Respiratory Complications from Tetraethylammonium Ion

Report of Two Deaths

By GEORGE A. McLemore, Jr., M.D., HAROLD D. Green, M.D., and THOMAS N. Lide, M.D.

Tetraethylammonium ion has been used quite extensively since 1946, when Acheson and Moe\textsuperscript{1, 2} demonstrated its action as a blocking agent, effective at both sympathetic and parasympathetic ganglia. Earlier, Burn and Dale\textsuperscript{3} and Hunt\textsuperscript{4, 5} had described the actions of certain quaternary ammonium bases which included the tetraethylammonium ion.\textsuperscript{6} This drug has been used therapeutically with varying success in a variety of disorders, including thrombosis obliterator, and arteriosclerosis obliterans\textsuperscript{6-9} coronary heart disease,\textsuperscript{10} hypertension and toxemia of pregnancy,\textsuperscript{11, 12} thrombophlebitis, Raynaud's phenomenon, trench foot and immersion foot,\textsuperscript{13} peptic ulcer,\textsuperscript{14, 15} poliomyelitis,\textsuperscript{16} herpes zoster and intercostal neuralgia.\textsuperscript{17} Diagnostically, tetraethylammonium chloride has been employed in the evaluation of many acrovascular conditions,\textsuperscript{18-20} in the selection of patients with hyperpertension for sympathectomy,\textsuperscript{21} and in the roentgen study of the small bowel.\textsuperscript{22}

Reports of serious reactions from the use of tetraethylammonium chloride have not been numerous, but unpleasant side effects have somewhat limited its usefulness,\textsuperscript{23} as has the necessity for parenteral administration due to apparent lack of absorption when given by mouth. Another disadvantage has been the relatively short duration of action due to rapid excretion by the kidneys. Fifty per cent appears in the urine in 30 minutes when given intravenously, and 50 per cent in four hours when given intramuscularly.\textsuperscript{24} Subcutaneous injection causes considerable irritation and tenderness, which may last for several hours, at the site of injection. For this reason this method of administration is not recommended. Intramuscular injection also produces some tenderness, mild burning and occasional muscular fasciculation, but the effect is more prolonged. The latter route of administration is probably the safest as regards systemic reactions in doses recommended not to exceed 20 mg. per Kg. of body weight. Rapid intravenous injection of tetraethylammonium chloride has been used by many reporters and is generally employed as recommended by Parke, Davis and Company in amounts not exceeding 7 mg. per Kg. of a 10 per cent solution.

The effects of rapid intravenous administration usually appear immediately and include metallic taste, a cold feeling, weakness, drop in arterial blood pressure, rise in pulse rate, ablation of sweating, lightheadedness, and difficulty of muscle movement without impairment of the deep tendon reflexes. Temporary loss of ocular accommodation usually occurs and may last several hours. Dyspnea and hyperventilation, similar to hysterical hyperventilation, together with retention and drying of bronchial secre-
REVIEW OF PREVIOUS REPORTS OF TOXICITY OF TETRAETHYLMONIUM CHLORIDE

Friedlich and Stansbury\textsuperscript{26} reported an instance of a severe reaction to the intravenous administration of Etamon in an emotionally unstable 37 year old female patient. After receiving 230 mg. of tetraethylmonium chloride, she developed peripheral collapse, hyperventilation, gasping respirations and shivering. She required intensive supportive therapy in the form of plasma, adrenaline and whole blood over a two day period before recovery. Schwartz\textsuperscript{27} reported the sudden death, without apparent cause, of a patient with rather severe bronchial asthma, following the use of tetraethylmonium bromide. Autopsy revealed generalized congestion and the possibility of ventricular fibrillation. In this case also the drug was administered intravenously, and the dose was 230 mg. The patient, a 63 year old white man, expired very suddenly; epinephrine and artificial respiration were not of benefit. Lasser and others\textsuperscript{28} reported a case of advanced hypertensive cardiovascular disease who developed circulatory collapse. This patient was a 33 year old white woman with severe hypertensive cardiovascular disease whose disease had continued to progress despite sympathectomy. She was given 500 mg. of tetraethylmonium chloride intravenously over a five minute period. Following the administration of tetraethylmonium chloride she developed peripheral collapse which was unsuccessfully treated with Coramine (nikethamide) and epinephrine. She died six hours later. Cyanosis and labored respirations were outstanding features, and at postmortem examination red cells, large macrophages, occasional polymorphonuclear leukocytes, and eosinophilic granular material were found in most alveoli. The other findings were those of advanced hypertensive cardiovascular disease with severe nephrosclerosis. Ham\textsuperscript{29} reported a case of purpura occurring three days after the administration of tetraethylmonium chloride but no causal relationship was established.

