PVC in each 24 hour period. He was recently readmitted to the CCU, and the drug was temporarily discontinued while ECG was being continuously monitored and recorded on a 24-hour Holter tape. Approximately ten hours after the last dose of lorcainide, the patient started having frequent multifocal PVCs which rapidly progressed to multifocal PVCs, pairs, triplets, and bigeminy. A total of 534 PVCs were counted from the Holter tape during this hour. A 25 mg bolus of lorcainide given 11 hours from the last oral dose completely suppressed all arrhythmias and oral therapy with lorcainide was resumed. Follow-up Holter tapes for the next 48 hours (two 24-hour tapes) again showed no PVCs while the patient remained ambulatory.

Pharmacokinetic Data

Blood samples were drawn prior to each loading dose of lorcainide and at frequent intervals from the end of the last intravenous dose (Fig 3). Samples were also drawn prior to and at 2, 4, and 6 hours, after an oral dose of 100 mg one week after therapy four times daily had begun. Plasma concentration/time relationship and calculated pharmacokinetic data are shown in Fig 3. The total area under the concentration/time curve from 0 to $\alpha$ (AUC) was calculated by a computer program with the trapezoidal rule. The decline in drug concentration during the elimination phase showed an excellent biexponential fit as determined by linear regression analysis, and the calculated half-life of the $\beta$-phase was 19.4 hours. The volume of distribution of lorcainide was 23 L, which suggests that the drug is distributed in vascular and extracellular space in the body. Data obtained after oral administration of lorcainide showed concentrations in the same range as observed during the acute intravenous phase.

Discussion

Lorcainide is a new and structurally distinct antiarrhythmic drug. Experimental pharmacologic and electrophysiologic data suggest that it belongs to the Class I antiarrhythmic drugs. Preliminary clinical reports from Europe suggest that lorcainide is orally effective, has a long plasma half-life, and is well tolerated.2-4 Unlike other investigators who used 100- or 200-mg boluses, we titrated the patient with 25-mg boluses of lorcainide and demonstrated a clear cut, dose-dependent decrease in PVCs. An excellent antiarrhythmic response coupled with a lack of adverse effects upon acute or chronic administration of lorcainide suggest that it may be a clinically useful drug for patients with cardiac arrhythmias. The waxing and waning of arrhythmias from the time of intravenous drug administration and the next 48 hours is very interesting and not previously reported. It is highly unlikely (because of the well-documented previous arrhythmias) that a spontaneous decrease in the arrhythmia frequency occurred between 24 and 40 hours, and we believe that the observed response was either due to lorcainide or one of its active metabolites. The waxing and waning of arrhythmias suggest a strong possibility of enterohepatic circulation of the drug (Fig 3). The pharmacokinetic data in this and other reports 5,6 suggest that adequate plasma concentration is achieved during oral therapy. Clinical efficacy of orally administered lorcainide was remarkable in this patient who was resistant to large doses of multiple antiarrhythmic drugs. Repeated ECG monitoring while ambulatory showed an almost 100 percent suppression of all dysrhythmias with lorcainide alone, and indeed, a careful attempt to discontinue the drug resulted in a prompt recurrence of the pretreatment arrhythmias in ten hours. However, the half-life of lorcainide in this patient was 19.4 hours, which suggests that the plasma concentration must be maintained in the upper range for maintenance therapy. Further studies are suggested to evaluate the ultimate usefulness of lorcainide as an antiarrhythmic drug.

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References


Acute Fluoride Poisoning Leading to Fatal Hyperkalemia*

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Marked peaking of the T waves later recognized as being due to hyperkalemia was noted in a patient with acute fluoride intoxication before developing refractory ventricular fibrillation. Such T wave changes have not been previously described in fluoride intoxication and should alert one to the presence of hyperkalemia complicating this condition, the presence of which may herald the onset of lethal ventricular arrhythmias.

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Acute fluoride poisoning produces severe, generalized, often lethal toxic reactions. However, the mechanism by which death occurs is not certain. The development of ventricular arrhythmias has been observed experimentally in dogs given sodium fluoride, and repetitive ventricular fibrillation unresponsive to electrical defibrillation has been reported in some cases of human poisoning. The following case report describes a patient with sodium fluoride poisoning who also developed repetitive ventricular fibrillation, and whose ECG prior to the development of the fatal arrhythmia showed marked peaking of the T waves suggesting hyperkalemia. Such a premonitory finding has not previously been described. In order to ascertain whether these electrocardiographic changes were directly attributable to ingestion of the fluoride ion in this patient, and in order to elucidate their mechanism of production, two mongrel dogs were acutely intoxicated with sodium fluoride solution given intravenously. Serial ECGs were obtained and correlated with the levels of serum electrolytes and arterial blood gases.

**CASE REPORT**

A 25-year-old black man was seen in the emergency room approximately 28 hours following intentional ingestion of a rat poison, a finely textured blue powder in an unmarked cylindrical cardboard container initially thought to contain arsenic but later found to contain sodium fluoride. He had been seen four years previously for mild hypertension at which time an ECG showed a sinus bradycardia and somewhat prominent voltage (Fig 1, column A).

