CLINICAL TOXICOLOGY, 6(2), pp. 153-162 (1973)

Hyperkalemia in Acute Digitalis Poisoning: Prognostic Significance and Therapeutic Implications

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INTRODUCTION

That digitalis inhibits the mechanisms which underlie the active transport of cations, the so-called "cation pump," has been known for many years [18]. The effects of this inhibition are most noticeable in cardiac muscle, where digitalis, in both therapeutic and toxic concentrations, causes potassium loss [5]. Administration of potassium salts has long been standard practice in the therapy of rhythm disturbances resulting from digitalis toxicity [11].

The aim of the present research, which was conducted in patients suffering from heavy digitalis overdosage, was to investigate the relationship between, on the one hand, the serum potassium levels in the initial stages of intoxication and, on the other hand, (a) the mortality and (b) the plasma digitalis levels.

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MATERIALS

Between January 1967 and April 1972, 115 patients were treated for acute digitalis poisoning at the Fernand Widal Toxicology Center, Paris. For the sake of homogeneity, only those who had taken the drug in the form of Digitaline Nativelle (digitoxin), either as a 0.1% tincture or as tablets, were admitted to the present study. Of these patients, numbering 111 in all, 20 were excluded for one of the following reasons. (a) Mildness of the symptoms and absence of electrocardiographic abnormality other than sinus bradycardia. (b) Presence of factors liable to lower serum potassium concentration, such as administration, within the preceding days, of diuretics, alkalinizing agents, or intravenous glucose. (c) Presence of factors liable to raise the serum potassium concentration, for example, circulatory failure, oliguria, acidosis [8], administration of excessive potassium, trauma to the blood at the time of withdrawal, or delay in conducting the potassium determination. (d) Period of more than 18 hr between ingestion of the drug and admission to the hospital. (e) Period of more than four days between ingestion of the drug and death.

After operation of these selections, there remained 91 patients, 20 men and 71 women, whose ages ranged from 15 to 94. In only 10 of these patients had overdosage occurred in the course of therapy. Most of the remaining 81 patients had taken digitalis with suicidal intention; a small minority had taken it accidentally. As far as could be ascertained, the doses ranged from 2 to 25 mg of Digitaline Nativelle. The intervals between ingestion of the drug and admission to the hospital varied from three to 18 hr.

METHODS

All blood samples were taken by arterial puncture, immediately after admission to the hospital.

Serum potassium levels were determined by flame photometry.

Serum digitalis levels were estimated by the method of Bourdon and Mercier [2]. This method is based upon two known facts: (a) digitalis inhibits transport adenosine triphosphatase (ATPase), an enzyme with a key role in active transport of potassium ions through erythrocyte cell membrane [1, 16]; (b) erythrocytes do not significantly distinguish rubidium from potassium. Plasma digitalis levels so determined are therefore an indirect measure both of membrane ATPase activity and of potassium uptake by

erythrocytes. The technique is a modification of that first introduced by Lowenstein and Corrill [9]. The plasma under investigation is incubated with washed human erythrocytes and a solution of rubidium. Since the uptake of rubidium by erythrocytes is inversely proportional to the concentration of digitalis in the plasma, this latter value can be determined by measuring the rubidium remaining in the incubation fluid. Rubidium is measured by atomic absorption spectrophotometry.

All patients underwent continuous electrocardiographic monitoring during the first four days of hospitalization.

RESULTS

A significant relation was found between initial serum potassium levels and mortality (Fig. 1). The mean serum potassium concentration on admission to the hospital was 6.15 ± 0.74 (2 SD) meq/liter in 24 patients who succumbed and 4.2 ± 0.52 (2 SD) meq/liter in 67 patients who recovered; the difference in the means is statistically significant ($P = 0.001$). No patient whose initial serum potassium level was above 5.5 meq/liter survived, and no patient in whom the initial serum potassium level was below 5 meq/liter succumbed. The mean serum potassium level in 70 normal control subjects was 3.56 ± 0.35 (2 SD) meq/liter. The intervals between ingestion of the drug and death in the 24 patients who died ranged from three hours to four days. The initial electrocardiographic changes in many of the patients who succumbed were mild.