Green and Ogle\textsuperscript{30} have used tetraethylmonium chloride in inducing a rise in skin temperature in peripheral vascular disease. In a series of 20 cases, they found few signs of toxicity in doses not exceeding 600 mg. given intravenously. Later, Green and others\textsuperscript{19} reported a larger series of skin temperature studies employing tetraethylmonium chloride, and mentioned a case of an elderly white man who expired during a skin temperature study after receiving only 7.8 mg. per Kg. of tetraethylmonium chloride in a normal saline infusion. This patient is reported as case 1.

Ulrich and co-workers\textsuperscript{30} gave tetraethylmonium bromide by slow intravenous infusion at a rate of 6 to 10 mg. per minute for four to eight hours. They found that elevated skin temperature could be maintained for six to eight hours in normotensive and hypertensive individuals by this method with few, if any, side reactions. From 12 mg. per minute up to 16 mg. per minute, the maximum amount used, moderate untoward effects were said to have occurred but they were not enumerated. The vehicle of infusion was not mentioned. The maximal rise in skin temperature was obtained with the largest amount, 16 mg., of tetraethylmonium bromide per minute.

Tetraethylmonium chloride has been used almost exclusively by intravenous infusion in normal saline by the group of workers on peripheral vascular diseases in the Department of Physiology and Pharmacology, and the Department of Internal Medicine at the Bowman Gray School of Medicine,\textsuperscript{19} and it has been used in this manner since May, 1947, with generally good results in obtaining a rise in skin temperature and relief of symptoms in vasospastic conditions. Sixty patients with a variety of vascular disorders and 50 normal medical students have received doses of tetraethylmonium chloride ranging from 300 mg. to 1800 mg. in
the saline diluent over periods of 30 to 45 minutes without serious untoward effects. The above patients were generally given the drug for diagnostic purposes while recording skin temperatures. Twenty of these cases were then treated over a period of days in the same manner, by intravenous infusion with close watch for toxic signs and symptoms. Only 3 cases showed any untoward signs, namely drop in systolic blood pressure of 30 to 40 points, weakness, and occasional dyspnea.

In view of the fact that the rise of skin temperature was nearly proportional to the amount of tetraethylammonium chloride infused per minute, the total amount of this drug used for treatment was cautiously raised over an extended period of time. It was found that the desired increase in skin temperature was obtained with a dose of 20 mg. per Kg. of body weight, usually given at the rate of 40 to 50 mg. per minute. Mild transient ill effects occasionally occurred, but no serious result was noted until this latter dose had been used on a total of 9 patients. The ninth patient died during the course of treatment. A summary of the clinical course and postmortem findings in this patient are reported as case 2.

**Case Reports**

**Case 1.** D. V. C., a 78 year old white man entered the North Carolina Baptist Hospital, Winston-Salem, N. C., on Sept. 15, 1949, because of severe and sudden pain and coldness in his right leg. A purple hue to the right foot and ankle up to the midcalf had developed three days prior to admission. No history of chest pain, heart disease or hypertension was obtained. He had been nauseated, however, and vomited once on the day of admission.

