REVIEW ARTICLE

CITRATE INTOXICATION*

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DURING THE PAST few years there has been increasing concern over the danger of citrate intoxication resulting from multiple transfusions of citrated blood.[1, 2] It is the purpose of this paper to discuss the normal metabolism of citric acid and to review the literature on citrate intoxication.

Citric acid is widely distributed in human tissues and fluids, but by far the highest concentration is in the bones.[3] It has been estimated that over 95% of the total citric acid of the body resides in the skeleton.[4] Although the significance of the tremendous concentration of citrate in bone is as yet uncertain, present information on the interrelationship of calcium and citrate metabolism suggests that it may be one of considerable importance. Citric acid combines with calcium to form a diffusible but poorly ionized complex.[5, 6] Much of the calcium bound to citrate is thus rendered biologically inactive, at least as far as its role in the function of cardiac muscle, skeletal muscle and blood clotting is concerned; calcium must be present in the ionized form to perform these functions. Normally, the concentration of citrate in human serum is quite low: between 2 and 3 milligrams per 100 millilitres, and the amount of calcium which is bound to it as a complex is quite insignificant: probably less than 0.5 mg. per 100 ml.[6]

Further relationships between citric acid and calcium metabolism have been demonstrated. It has been shown experimentally that injections of parathyroid extract are followed by rises in serum citrate levels and that, after parathyroidectomy, the concentration of citrate in the serum decreases.[7, 8] However, comparable rises in citrate levels occur after intravenous injections of calcium salts.[7] Moreover, elevated serum citrate levels have been found in various other hypercalcæmic states such as hypervitaminosis D and metastatic carcinoma. It would appear therefore that serum citrate concentrations are in some way determined by the amount of calcium in the body fluids and that, when the concentration of calcium in the serum is increased, the serum citrate also rises, and vice versa. The changes in citrate levels occurring in the aforementioned conditions are not sufficiently great to be of clinical significance.

There is evidence which suggests that the administration of vitamin D has an influence on citrate metabolism which is primary rather than secondary to coincident changes in calcium metabolism. In human and experimental rickets, serum citrate levels are low irrespective of calcium levels, and the administration of vitamin D to rachitic rats results in a prompt increase in citrate concentration which is not preceded by a change in calcium levels.[9, 11]

The role of citric acid in the intermediary metabolism of carbohydrate, fat and protein has been more clearly defined. Citric acid is an important member of the Krebs tricarboxylic or citric acid cycle. This cycle forms the common metabolic pathway wherein the 2-carbon or acetate fragments derived from the breakdown of carbohydrate, fat and protein undergo final oxidation to carbon dioxide and water with the release of energy. This system has been demonstrated in many tissues but the most important sites probably are the liver and muscle. The remarkable ability of the healthy liver to metabolize citrate has been demonstrated in animal experiments in which livers were perfused with citrate. It was found that 100 times the normal concentration of citrate in blood could be cleared in one passage through the liver.[12] However, in hepatic dysfunction, an increase in resting values of serum citrate and slower removal of injected citrate have been observed.[12] In addition to its utilization by liver and muscle, citric acid is excreted and concentrated by the kidney.[13] The concentration of citric acid in the urine is normally 15 to 20 times that of serum.

Because of its rapid utilization under normal conditions, citrate has been regarded as a perfectly safe anticoagulant for blood and the danger of citric acid intoxication resulting from the transfusion of citrated blood has been thought to be negligible.[14] But there now appears to be good evidence that citrate concentrations may rise to toxic levels when large quantities of citrated blood are given rapidly.

Evidence of citrate intoxication occurring in humans was first presented by Wexler *et al.*[15] They found tremendous increases of serum citrate concentrations in erythroblastotic infants receiving exchange transfusions. In one case the serum citrate was 150 mg. per 100 ml., which is 50 times or more the concentration normally present in serum. Tetany has occurred in some infants[15, 16] and deaths have been reported.[15-17]

During exchange transfusions in infants blood is given very rapidly, 500 ml. usually being administered in one hour. This results in citrate being infused at a rate of approximately 5 to 10 mg. per kg. of bodyweight per minute. Such rapid rates of citrate administration are unlikely to occur in adults. Studies which are applicable to conditions in adults have been reported by Bunker and his associates.[18] Serum citrate levels were determined in 130 patients who were transfused with varying amounts of citrated blood. There was no serious accumulation of citrate when the rate