The correlation between the doses of Digitaline said to have been ingested and the plasma digitalis levels was positive but not statistically significant ($r = 0.417$, $n = 20$, $0.10 > P > 0.05$) (Fig. 2).

Correlation between serum potassium levels and plasma digitalis levels was likewise positive but not significant ($r = 0.304$, $n = 24$, $P > 0.10$) (Fig. 3).

No relation was found between dosage and mortality; 13 patients who had taken 10 to 20 mg of Digitaline survived, whereas six patients who had taken between 3 and 5 mg of the same preparation died.

DISCUSSION

That acute digitalization raises the serum potassium level was shown experimentally by Lown et al. in 1957 [12]. In digitalized

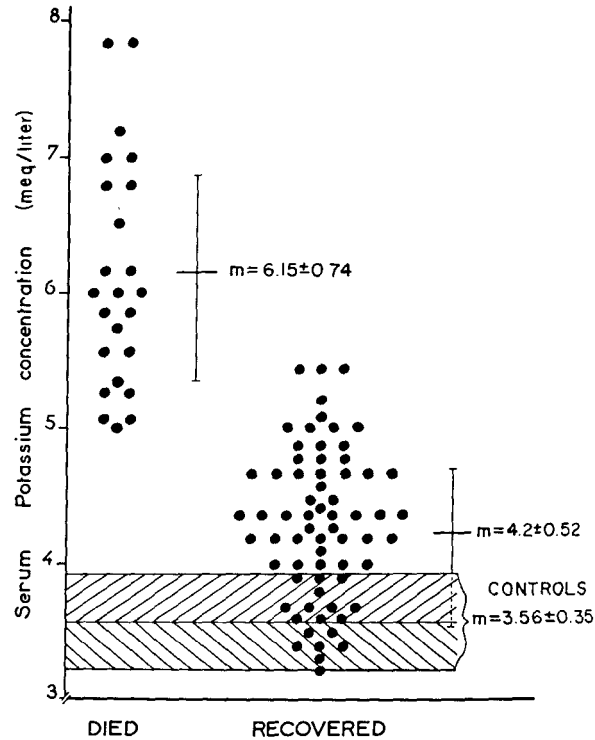

FIG. 1. Acute digitalis intoxication. Initial serum potassium levels in 24 patients who died and in 67 patients who recovered (P = 0.001), compared with levels in 70 normal control subjects. Means are ±2 standard deviation.

dogs, a rise in arterial serum potassium occurred in 93% of digitalizations averaging 0.64 meq/liter.

The therapeutic administration of digitalis is known to result in a small elevation of serum potassium, due to (a) a generalized release of potassium from many tissues, chiefly the liver, and (b) the inhibition of uptake of the released potassium by skeletal muscle [10].

Potter [15], found hyperkalemia in four of 23 patients suffering from self-administered overdoses of digitalis. Elevation of serum potassium levels (to about 6 meq/liter) occurred during

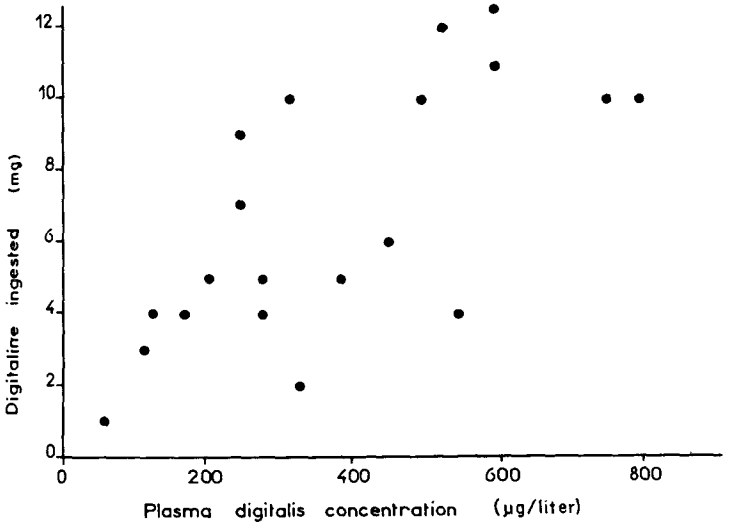

FIG. 2. Acute digitalis intoxication. Correlation between alleged dosage of Digitaline and plasma digitalis levels in 20 patients ($r = 0.417$, $0.10 > P > 0.05$).

the first hours of intoxication. It was generally of short duration, normal levels being regained within 24 hr.