On admission the temperature was 99 F., the pulse 84 beats per minute, respirations 18, and blood pressure, 150/90 in both arms. He was a fairly well-developed, elderly, slightly obese, white male in acute distress. His eyes revealed an arcus senilis and grade II arteriosclerotic changes in the fundi. The lungs were clear. The heart was normal in shape and size with a regular sinus rhythm, with sounds of good quality, but with an occasional premature systole. The distal portion of the right lower extremity was cool and purple in color below the midcalf. Pulsation could not be obtained in the popliteal, tibial or dorsalis pedis arteries of the right leg, and the right femoral pulsation was not as strong as the left.

Laboratory examination showed a normal urin-

alysis except for 20 white cells per high powered field and an occasional granular cast. The hemoglobin was 16 Gm., and the corrected sedimentation rate 10 mm. in one hour. The white blood cell count was 14,750, with a slight increase in the segmented polymorphonuclear leukocytes.

His hospital course was brief. Shortly after admission, he was placed in the constant temperature room at 20 C. where a skin temperature study was started, using tetraethylammonium chloride, 1000 mg. in 300 cc. of dextrose and saline. He vomited about one-half cupful of light brown material at the start of the study before administration of the tetraethylammonium chloride was begun but became quiet after this while the infusión was being carried out. Seventeen minutes after the infusion was started, his blood pressure dropped from 140/80 to 120/60; he again became nauseated but did not vomit. The infusion was stopped for five minutes whereupon his blood pressure returned to the original level; the pulse remained slow, 65 to 70 per minute. The infusion was then continued until 650 mg. of tetraethylammonium chloride had been given, when suddenly his blood pressure became unobtainable, his pulse rapid and weak, his respirations shallow and weak and he became very relaxed and did not respond. A total of 1 cc. of 1:1000 epinephrine, 0.5 cc. intravenously and 0.5 cc. intramuscularly, was not successful in reviving the patient, nor was artificial respiration. He was pronounced dead 40 minutes after the start of the skin temperature study.

Autopsy findings revealed a severe generalized arteriosclerosis, with occlusion of the anterior descending branch of the left coronary artery. The heart was slightly hypertrophied, weighing 400 Gm. Congestion was prominent throughout all organs, with edema and hemorrhage into the pulmonary alveoli, and petechial hemorrhages of the gastric mucosa. Fatty metamorphosis was moderate in the liver, but there was no lobular necrosis. The kidneys were small and scarred, with sclerosis of the arteries and arterioles, and glomerular and interstitial fibrosis.

**Case 2.** E. S. H. was admitted to the North Carolina Baptist Hospital, Winston-Salem, N. C., on Dec. 23, 1949. He was a 33 year old white grocer, veteran of the Battle of the Bulge, Dec. 1944. During 1944 he had suffered “trench foot” from long exposure to cold, wet weather and was hospitalized for several weeks of treatment. He was then sent back to the front and later discharged without disability. He was without symptoms for the following three years. In the winter of 1947 to 1948, his feet began to pain him. The pain was more severe in cold weather and after walking a short distance. The feet would become blue and cold and would usually swell. He had no difficulty in warm weather. He was admitted for treatment with tetraethylammonium chloride with a diagnosis of Raynaud’s phenomenon.
secondary to "trench foot." He gave a history of consuming about a quart of whiskey per day "for relief of the pain in his feet."

On admission the temperature was 98.8 F., pulse 112 per minute, respirations 18 per minute, weight 175 pounds and arterial blood pressure 146/104. He was a well developed, well nourished white man who was moderately nervous. Physical examination was generally unremarkable except for an upper denture and coldness and pallor of both feet. The latter was intensified and accompanied by severe pain when the feet were immersed in cold water. The feet became a blotchy purple upon removal from the cold water.

Laboratory findings were all within normal limits, with the exception of a corrected sedimentation rate of 23 mm. in one hour. The patient's prothrombin time was 14.5 seconds with a control of 15 seconds.

