CLINICAL STUDY

Therapeutic analysis in Chinese patients with thyrotoxic periodic paralysis over 6 years

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Abstract

Objective: To characterize the course of therapy in a large cohort of Chinese patients with thyrotoxic periodic paralysis (TPP), a reversible electrolyte emergency fraught with therapeutic challenges.

Design and methods: In this prospective interventional study, 78 patients with TPP (75 males and three females with an age range of 16–48 years) were consecutively enrolled over a 6-year period. Intravenous KCl at a rate of 10 mmol/h was administered until muscle strength recovered. Serum potassium (K^+) and phosphorus concentrations were measured hourly during the paralytic attack and for 6 h after recovery.

Results: The serum potassium (K^+) on attack was 2.1 ± 0.2 mmol/l. The dose of KCl administered to restore muscle strength was 63 ± 32 mmol, and peak serum K^+ concentration after recovery was 5.3 ± 0.5 mmol/l. A paradoxical fall in serum K^+ concentration >0.1 mmol/l difference between presentation and treatment nadir was observed in approximately one-fourth of TPP patients ($n=20$). These patients had significantly higher serum-free thyroxine concentration, systolic blood pressure, and heart rate on presentation, as well as serum phosphate concentration on recovery. They not only needed much more KCl supplementation (104 ± 34 vs 48 ± 19 mmol, $P<0.001$), but also had significantly more severe rebound hyperkalemia (5.8 ± 0.5 vs 5.1 ± 0.4 mmol/l, $P<0.001$) on recovery than those who did not have paradoxical hypokalemia. There was a positive correlation between the dose of KCl administered and the difference between peak and nadir serum K^+ (ΔK^+) ($r=0.68$, $P<0.001$).

Conclusions: TPP patients who do not develop paradoxical hypokalemia need a smaller KCl dose to achieve recovery, whereas those who develop paradoxical hypokalemia have more severe hyperthyroidism and hyperadrenergic activity and may require blockage of intracellular K^+ shift to prevent rebound hyperkalemia.

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Introduction

Thyrotoxic periodic paralysis (TPP), characterized by acute hypokalemia-related muscle weakness due to an acute shift of potassium (K^+) into cells in the setting of hyperthyroidism, is a potentially reversible medical emergency fraught with diagnostic and therapeutic challenges (1, 2). In contrast to familial periodic paralysis caused by calcium (Ca^{2+}) or sodium (Na^+) channelopathies (*CACNA1S* and *SCN4A* genes) of skeletal muscle in western populations, TPP is the most common cause of periodic paralysis in Asia (3–5). With globalization and immigration, TPP is no longer confined to certain geographic areas and has been increasingly reported throughout the world (6, 7). Patients with TPP often have subtle symptoms of hyperthyroidism (8, 9). Some characteristic findings

of TPP can help to establish the diagnosis when rapid thyroid function tests are unavailable in the emergency department (ED). These characteristics include adult male without a family history of periodic paralysis, systolic hypertension, tachycardia, high QRS voltage, or first-degree atrioventricular (AV) block on electrocardiogram (ECG), as well as typical acid–base and electrolyte findings such as normal blood acid–base state, hypokalemia with low urinary K^+ excretion, hypophosphatemia with hypophosphaturia, and hypercalciuria (1, 9–13).

The current therapy for TPP includes acute intravenous or oral potassium chloride (KCl) administration to hasten the recovery of muscle strength and prevent cardiac arrhythmia and respiratory arrest (14). The danger of exogenous K^+ administration is the development of rebound hyperkalemia upon recovery because

the administered and shifted K^+ are rapidly released from cells when the driving force of intracellular K^+ shift subsides (1, 4, 15). Nonetheless, some TPP patients have recovered without treatment or with only small doses of KCl supplementation (1, 15, 16). A large number of TPP patients are needed to delineate the optimal strategy for better and safer treatment. The aim of this prospective study was to analyze and characterize the therapeutic course in 78 TPP patients over a 6-year period. New results to be reported indicate that TPP patients who do not develop a 'paradoxical hypokalemia' need a smaller KCl dose to achieve recovery. Those who develop paradoxical hypokalemia have more severe hyperthyroidism and hyperadrenergic activity and need more KCl to restore muscle strength with subsequent development of more severe rebound hyperkalemia after recovery.

Patients and methods

Study subjects

The study protocol was approved by the Ethics Committee on Human Studies at Tri-Service General Hospital, National Defense Medical Center, in Taiwan, ROC. Patients with TPP were enrolled in this study over a 6-year period from January 2002 to December 2007, including 12 patients reported previously (12). TPP was defined as acute muscle weakness with an inability to ambulate and serum K^+ concentration <3.0 mmol/l associated with a low K^+ excretion in the presence of hyperthyroidism confirmed by thyroid function tests. Other causes of hypokalemic paralysis were excluded. All patients were admitted to ED for the first time and did not receive any nonselective β -blockers prior to and during therapy. Patients were also excluded if KCl treatment had been given before the ED visit.