In 70 cases of acute digitalis poisoning studied by Gaultier et al. [4] and by Jouannot et al. [7], the mean serum potassium level on admission to the hospital was 5.5 ± 1.4 (SD) meq/liter in 14 patients who died, and 4.4 ± 0.82 (SD) meq/liter in 56 patients who recovered.

Smith and Willerson [19] reported a patient who died with refractory hyperkalemia (7.7 to 9.8 meq of potassium per liter) and high-grade atrioventricular block after suicidal ingestion of 23 mg of digoxin. The patient's serum digoxin level (42 ng/ml) was the highest in their series of five cases of massive digitalis poisoning.

Chung and Thomas [3], on the other hand, found no definite correlation between serum potassium levels and the severity of the cardiac arrhythmia or of the patient's condition. The serum potassium levels were normal or subnormal in all their 17 patients.

A relation between the severity of hyperkalemia in digitalis poisoning and the severity of the poisoning at first seems

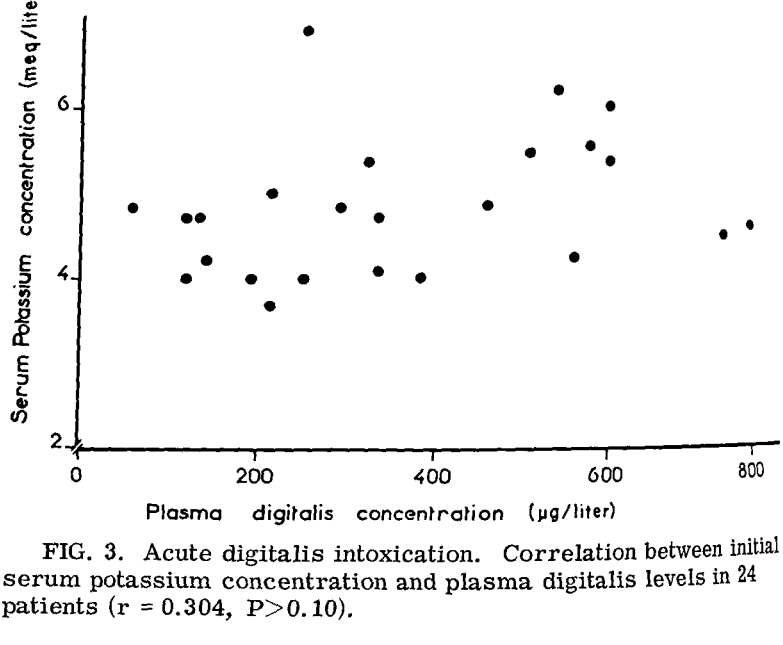

FIG. 3. Acute digitalis intoxication. Correlation between initial serum potassium concentration and plasma digitalis levels in 24 patients ($r = 0.304$, $P > 0.10$).

paradoxical, since (a) digitalis causes potassium depletion, and (b) administration of potassium is a time-honored measure in the treatment of digitalis intoxication.

The paradox, however, is only apparent. Myocardial potassium depletion does, in fact, occur in digitalis toxicity, but it is an intracellular depletion. The interrelationships between intracellular and extracellular potassium and digitalis toxicity are highly complex, and are as yet far from having been fully elucidated. The serum potassium concentration is only indirectly related to the myocardial threshold to digitalis toxicity. It is likely that the critical factor in determining this threshold is the potassium concentration within the myocardial cell, or, more specifically, the gradient of potassium between intracellular and extracellular fluid across the cell membrane [10]. There is general agreement that toxic doses of digitalis cause myocardial potassium depletion, and that this is more likely to be due to diminished potassium influx than to increased potassium efflux [5]. The reduced intracellular potassium influx results from

inhibition by digitalis of membrane AT Pase [13], and hyperkalemia is an index of the degree of inhibition. In diuretic-induced hypokalemia, which is known to predispose to digitalis toxicity, the potassium depletion is probably both intracellular and extracellular.

