the oxygen content of the mixed venous blood. 4. It is concluded: a) that the remarkable protection afforded against X-rays by β-mercaptoethylamine is not due to tissular

anoxia, b) that the temporary anoxia produced by large doses of cysteine can explain only partially the radioprotective action of the substance.

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Effect of Chlorpromazine on Emesis after Radiation. (21076)

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Radiation sickness is an ever present danger when ionizing radiations are employed for diagnostic, therapeutic, or experimental purposes. The importance of this syndrome clinically is abundantly evident from the impressive number of references in the radiological literature. Nausea and vomiting are among the most characteristic symptoms of this disorder and numerous medications have been employed for their relief with equivocal results. Various antihistamines(1,2), vitamin (3), and hormonal(4,5) preparations, as well as other miscellaneous compounds(6,7,9) have been advocated. Recently, (dimethylamino-1-n propyl-3) - N - (2-chloro) - phenothiazine HCl (chlorpromazine) has been reported to give striking relief of nausea and vomiting in a large series of clinical patients(9). To our knowledge, no preparation has been shown to protect animals from vomiting after irradiation. In fact, such protection has only been reported(10) after destruction of the chemoceptive trigger zone described by Borison and Wang(11). Since chlorpromazine protects dogs against other emetic stimuli acting upon this area (apomorphine(12), hydergine(13), motion(14)), it was of obvious interest to test its effectiveness against radiation emesis as well.

Methods. As controls, 12 normal mongrel dogs, weighing from 7 to 13 kg, were fed commercial dog food and 30 minutes later irradiated with 800 r. A Picker deep therapy x-ray unit was employed with 260 KVP and 18 MA. The external filtration was 1 mm Al and 0.50 mm cu plus 0.25 mm cu inherent filtration. The target-to-object distance was 118 cm and the dose rate 13 r/minute in air. The dog received half the radiation dose on one side of the body, at which time he was turned and given the remainder of the dose. After irradiation, the dogs were observed from 4 to 6 hours, unless vomiting occurred earlier. Another group of normal dogs within the same weight group received subcutaneously 5 or 10 mg of chlorpromazine†/kg body weight freshly prepared in 0.9% saline. They were immediately fed and 30 minutes later irradiated with 800 r as described above. On one occasion, a solution of chlorpromazine was not used for 2 hours, during which time it assumed a slightly brown color. To test the effect of such standing, 5 dogs received 10 mg/kg of a chlorpromazine solution allowed to "age"

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