A skin temperature study carried out the day of admission, showed a very good response of his feet and hands to 1580 mg. of tetraethylammonium chloride given in 250 cc. of saline over a 37 minute period. Since he experienced no apparent ill effect, he was started on a course of tetraethylammonium chloride therapy. Fifteen hundred mg. in 200 cc. of normal saline were given four times a day over a 30 minute period for a total of four days. Four hours usually elapsed between each infusion. Careful checks were made of blood pressure at 10 minute intervals throughout and following each infusion. At no time did either systolic or diastolic pressure drop more than 8 to 10 mm. Hg. His pulse was elevated much of the time during his hospital stay (100 to 126 per minute). He was given a total of 600 mg. of dicumarol over a five day period but he never displayed any signs of toxicity and his prothrombin time never exceeded 19 seconds with a control of 17 seconds.

On his sixth hospital day, Dec. 27, 1949, he was given the second infusion for that day, three and one-half hours after the previous infusion. Twenty minutes after the completion of this second infusion, which was given over a period of 35 minutes, he suddenly became excited, appeared to be in collapse and stopped breathing. Manual artificial respiration was begun immediately but was of little avail in that the patient's thoracic cage was apparently fixed in inspiration. Positive pressure artificial respiration was started 20 minutes later, but it also failed to correct the developing cyanosis. Adrenaline given intravenously was used in an attempt to maintain blood pressure, and 2 cc. of Coramine (nikethamide) were administered intravenously in an effort to stimulate respiration. Tracheotomy was performed in belief that there might be tracheal or laryngeal obstruction. Strong heart action was maintained for approximately 30 minutes but spontaneous respiration was never resumed. The blood pressure dropped gradually and the patient became intensely cyanotic. He was declared dead one hour and five minutes after completion of the infusion.

At autopsy there was generalized congestion of all organs, with petechial hemorrhages of the lungs, pleura, pericardium and mucosa of the gastrointestinal tract, particularly the ileum. Pulmonary edema with focal hemorrhages, and with acute bronchitis was prominent, but there was no pneumatic consolidation. The liver weighed 3000 Gm. and showed extreme fatty metamorphosis and congestion without demonstrable increase in fibrous tissue. There was extensive cloudy swelling and necrosis of the renal tubular epithelium. Cardiac hypertrophy, predominantly involving the left ventricles, was moderate (530 Gm.).

Discussion of Cases

The death of the 78 year old patient, case 1, was obviously due to the recent myocardial infarction which was not suspected ante mortem. His death was attributed to circulatory collapse. Respiratory difficulties were probably secondary.

The unexpected death of case 2 gave rise to much speculation as to the actual cause of the marked respiratory symptoms and fixation of the chest in inspiration. A total of sixteen previous infusions of the same amount had been administered over the same length of time for five days under close supervision, especially of blood pressure and pulse. He had been kept lying flat on his back for one hour after completion of each infusion. Though he had complained of blurred vision and slight dyspnea, no significant decline of blood pressure, no fever and no sign of collapse were ever noted. There were no signs or symptoms of pneumonia. The possibility of a correlation between the dicumarol therapy and the changes in the liver was considered; it was, however, felt to be unlikely in view of the failure of his prothrombin time to exceed 10 seconds, despite a total administration of 600 mg. over a five day period. The death may therefore have been due to depression of the respiratory center by the tetraethylammonium chloride. There were no signs of renal damage that might have caused retention of the tetraethylammonium chloride. Nevertheless it is possible that a chronic cumulative toxic effect of the tetraethylammonium chloride was responsible for the respiratory depression. It is possible that the fatty meta-
morphosis in the liver may have contributed in some unknown manner to the chronic toxicity of the tetraethylammonium chloride since all 4 of the dogs (described below) survived considerably larger doses of tetraethylammonium chloride than this patient received.