The elevated salivary potassium concentration in digitalis toxicity, recently reported by Wotman et al. [20], is probably in our view, also due to digitalis inhibition of membrane AT Pase, although the authors themselves do not subscribe to this interpretation.

The mildness of the initial electrocardiographic changes in many of our patients who subsequently died suggests that serum potassium level is a better guide to prognosis than electrocardiography.

The poor correlation between serum potassium levels and plasma digitalis levels (Fig. 3) is disappointing in view of the key role played by membrane AT Pase in the method employed for determining plasma digitalis. Pébay-Peyroula et al. [14], also estimating plasma digitalis by the method of Bourdon and Mercier [2], found no close correlation between plasma digitalis levels and the severity of digitalis poisoning. The dominant factors in prognosis, according to these workers, are age, presence or absence of pre-existing heart disease, and degree of fluid and electrolyte imbalance. To these factors we would add a fourth, the blood potassium concentration in the early stages of toxicity.

The presence of hyperkalemia in the initial stage of digitalis poisoning has important therapeutic implications.

Since 1967, it has been the practice at this Toxicology Center to treat patients with digitalis intoxication associated with hyperkalemia by temporary pervenous pacemaker catheter. In several of these patients, cardiac manifestations of digitalis toxicity were mild—isolated first-degree atrioventricular block—but, because their serum potassium concentrations exceeded 5 meq/liter, it was nevertheless decided to proceed with pervenous pacing, and this was done without awaiting the results of plasma digitalis estimations, which require 48 hr. In every case the decision was justified by subsequent rapid increase in the degree of block or by onset of myocardial hyperexcitability.

It is obvious that, in the presence of hyperkalemia, there is no rationale for the administration of potassium salts.

Hyperkalemia is a pointer, not a contributory factor, to severe digitalis poisoning, and therefore does not require treatment per se. In particular, it is not an indication for attempts to encourage intracellular influx of potassium by alkalinization or by the administration of glucose and insulin. Nor does it

call for attempts to remove potassium from the body by the use of cation exchange resins such as polystyrene sulfonate (Kayexalate) or by dialysis. Experience has shown that these procedures do not affect cardiac disturbance in digitalis toxicity, and do not improve the prognosis.

Since, as has been shown, the presence of hyperkalemia is evidence of excessive inhibition of membrane ATPase by digitalis, with consequent reduced intracellular inflow of potassium, restoration of ATPase activity is the rational aim of therapy.

The stimulating action of barium on ATPase is well known, and has been demonstrated in vitro by Henn and Sperelakis on ouabain-inhibited ATPase [6]. Because of this property, Roza and Berman [17] have suggested that there may be a place for barium carbonate or barium chloride as antidotes in digitalis poisoning. The acute toxicity of soluble barium salts would appear to render this proposal impracticable.

SUMMARY

In 91 patients who had taken excessive doses of digitalis, a significant relation was found between serum potassium levels, determined 3 to 18 hr after ingestion of the drug, and mortality. The mean initial serum potassium concentration, in milliequivalents per liter, was 6.15 ± 0.74 (2 SD) in 24 patients who died, 4.2 ± 0.52 in 67 patients who recovered, and 3.56 ± 0.35 in 70 normal control subjects. The serum potassium levels did not correlate significantly with the plasma digitalis levels determined by measurement of uptake of rubidium by erythrocytes. Initial serum potassium levels proved a more reliable guide to prognosis than initial electrocardiographic findings. Digitalis-induced hyperkalemia is the expression of inhibition by digitalis of membrane adenosine triphosphatase, resulting in reduced entry of potassium into the myocardial cell and consequent fall in myocardial threshold to digitalis toxicity. Therapy in digitalis poisoning should be directed to restoration of the activity of membrane adenosine triphosphatase. In the presence of severe hyperkalemia, a "demand" pacemaker should be implanted, irrespective of plasma digitalis level, and even in the absence of marked electrocardiographic abnormalities.

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