Methods

All TPP patients received a standard 12-lead electrocardiogram (ECG). Blood pressure was recorded every 3 min, and ECG monitoring was recorded continuously on an ECG oscilloscope (Hewlett Packard). Average blood pressure and heart rate in the first hour were presented. Muscle strength was graded on a 5-point scale by manual muscle testing (15). In general, grade 5 (normal) was defined as muscle movement through complete range of motion (ROM) against gravity with full resistance. Grade 4 (good) was defined as muscle movement through complete ROM against gravity with moderate resistance. Grade 3 (fair) was defined as muscle movement through full ROM against gravity only. Grade 2 (poor) was defined as muscle movement through full ROM with gravity eliminated. Grade 1 (trace) was defined as palpable muscle contraction

without joint movement. Grade 0 (zero) was defined as no muscle movement or palpable contraction (total paralysis).

Arterial or venous blood samples for biochemistries and thyroid function tests were obtained through an indwelling catheter. A spot urine sample was collected as previously described (4). After the collection of baseline data, all TPP patients received intravenous KCl administration at a rate of 10 mmol K^+ /h in normal saline (125 ml/h) until muscle strength had recovered sufficiently for ambulation. The fixed dose of 10 mmol/h chosen in this study was based on patients' tolerance to the amount and rate of KCl therapy. However, intravenous KCl administration at a rate of 20 mmol/h was given if ventricular arrhythmia occurred on the ECG monitor or respiratory insufficiency developed during therapy. Muscle strength, serum K^+ and phosphate concentration were measured hourly during the attack and for 6 h after recovery. The lead time by history, time to recovery, and total amount of KCl administered were recorded.

Blood gases were measured with an ABL 510 (Radiometer, Copenhagen, Denmark). Biochemical values including serum and urine Na^+ , K^+ , chloride (Cl^-), ionized calcium (Ca^{2+}), magnesium (Mg^{2+}), phosphate, creatinine, urea nitrogen were determined by automated methods (Roche Diagnostic GmbH). Serum total triiodothyronine (T_3), free thyroxine (fT_4), and TSH concentrations were measured by commercial kits (Diagnostic Products Corporation, Los Angeles, CA, USA). The urine K^+ to creatinine ratio (K^+/Cr), an index of the K^+ excretion rate, was calculated using their respective concentrations in mmol/l terms. The fractional excretion of Ca^{2+} (FE_{Ca}) and phosphate (FE_P) expressed in % were calculated to assess the tubular reabsorption of these molecules.

Definition

The lead time was defined as the time from the onset of paralytic attack noted by the patients or family to the start of KCl therapy. The recovery time was defined as the time from the start of KCl therapy to the recovery of sufficient muscle strength to ambulate. Nadir and peak serum K^+ concentrations were the lowest serum K^+ level during KCl therapy and the highest after recovery respectively. Paradoxical hypokalemia was defined as a further fall in serum K^+ concentration of at least 0.1 mmol/l during KCl therapy because this small K^+ concentration difference has laboratory significance based on serum K^+ analysis within-run precision (0.20, 0.29%) and between-run precision (0.62, 0.57%), and rigorous intra-laboratory quality control (IQC). Rebound hyperkalemia was defined as a peak serum K^+ concentration >5.0 mmol/l. Δ Serum K^+ is the difference between the peak and nadir K^+ concentration.

Statistical analysis

Results are expressed as mean $\pm$ s.d. The unpaired Student's *t*-test was used to compare the differences in variables between TPP patients with and without paradoxical hypokalemia. The Mann-Whitney *U* test was used when the variables between two subgroups were not normally distributed. A correlation coefficient was calculated between Δ serum K^+ and the quantity of KCl administered. Differences were considered significant at a *P* value <0.05 .

Results

Patient characteristics

The age of patients with TPP ranged from 16 to 48 years with mean age of 30 years. The lead time was 3.4 ± 1.4 h. All except three were male (75 out of 78, 96%). Their onset of paralysis occurred mostly in the early morning (47 out of 78, 60%) with predominant lower extremity hemiplegia (52 out of 78, 67%) at presentation. Their body mass index was 24.3 ± 3.1 kg/m². Systolic blood pressure was relatively high (138 ± 13 mmHg), as was resting heart rate (99 ± 14 beat/min). Relative tachycardia, first-degree AV block, and prominent U waves on ECG monitoring were commonly observed (data not shown). The muscle strength of the upper and lower extremities was graded as 3.2 ± 1.1 and 0.7 ± 0.6 respectively. Thyroid function tests clearly showed elevated T_3 (240 ± 79 ng/dl), fT_4 (3.5 ± 1.1 ng/dl), and suppressed TSH (all <0.03 μ U/ml). Among the biochemistries, all of them had marked hypokalemia (K^+ 2.1 ± 0.2 mmol/l) associated with low urine K^+ excretion rate (K^+/Cr 1.2 ± 0.2 mmol/mmol), suggesting that increased shift of K^+ into cells was responsible for the hypokalemia. Their acid-base status was normal (pH 7.40 ± 0.02 , HCO_3^- 23 ± 2 mmol/l). They also had lower serum phosphate concentration (2.5 ± 0.6 mg/dl) with low urine phosphate excretion, indicating a concomitant phosphate shift into cells. Their urine calcium excretion was higher (FE_{Ca} $3.6 \pm 1.5\%$) despite normal serum ionized Ca^{2+} concentration (4.8 ± 0.2 mg/dl).

