STUDIES ON THE DETOXICATION OF LOCAL ANESTHETICS

Protective Action of Intravenous Injections of Calcium Salts on the Respiratory and Circulatory Effects of Pontocaine Hydrochloride *

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The protective effects of a series of calcium salts on toxic, sublethal and lethal doses of procaine hydrochloride and butyn sulfate were studied in guinea pigs in previous publications (1). The drugs in these experiments were injected intramuscularly. In the present report the protective effects of calcium salts on the systemic toxicity of pontocaine hydrochloride were investigated by means of intravenous injections. Cats served as experimental animals. Urethane, in 25 per cent. aqueous solution, was used as a convenient basal anesthetic in all experiments, in doses of 1.25 Gm./Kg. of body weight. The systemic blood pressure (from the carotid artery) and the respiration (from the trachea) were recorded on a kymograph. The concentration of pontocaine-HCl was 0.5 per cent. in Ringer's solution,‡ prepared immediately before its direct injection into the femoral vein. The rate of administration was kept constant (ten to fifteen seconds per injection). All experiments were performed *without artificial respiration* in order to determine the true detoxicating effects of calcium salts on the circulatory and respiratory disturbances produced by pontocaine-HCl. The vagus nerves were kept intact. We compared in the records of all experiments: (1) the mean blood pressure in mm. mercury, indicated by the midpoints of the amplitudes of the manometric oscillations, their latitudes (i.e., the range of amplitude), the pulse rate, etc., and (2) the respiratory rate per minute and its type. These comparisons were made at the second, fourth, eighth and sixteenth minute after each injection.

The dose of 2 mg./Kg. of pontocaine-HCl which led to 80 per cent. of deaths with the first administration was determined as the M. L. D. (minimal lethal dose). In 20 animals tested, death occurred with the first dose in 16 animals, with the second dose in the remaining

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‡ 1.0 per cent. pontocaine-HCl in Ringer's solution: pH 6.7.
0.1 per cent. pontocaine-HCl in Ringer's solution: pH 7.0. Ernst (2).

TABLE I

INFLUENCE OF CALCIUM SALTS ON THE BLOOD PRESSURE EFFECTS OF PONTOCAINE-HCl

Minutes after injection	Procedure	Average blood pressure mm Hg	Procedure	Average blood pressure mm Hg	Procedure	Average blood pressure mm Hg	Procedure	Average blood pressure mm Hg
	Initial Value	126.3	Initial Value	120.9	Initial Value	121.1	Initial Value	129.9
2	200 mg./Kg. of Ca-levulinate (29.47 mg./Kg. Ca) 14 cats	137.1	200 mg./Kg. of Ca-gluconate (18.60 mg./Kg. Ca) 12 cats	148.6	100 mg./Kg. of Ca-lactate (17.52 mg./Kg. Ca) 10 cats	152.9	100 mg./Kg. of calcium chloride (36.04 mg./Kg. Ca) 10 cats	132.7
4		146.6		155.4		155.8		149.4
8		149.8		155.9		152.1		161.1
16		151.8		157.0		150.1		162.2
2	First dose of 2 mg./Kg. of pontocaine-HCl tolerated by 12 cats (85.7%)	106.8	First dose of 2 mg./Kg. of pontocaine-HCl tolerated by 9 cats (75%)	94.6	100 mg./Kg. of Ca-lactate (17.52 mg./Kg. Ca) 10 cats	157.4	First dose of 2 mg./Kg. of pontocaine-HCl tolerated by 6 cats (60%)	98.8
4		112.0		111.1		155.6		113.0
8		115.6		113.7		151.4		131.0
16		118.2		116.7		148.8		128.3
2	Second dose of 2 mg./Kg. of pontocaine-HCl tolerated by 9 cats (64.2%)	84.7	Second dose of 2 mg./Kg. of pontocaine-HCl tolerated by 6 cats (50%)	77.4	First dose of 2 mg./Kg. of pontocaine-HCl tolerated by 7 cats (70%)	93.6	Second dose of 2 mg./Kg. of pontocaine-HCl tolerated by 3 cats (30%)	94.7
4		84.1		84.0		104.7		110.0
8		88.7		92.6		109.4		128.7
16		95.3		97.2		111.3		124.0
2	Third dose of 2 mg./Kg. of pontocaine-HCl tolerated by 6 cats (42.8%)	69.5	Third dose of 2 mg./Kg. of pontocaine-HCl tolerated by 3 cats (25%)	71.5	Second dose of 2 mg./Kg. of pontocaine-HCl tolerated by 4 cats (40%)	77.8	Third dose of 2 mg./Kg. of pontocaine-HCl tolerated by 1 cat (10%)	93.2
4		79.8		79.0		94.5		113.0
8		84.3		84.5		98.3		115.2
16		88.0		95.5		102.2		113.0
2	Fourth-eighth dose of 2 mg./Kg. pontocaine-HCl tolerated by 2 cats (14.2%)	60.6	One cat tolerated 7 doses and died with the eighth (8.3%)		One cat tolerated the third dose and died with the fourth (10%)			
4		61.8						
8		63.2						
16		65.2						
	Time of death (average) 5.20 minutes after injection.		Time of death (average) 3.60 minutes after injection.		Time of death (average) 5.20 minutes after injection.		Time of death (average) 7.20 minutes after injection.	
	Group mean: *3.64		Group mean: *2.83		Group mean: *2.20		Group mean: *2.00	