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of transfusion in adults without liver disease did not exceed 500 ml. every 30 minutes. However, when the rate was doubled to 500 ml. every 15 minutes, about one-half of the patients without liver disease and all those with liver disease had serum citrate levels above 9 mg. per 100 ml. Serum citrate concentrations above this level are apt to result in significant reduction of the amount of *ionized* calcium in the extracellular fluids. It is unlikely, however, that levels of *ionized* calcium are seriously reduced by citrate concentrations of less than 25 mg. %. In this series of 130 cases, there were seven patients who had citrate concentrations greater than 25 mg. per 100 ml. The calculated rate of infusion of citrate in these seven cases was usually 1.0 mg. per kg. of bodyweight per minute, or more. Although the authors report that it was usually necessary to give blood at the rate of 500 ml. every 15 minutes before such a rate of citrate infusion occurred, these figures are not necessarily applicable when blood is obtained from the banks of many Canadian hospitals and from the Canadian Red Cross. Blood obtained from these sources may have a higher citrate content than that supplied by the blood bank of the Massachusetts General Hospital, which was the source of some of the blood used in this study. When blood with higher citrate content is used, a dangerous rate of citrate infusion, namely 1.0 mg. per kg. of bodyweight per minute, may occur when 500 ml. are given every 30 minutes or faster.

Data obtained in the study of Bunker and associates also suggest that there is increased danger of citrate intoxication in hypothermia and during any cardiac or great vessel surgery which produces mechanical obstruction to the hepatic circulation.

As yet no direct toxic effect of the citrate ion has been demonstrated. The harmful results of citrate accumulation are presumably due to depression of *ionized* calcium levels. Hastings and his associates[5] have suggested a formula for the calculation of *ionized* calcium levels when values for the total concentrations of calcium and citrate are known. If one calculates the level of ionized calcium in the serum when the citrate concentration rises to 25 mg. per 100 ml., values of 2.2 mg. per 100 ml. or less may be obtained, the normal level being 4.0 to 5.0 mg. %. When the concentration of ionized calcium in the extracellular fluids is decreased to such a degree, tetany and impairment of cardiac function are apt to occur.

Tetany has been reported in children but was not observed in any of the patients studied by Bunker and his associates.[18] In the Toronto General Hospital tetany has been observed in one patient thought to have had citrate intoxication. The diagnosis was not proven because citrate determinations were not being performed at that time.

CASE REPORT*

The patient, a 29-year-old woman suffering from a severe delayed post-partum hæmorrhage, was admitted to hospital in profound shock. A dilatation and curettage was performed immediately but severe bleeding continued and shock persisted for at least four hours despite transfusions with large quantities of blood and dextran. Four hours after admission to hospital a hysterectomy was performed; in the lower uterine segment a tear was found, which was presumably the cause of the post-partum hæmorrhage. During the operation it was difficult to control the bleeding. In the postoperative period the systolic blood pressure was maintained at 100 mm. Hg until shortly before death but her Hb. level was never above 6.5 g. per 100 ml. Nine hours after the operation she suffered tetany, which responded to the intravenous administration of calcium gluconate. Later, hyperventilation occurred followed by decreasing levels of consciousness and finally convulsions; she died 32 hours after admission to hospital.

At autopsy there was marked cerebral œdema and evidence of widespread tissue anoxia.

During the first 16 hours in hospital this patient received eight litres of citrated blood. Most of the blood (six litres) was given during the first five hours and in this period the rate of citrate infusion was 1.36 mg. per kg. of bodyweight per minute—a rate likely to produce toxic citrate levels. The total serum calcium was normal, as is usually the case in citrate intoxication. The patient also had an unexplained metabolic acidosis which ruled out hyperventilation as a cause of her tetany. Her venous blood pH was 7.22; serum sodium, 136 mEq./l.; serum potassium, 4.2 mEq./l.; serum chlorides, 108 mEq./l.; and carbon dioxide combining power, 7.7 mEq./l. In the absence of hypocalcæmia and alkalosis it was concluded that the tetany was probably due to citrate intoxication. Whether citrate intoxication was a significant factor in causing death is uncertain.