The examination was otherwise unremarkable except for a tachycardia of 180 beats per minute and the presence of gallop rhythm. Specifically, pupils were equal and briskly reactive to light, and there was no cyanosis. The stool was positive for occult blood.

Initial lab work was generally unremarkable except for slight hemococoncentration with hematocrit value of 48 percent and hemoglobin level of 16.4 g/100 ml. Serum electrolyte levels were as follows: Na, 148 mEq/L; K, 4.2 mEq/L; Cl, 105 mEq/L; and CO₂, 17 mEq/L. A 12-lead ECG (Fig 1, column B), performed 45 minutes later showed striking T wave peaking. Although a calcium level was not determined, the QT interval corrected for rate was 0.45 sec at this time, compared to 0.36 sec on the previous ECG. A general toxicology screen was reported later as negative for alcohol and other drugs and for arsenic.

Since the patient was initially thought to have ingested arsenic, 300 mg of dimercaptoprol (BAL) was injected intramuscularly. A nasogastric tube was inserted yielding a thick, whitish aspirate with blood streaks. Gastric lavage was performed with 3,000 ml of milk, and the patient was treated with intravenous fluids consisting of dextrose and saline and was placed on a cardiac monitor. Approximately one hour after admission, he developed ventricular fibrillation. Initial defibrillation was successful; however, the ventricular arrhythmias recurred in spite of intravenous administration of lidocaine (Xylocaine) and repeated defibrillation. In addition, he developed profuse drainage of bright red blood from the nasogastric tube, and after 30 minutes of unsuccessful resuscitation was pronounced dead.

An autopsy revealed severe congestion of lungs and liver, mild left ventricular hypertrophy, and normal coronary arteries. There was marked hyperemia of the serosa of both stomach and esophagus, the mucosa of the stomach was markedly congested, and the lumen contained 50 ml of purplish brown fluid. Analysis of the stomach contents and of the powder originally ingested by the patient revealed a high concentration of fluoride ions.

**EXPERIMENTAL DATA**

Two mongrel dogs under pentobarbital sodium (Nembutal) anesthesia were intoxicated with 500 mg sodium fluoride given as a 0.8M solution in 5 percent dextrose/water over a 45 minute period. Marked peaking of the T waves in both standard and precordial leads was noted at 30 minutes which became even more striking over the next 30 minutes (Fig 2). Immediately
prior to death, transient ST sagging was noted in the anterolateral leads, quickly followed by respiratory arrest, bradycardia, and finally ventricular fibrillation. Serial electrolyte determinations revealed a progressive rise in potassium level during this time in the absence of any evidence of acid-base disturbance. The final potassium levels were 6.9 and 6.1 mEq/L, respectively, in the two experimental animals. Although calcium levels fell just prior to death, QT intervals corrected for rate were identical to baseline values.

**DISCUSSION**

The toxicity of compounds containing fluoride are primarily related to their individual solubilities, for example: potassium fluoroborate and potassium hexafluorophosphate, being almost insoluble, are practically nontoxic because the fluoride ion is so tightly bound that it passes through the body with very little being released for absorption. In contrast, sodium fluoride is highly soluble, can easily dissociate, and is readily absorbed. Since the fluoride ion has an extremely strong affinity for cations, hypocalcemia due to this mechanism is thought to be responsible for many of the various manifestations of fluoride toxicity including tetany, seizures, depression of the central nervous system, and impairment of blood coagulation. In fact, the most severe form of hypocalcemia ever recorded in a human being was reported in a case of fluoride poisoning. Additionally, other metallic ions such as zinc, manganese, and magnesium may be rendered unavailable by fluoride, which could result in inhibition of numerous enzyme systems dependent on these trace metals. Thus, prophylactic administration of cations including calcium and magnesium, but also in addition, solutions containing potassium have been suggested for the treatment regimen in fluoride poisoning.8

The occurrence of ventricular fibrillation following fluoride intoxication has previously been reported in two human cases. The arrhythmias were unusual in that they were repetitive and not responsive to repeated electrical defibrillation. In addition, lethal doses of sodium fluoride in experimental animals have also resulted in ventricular arrhythmias and shock. Our patient showed marked peaking of the T waves resembling hyperkalemia prior to the development of intractable ventricular fibrillation. Continuous infusion of sodium fluoride in our two mongrel dogs also reproduced these T wave changes, and when peaking of the T waves became apparent, hyperkalemia was present. The appearance of hyperkalemia in acute fluoride toxicity has not been previously reported, although in reviewing previous case reports and animal work, slight peaking of the T waves appears to be present in monitor leads but is not commented upon.

Among the enzymatic reactions interfered with by sodium fluoride are those of carbohydrate metabolism. These reactions have been used to study potassium fluxes between red blood cells and serum. Blood samples to which sodium fluoride has been added when incubated at 37°C show a sharp rise in serum potassium in contrast to control samples where metabolic activity is not inhibited, in which the serum potassium in fact decreases. It is quite possible such a mechanism could be responsible for the production of acute hyperkalemia clinically.