* By the term "group mean" we refer to the total number of M. L. D. required to kill all animals of the group divided by their number. This group mean, with pontocaine-HCl alone, is 1.20. (It required 24 M. L. D. to kill 20 animals.)

4 animals within two to three minutes after the injection. These 4 animals barely stood the first dose, showing a very low blood pressure and a very slow, gasping respiration. Half of this dose, namely, 1 mg./Kg. was tolerated in all cases (6 animals) with a drop of the mean blood

pressure and the respiratory rate by about 10 per cent. The intermediate dose, 1.5 mg./Kg. (6 animals) was tolerated once, though with a 50 per cent. decrease of blood pressure and a 75 per cent. decrease of the respiratory rate on the average. The second dose was lethal.

The table shows in a survey the mortality rate and the average blood pressure values with the M. L. D. of 2 mg./Kg. pontocaine-HCl after injection of four different calcium salts. The values are the averages, calculated from the individual values from the surviving numbers of each subgroup. The investigated calcium salts increased the mean blood pressure over the initial value by 20.0–29.8 per cent.; the respiratory rate was slightly decreased with no change in regularity and with a somewhat greater depth. When the M. L. D. of pontocaine-HCl was tolerated by a certain number of animals (as indicated in the table) under the premedication with calcium salts, there were observed *uniformly* a sharp, deep drop of the mean blood pressure after the injection and a slow, gradual rise subsequently (partial recovery). This recovery did not reach the pre-injection levels and hence, with an increasing number of tolerated doses, the level of the systemic blood pressure was more and more lowered. With regard to respiration, in all subgroups which tolerated the M. L. D., a cessation was observed for a short time; then respiration was resumed again; shallow, gasping and slow in the beginning, but gradually increasing in rate and depth, eventually settling down to a rate slower than preceding the pontocaine injection, but regular in rhythm.

Paralysis of the respiratory mechanism is the chief cause of death by pontocaine hydrochloride (3); the heart beats about two minutes after the cessation of respiration before finally failing. With a feeble respiration still persisting, the oxygen supply may be sufficient to maintain circulation at a hypotensive level. However, it is probable that a direct toxic action on the heart exists also. It is evident (see table) that the degree of protection exerted shows a quite distinct *gradation* with the four investigated calcium salts. The total amount of the cation Ca introduced into the circulation (see table, mg./Kg. Ca) is not directly related to the degree of protection in the sense that a larger amount would lead consistently to a better protection.* The increased blood calcium level immediately after injection and for a certain time thereafter, however, in all probability plays a role. This is indicated by our results with $CaCl_2$, where the simple chloride ion, abundant in the body in any case, accompanies the cation Ca. How long a hypercalcemia persists and at what rate it decreases *is not known* for the three of the organic calcium salts used in these investigations. We have data, however, with regard to $CaCl_2$.

* The ionization of the calcium salts used in this investigation is as follows: Specific electric conductivity of 0.1 N solution at 25° C. Ca levulinate 5.70.10–3; Ca gluconate 3.33.10–3; Ca lactate 5.02.10–3; $CaCl_2$ 14.72.10–3. These values were unknown except for $CaCl_2$; the determinations were performed by M. Spiegel-Adolf at Temple University, Philadelphia, for us and we are very grateful for this expert help.

Heubner and Rona (4) increased the blood calcium level two- and threefold immediately after the injection of calcium chloride intravenously into cats; the level remained high for about one-half hour and the pre-experimental values were regained after about two hours. Walters and Bowler (5) found complete elimination of 82.5 mg./Kg. of $CaCl_2$ injected intravenously into dogs after approximately four hours. Jansen (6) observed that the blood calcium level returned to normal values about two hours after having injected 160 mg./Kg. of $CaCl_2$ intravenously in man; during that time the respiratory rate was decreased by about 30 per cent., which was synchronous with a mild bradycardia and an increase in blood pressure, the latter abating with progressive elimination. In our experiments, the increase of the mean blood pressure above the initial values was within a close range of variations for all four calcium salts (see table); the respiratory rate decreased from 14–24 per cent. and showed in 1 case only, with calcium gluconate, a slight increase of about 12 per cent. We may remark here, that, because of its high molecular weight, this salt supplies the body with the smallest amount of mg./Kg. Ca.