The harmful effects of citrated blood on the action of cardiac muscle are a much more serious manifestation of citrate intoxication. These effects are a decreased force of systolic contraction with resultant hypotension and a tendency towards arrhythmias, especially ventricular fibrillation. The isolated frog heart preparation of McLean and Hastings[19] stops beating when the level of ionized calcium in the perfusing fluid falls to 2.0 mg. %. Clinically, hypotensive episodes have been encountered when citrate levels were excessively high even though blood replacement seemed adequate. Such hypotensive episodes have responded to the intravenous administration of calcium salts.[18]

The adverse effect of citrated blood on cardiac function has been demonstrated experimentally by Cookson *et al.*[20] in animals. They performed experiments on 22 dogs. In each dog, shock was produced by the rapid withdrawal of 45 to 50% of the calculated blood volume.

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*The author wishes to thank Professor D. E. Cannell of the Dept. of Obstetrics and Gynæcology for permission to report this case.

In one-half of the animals the blood was then replaced with heparinized blood. All these dogs showed immediate and complete recovery from shock. In the remaining animals, citrated blood was used for replacement. Only one of these dogs showed rapid and complete recovery. In the dogs that failed to respond, cardiac output was greatly reduced and the right atria were engorged. Depression of heart action was reversed in several experiments by an intracardiac injection of 3 to 5 ml. of 10% calcium chloride. These investigators also had the impression that hypothermic dogs were more susceptible to citrate intoxication. When such animals were transfused with citrated blood under the experimental conditions described above, the incidence of cardiac arrest was high.

Disturbances in blood coagulation have also been noted after multiple transfusions with citrated blood. It has been suggested that these hæmorrhagic complications might be due in part to the marked lowering of ionized calcium resulting from citrate accumulation. Stefanini[21] has reported a slight prolongation of clotting time when the *ionized* calcium level falls to 2.0 mg. %. However, factors other than lowering of ionized calcium levels are probably of much greater importance. Recent studies[22, 23] suggest that thrombocytopenia and diminished concentrations of prothrombin accelerator factors may be the responsible causes. Such an explanation seems reasonable because stored blood has a decreased titre of prothrombin accelerators, and platelets are almost non-existent.

The answers to certain problems concerning citrate intoxication cannot be found in the available literature on the subject. For instance, present information does not indicate how long serum citrate levels might remain elevated once the state of citrate intoxication has been established. If our patient referred to in this paper actually did suffer from citrate intoxication, there is a suggestion that high citrate levels may persist for several hours after the rate of transfusion is greatly reduced. During the first five hours in hospital this patient received six litres of blood but had no tetany. In the ensuing nine hours she received only an additional two litres of blood, given at widely spaced intervals, and yet at the end of this time tetany developed. Our patient also had a metabolic acidosis, the cause of which was not determined; there was no evidence of renal insufficiency, diabetes or ketosis. It is possible that this acidotic state could also have been due to citrate intoxication. Although trisodium citrate is the salt commonly used for anticoagulant purposes, the serum sodium does not become elevated despite marked rises in citrate levels.[15] Theoretically a high citrate concentration in the extracellular fluids, by increasing the anion content without any material alteration of the cations, should produce a metabolic acidosis. It is hoped that future studies will clarify this aspect of the problem.

Treatment of established or incipient citrate intoxication is by intravenous injection of calcium salts. Attacks of tetany, depressed heart action and hypotensive episodes have all been reported to respond to such treatment. However, it is difficult to calculate the correct dose of calcium since *the total serum calcium usually remains within normal limits.* Determination of the level of *ionized* calcium in the serum would aid in the calculation of the proper dose but the only available method is a biological one utilizing the frog heart preparation of McLean and Hastings and it is not suitable for routine hospital purposes. Likewise, citrate determinations are difficult and cannot be done in most routine laboratories. Since the treatment of the condition is unsatisfactory, the avoidance of excessively large or rapid transfusions of citrated blood is advisable. This is especially desirable when factors such as liver disease, hypothermia or obstruction to the hepatic circulation increase the likelihood of citrate intoxication.