As illustrated by the present report, the development of hyperkalemia can be fulminant and fatal. Thus, this possibility should be carefully watched for by continuous electrocardiographic monitoring in all patients with acute sodium fluoride poisoning. Peaking of T waves is an early manifestation and has preceded the onset of ventricular arrhythmias in this case report, in our animal studies, and probably in previous clinical and experimental reports where the abnormality seems to have

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**Figure 2A.** Baseline ECG of experimental dog prior to infusion of sodium fluoride. B. Tracing taken 55 minutes later showing marked peaking of T waves in almost all leads. These changes were apparent after 30 minutes of infusion. Potassium levels in both experimental animals were always elevated when these T wave changes appeared, 6.9 mEq/L in this instance.
been unrecognized.\textsuperscript{3,4} In addition to avoiding the injudicious administration of solutions containing potassium for these patients, one should rather be prepared instead to attempt the lowering of the serum potassium level by appropriate means.

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\textbf{Hypocalcemic Cardiomyopathy*}

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Two patients with cardiomegaly and congestive heart failure were found to be grossly hypocalcemic secondary to previously undiagnosed hypoparathyroidism. The cardiac failure was refractory to digitalis preparations and diuretics but responded dramatically when specific therapy restored the serum calcium to normal. The mechanism of congestive heart failure in hypocalcemia is discussed, and their association constitutes one form of reversible cardiomyopathy which should be kept in mind when a patient fails to respond to conventional antifailure therapy.

Studies over the last decade have confirmed the central role of calcium in excitation-contraction coupling and thus in overall myocardial performance.\textsuperscript{5,4} Defects in calcium ion release or binding were also found in clinical or experimental heart failure.\textsuperscript{6,4} Although in animal experiments hypocalcemia has been shown to lead to cardiac decompensation, the occurrence of congestive heart failure resulting from hypocalcemia is quite rare in clinical practice. Only occasional cases have been described, mostly in the pediatric literature.\textsuperscript{6-7} We describe two patients, one child and one adult, with severe congestive cardiac failure associated with profound and long-lasting hypocalcemia secondary to hypoparathyroidism. The failure of conventional treatment with digitalis and diuretics and the steady favorable response to treatment with calcium alone, which eventually resulted in complete recovery, help to establish that myocardial decompensation in these two patients was indeed due to calcium depletion.

\textbf{Case Report}

Case 1

A ten-year-old girl was referred to Mouassat Hospital (Damascus University) for evaluation of a three-month history of congestive heart failure, complicated by episodic pulmonary edema and unresponsive to digitalis and diuretics. One year earlier she had an attack of "spasm" in both hands which recurred several times later. Three months before referral she had generalized convulsive seizures accompanied by loss of consciousness. Convulsions recurred monthly despite prophylactic oral treatment with phenytoin and phenobarbital. Important aspects of her past history included the loss of four permanent teeth seven months earlier and stridor that was attributed to "large tonsils."

Physical examination on admission revealed: pulse rate, 105/min; blood pressure, 105/70 mm Hg; temperature, 37.2\degree C and respiratory rate, 26/min. Nutritional status was good. The thyroid was not enlarged. There was mild tonsillar hypertrophy without inflammation. Jugular veins were distended with a positive hepatojugular reflux. The first heart sound was accentuated; a grade 2/6 ejection systolic murmur and a loud third heart sound were audible at the apex and near the sternal border. Bibasilar pulmonary moist rales were heard. Liver edge was palpable 3 cm below the right costal margin. Deep tendon reflexes were slightly depressed, Chvostek's and Trousseau's signs were clearly positive.

Chest x-ray film on admission (Fig 1) showed generalized cardiomegaly and congested pulmonary vessels with acute pulmonary edema. The electrocardiogram (Fig 2) showed borderline increase in QRS voltage and marked prolongation of QT interval at the expense of the ST segment.

Significant laboratory findings included: calcium, 3.2 mg/100 ml; phosphorus, 8.5 mg/100 ml; alkaline phosphatase, 320 U/L. Twenty-four hour urinary calcium was 36 mg (normal: 100-200) and phosphorus was 97.2 mg (normal: 900-1300).

Right heart catheterization revealed normal oximetry, pulmonary artery pressure of 30/16 mm Hg with a mean pressure of 22 mm Hg, and mean pulmonary artery wedge pressure of 16 mm Hg.

Therapy was started with calcium gluconate 4 gm daily and weekly injections of 600,000 units of vitamin D\textsubscript{2}. Digitalis, diuretics and phenytoin were discontinued one week later after serum calcium levels reached 5.1 mg/100 ml. All manifestations of heart failure improved gradually. Following one month of therapy, serum calcium rose to 8.5 mg/100 ml, and phosphorus fell to 6.7 mg/100 ml. The patient became

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