Studies on Animals

Gruhzit and others studied the acute and chronic toxicity of tetraethylammonium chloride in mice, rats, rabbits and dogs. They reported little toxicity even after 2636 mg. per Kg. were given orally, but moderate signs were noted after 25 mg. per Kg. were given intramuscularly. These consisted of incoordination, ptosis of eyelids, mydriasis, and hyperemia of ocular, nasal and buccal membranes. As expected, these toxic signs were more marked with intravenous administration without diluent; at the dose which produced death in 50 per cent of the animals, the above signs were intensified with the addition of hyperpyrexia, spasticity, and respiratory and circulatory depression eventually leading to death over a period varying from immediately following administration to two and one-half hours after administration. No changes could be found in the blood studies, total nonprotein nitrogen, bromsulfalein test, total serum protein, albumin and globulin ratios, or in repeated urinalysis. The underlying histopathologic changes were those of severe congestion, stasis, edema, and anoxia.

We have carried out preliminary toxicity studies in 4 dogs. These dogs were given tetraethylammonium chloride in 100 cc. of normal saline over a 30 minute period four times a day. They received initial doses of 20 mg. per Kg. per infusion for two days. The dose was then increased by 5 mg. per Kg. every two days thereafter. The dogs died after receiving 24, 25, 41 and 49 infusions. The amounts of tetraethylammonium chloride which they were receiving per infusion just prior to death were 30, 35, 45 and 50 mg. per Kg. respectively. The respiratory complications in these animals largely simulated the effects noted in the second case report, namely, difficult irregular respirations, with respiratory cessation as the cause of death in each of the 4 dogs. Fixation of the thorax in inspiration was noted in 3 of the 4 animals, as was the case in case 2. The lethal dose was slightly higher than that reported by Gruhzit who used tetraethylammonium chloride undiluted, and who reported the minimum lethal dose to be 36 mg. per Kg.

The autopsy findings in all 4 dogs were similar, except in dog no. 2, in which an extensive confluent bronchopneumonia was found. The prominent and pertinent features of the autopsies were the edema and focal hemorrhage into the pulmonary alveoli and the extreme generalized congestion of the systemic and pulmonary blood vessels. Hyperemia of the gastrointestinal mucosa was present in each dog, the site of the change being predominantly the stomach and upper part of the small intestine. There was no necrosis of the hepatic cells, and there was but slight degeneration of the renal tubular epithelium; this was limited to the loops of Henle.

Reardon and others described the effects of prostigmine in counteracting the toxic actions of tetraethylammonium chloride in dogs and man. The use of prostigmine could not be found in the cases described earlier in this article, nor in other reports reviewed. Prostigmine has been unsuccessful in preventing respiratory failure thus far in our studies on other dogs which will be reported in full at a later date.

Summary and Conclusions

A review of the more serious ill effects of tetraethylammonium chloride is presented. At least two deaths following its use have been reported. Two additional deaths following tetraethylammonium chloride are presented in this paper as case reports. Myocardial infarction with circulatory collapse was the probable cause of death in case 1. Case 2 had tolerated without incident 20 mg. per Kg. of tetraethylammonium chloride, intravenously, four times a day at four hour intervals for five days; each infusion had required at least 30 minutes. On the sixth day of treatment, the patient died at the conclusion of the second infusion for that day. This case showed at autopsy generalized congestion, pulmonary edema with focal hemorrhages and acute bronchitis, and fatty metamorphosis and congestion of the liver. Chronic
alcoholism was probably responsible for the changes in the liver. Death was due to respiratory failure.

Four dogs received tetraethylammonium chloride in an intravenous infusion over a 30 minute period four times a day. All 4 dogs died with respiratory failure. Three of the 4 dogs revealed cessation of respiration in the inspiratory phase. Postmortem pulmonary findings on all 4 dogs revealed edema and focal hemorrhage into the pulmonary alveoli, and generalized congestion including the lungs. The lethal doses in these 4 dogs ranged from 30 to 50 mg. per Kg. (average 40 mg. per Kg. per infusion).

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GEORGE A. MCLEMORE, JR., HAROLD D. GREEN and THOMAS N. LIDE

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