A suitable substitute for citrated blood is being sought. Oxygenated red cells suspended in Ringer-Locke gelatin solution,[20] red cells suspended in salt-free dextran[24] and blood from which calcium has been removed by passage over an ion exchange resin[18] have all been suggested as alternative materials for blood transfusions. The disadvantage of all these substitutes is the complicated method of their preparation.

SUMMARY

1. When citrate is injected at the rate of 1.0 mg. per kg. of bodyweight per minute, there is danger of its accumulation to toxic levels. Such a rate of citrate infusion occurs when blood from many hospital and Red Cross banks is transfused at the rate of 500 ml. every 30 minutes or faster.

2. The danger of citrate intoxication is greater in the presence of liver disease. In patients undergoing cardiac and great vessel surgery, mechanical obstruction to the hepatic circulation could have a similar effect. Induced hypothermia might also increase the danger since many metabolic processes, including the rate of citrate utilization, are apt to be depressed by lowered body temperatures.

3. The toxic effects of citrate are thought to result from decreased levels of ionized calcium in the extracellular fluids. Marked lowering of *ionized* calcium levels may result in tetany and impaired heart action. The latter may lead to hypotension despite adequate blood replacement and also to an increased danger of ventricular fibrillation and cardiac arrest.

4. The treatment of citrate intoxication is by the intravenous administration of calcium salts. However, such treatment is not completely satisfactory and there is need for an easily pre-

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pared alternative to citrated blood for transfusion purposes. If possible, it is desirable to avoid the rapid transfusion of large amounts of citrated blood.

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PUBLIC RELATIONS FORUM

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PUBLIC ATTITUDES TOWARDS DOCTORS. V.

THERE WAS A TIME when the course of a public relations program was guided "by guess, by God and by intuition." Fortunately, the folly of such haphazard programming has been recognized by most practitioners. Today facts form the bedrock of the sound public relations program and on this foundation creative intelligence and imagination build.

One of the most effective fact-finding tools used in public relations is the public opinion survey. This type of research attempts to measure the extent and intensity of public attitudes and/or to determine the reasons for such attitudes.

The last four articles in this column reported some of the important findings of such a public opinion study conducted for the American Medical Association. Unfortunately, this particular survey answered only the question "How much?" not "Why?" However, armed with only this information one may attempt, albeit skating on thin ice,* to suggest reasons for some of the attitudes reported and to examine some of the implications of the findings.

THE FAMILY DOCTOR

Perhaps the two most important facts revealed by the survey are:

1. People who have a family doctor hold more favourable attitudes towards the medical profession than those who have no doctor.

2. People hold their own doctor in greater esteem than they do doctors generally.

The first of these findings points up the importance of promoting the family doctor concept. The family doctor is frequently the individual's only contact with the medical profession. For many laymen, lacking contact with the profession, medicine and its practitioners have always been surrounded by an aura of myth, magic and mystery. People fear the unknown and probably dislike that which they fear.

The family doctor can do much to dispel this fear and to prove to his patients that the doctor is a likable human being, not an impersonal demi-god.

But to urge people to acquire a family physician is not enough. Some mechanism must be set up through which people may make a wise choice of doctor on the bases of propinquity, age, sex, religion, etc. It is encouraging to learn that the College of General Practice is actively studying this problem and is urging its provincial chapters to develop a program to meet this need. The British Columbia Division of the C.M.A., too, has offered its assistance to persons seeking a family doctor.

In addition to helping to improve public attitudes towards the medical profession, it is obvious that acquisition of a family doctor will do much to eliminate the public criticism that doctors are difficult to reach in an emergency. But more of this criticism later.

The revelation that people think much more highly of their own doctor than they do of doctors generally poses a most difficult public relations problem. The reason for this phenomenon is no doubt complex and consequently the solution will not be simple.

To the individual his family doctor is someone very special. The choice has probably been his own. Because of this ego involvement, to say that all doctors are as good as his own would be a reflection on his own judgment. But personal experience is also an important factor. The medical profession has acquired a stereotyped personality through publicity seen in the newspapers, magazines and on television, and heard on the radio and from neighbours. From experience the patient knows his own doctor as

*A Toronto psychologist, Grant McMurray, Ph.D., is a "partner on skates". I should like to acknowledge his help in assessing the "public mind" as reflected in the survey results.