Ca levulinate exerts the greatest protective effect and calcium chloride the least, in our experiments. The sequence of effectiveness is very similar to results with the same salts with intramuscular, separate injections in guinea pigs (1), the salts being used as protective agents against the toxic systemic actions of procaine-HCl and butyn sulfate. In these previous experiments local absorption factors entered the picture, which have been here eliminated. One can conclude, as already elaborated (1), that the anions play an important role at the sites of action of the local anesthetics, the protective effects exerted by them varying according to their chemical constitution. Comparative experiments with the sodium and potassium compounds of the Ca salts here investigated (using the same technique as in that report) bear out that assertion and will be published later.

We have studied the protective actions of calcium salts on lethal doses of pontocaine-hydrochloride given intravenously, since that route is the most toxic form of administration; hence even a mild degree of detoxication points to a definite action of the protecting agent. If, under these severe conditions, protective actions are exerted, we may ask ourselves, "could that not justify a tentative recommendation of certain calcium salts—particularly Ca levulinate and Ca gluconate—as precautionary measures, and as additional safeguards, against undesirable side-effects in man, where much lower doses of local anesthetics are used?"

SUMMARY

1. The effects of pontocaine hydrochloride on respiration, circulation and mortality were studied in cats (under urethane narcosis) with and without a previous intravenous injection of Ca levulinate (200

mg./Kg.), Ca gluconate (200 mg./Kg.), Ca lactate (200 mg./Kg.) and $CaCl_2$ (100 mg./Kg.). These calcium salts raised the mean initial blood pressure between 20.0–29.8 per cent., whereas the initial respiratory rate decreased, as a rule, between 14–24 per cent., the respiration remaining, however, regular and becoming slightly deeper.

2. The M. L. D. (minimal lethal dose) of 2 mg./Kg. pontocaine-HCl was used in all experiments. This dose, given alone, killed 80 per cent. of animals (20) with the first injection, and the remaining 20 per cent. with the second injection within 2.6 minutes (average). One may contrast these survival percentages, 20 and 0 with those under calcium salt premedication of 60–86 and 30–64 for the first two injections of 2 mg./Kg. of pontocaine hydrochloride, respectively.

3. Under premedication with calcium salts a certain number of animals tolerated this M. L. D. several times. When the dose is tolerated, the blood pressure falls, first deeply and steeply, and then shows a gradual rise in all subgroups. The number of M. L. D. required to kill all animals of the group under calcium salt protection, as compared with the results with pontocaine-HCl alone, was with Ca levulinate 3.03 times, with Ca gluconate 2.36 times, with Ca lactate 1.83 times and with $CaCl_2$ 1.66 times as large. The time of death after injection is materially longer in all groups when under partial protection by calcium salts (3.6–7.2 minutes against 2.6 minutes with pontocaine alone, average values). The best results toward partial protection were achieved with Ca levulinate; the least protective action was exerted by $CaCl_2$.

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The International College of Surgeons has announced a prize of $250.00 and a gold medal for the best essay on Anesthesiology. These essays must reach the office of Dr. Max Thorek, 850 West Irving Blvd., Chicago, Ill., not later than May 1, 1941. They must be typewritten, in English, in manuscript form, double-spaced, and must not exceed 5,000 words in length. The original must be accompanied by four carbon copies.

The Committee of Awards consists of the following:

Dr. Andre Crotti, International Past-President.
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All inquiries are to be addressed to Dr. Max Thorek, 850 West Irving Blvd., Chicago, Ill. Competition is open to all who are interested in the subject.

The Council on Scientific Assembly of the American Medical Association has announced the officers of the new section of the Scientific Assembly of the Association to be called the Section on Anesthesiology. The appointments are as follows: Dr. Ralph M. Waters, Madison, Wisconsin, Chairman; Dr. T. J. Collier, Atlanta, Georgia, Vice Chairman, and Dr. John S. Lundy, Rochester, Minnesota, Secretary. Dr. John H. Evans, Buffalo, New York and Dr. Henry S. Ruth, Philadelphia, Pennsylvania, together with Dr. Waters as Chairman, were appointed to serve as members of the Executive Committee. Dr. Ruth was appointed to serve as a member of the House of Delegates of the Association representing the Section on Anesthesiology at the annual session to be held in Cleveland in 1941.