Recovery time and KCl dose The recovery time and total amount of KCl supplementation were 6.3 ± 3.2 h and 63 ± 32 mmol (from 10 to 180 mmol) respectively. Mean serum K^+ concentration was 3.1 ± 0.3 mmol/l when muscle strength recovered sufficiently for ambulation. One patient and four patients recovered with 10 and 20 mmol KCl respectively. These patients may have been on the road to recovery before the KCl supplement or are very sensitive to KCl therapy.

Rebound hyperkalemia Mean peak serum K^+ concentration was 5.3 ± 0.5 mmol/l, with rebound hyperkalemia (>5.0 mmol/l) occurring in 59%

Figure 1 Course of serum K^+ concentrations in TPP patients treated with KCl therapy. Black columns denote TPP patients with paradoxical hypokalemia, and white columns denote those without paradoxical hypokalemia. **P* <0.001 when nadir and peak serum K^+ concentrations were compared between the two groups.

(46 out of 78) of all patients. Among these 46 patients, 20 had peak serum K^+ concentration >5.5 mmol/l. Out of the 20 patients, eight needed treatment with cationic binders and loop diuretics due to typical ECG findings of hyperkalemia such as tented T waves.

Paradoxical hypokalemia We observed that a paradoxical fall in serum K^+ concentration occurred during KCl therapy in approximately one-fourth of the TPP patients (20 out of 78, 26%). Their nadir serum K^+ concentration was 1.8 ± 0.2 mmol/l, occurring on the third hour (2.2 ± 0.7 h) after initiation of KCl supplementation (Fig. 1). Patients with paradoxical hypokalemia had much longer recovery time (10.4 ± 3.4 vs 4.8 ± 1.9 h, *P* <0.001) and much larger KCl supplementation (104 ± 34 vs 48 ± 19 mmol, *P* <0.001) than those who did not develop paradoxical hypokalemia (Fig. 2). Upon recovery, patients with paradoxical hypokalemia had significantly higher rebound hyperkalemia (5.8 ± 0.5 vs 5.1 ± 0.4 mmol/l, *P* <0.001)

Figure 2 Total KCl dose administered in TPP patients with and without paradoxical hypokalemia. Shaded column denotes TPP patients with paradoxical hypokalemia, and white column denotes those without paradoxical hypokalemia. **P* <0.001 .

Figure 3 Correlation between the total administered KCl dose and Δ serum K^+ concentration. Filled triangle denotes TPP with paradoxical hypokalemia, and open circle denotes those without paradoxical hypokalemia.

and Δ serum K^+ concentration (4.0 ± 0.5 vs 3.0 ± 0.3 mmol/l, $P < 0.001$) than those without paradoxical hypokalemia. There was a positive correlation between the dose of KCl administered and the difference between peak and nadir serum K^+ (ΔK^+) ($r = 0.68$, $P < 0.001$; Fig. 3).

As shown in Table 1, TPP patients with paradoxical hypokalemia had no significant difference in lead time, but significantly higher systolic blood pressure

Table 1 Clinical and laboratory features in thyrotoxic periodic paralysis patients without and with paradoxical hypokalemia.

	(-) (n=58)	(+) (n=20)
Clinical manifestations		
Lead time (hours)	3.4 ± 1.4	3.5 ± 1.3
Age (years)	29 ± 8	31 ± 8
Body mass index (kg/m ²)	24.5 ± 1.7	23.8 ± 2.5
Systolic blood pressure (mmHg)	133 ± 8	$147 \pm 15^*$
Diastolic blood pressure (mmHg)	76 ± 10	75 ± 8
Heart rate (beats/minute)	94 ± 9	$110 \pm 11^*$
Upper limbs muscle strength (grade)	3.3 ± 1.1	3.1 ± 1.1
Lower limbs muscle strength (grade)	0.8 ± 0.6	0.6 ± 0.7
Laboratory findings		
Serum		
TSH (μ U/ml)	<0.03	<0.03
Triiodothyronine (ng/dl)	226 ± 77	278 ± 96
Free thyroxine (ng/dl)	3.1 ± 1.0	$4.4 \pm 1.1^*$
Na^+ (mmol/l)	139 ± 2	139 ± 3
K^+ (mmol/l)	2.1 ± 0.2	2.2 ± 0.2
Cl^- (mmol/l)	106 ± 2	106 ± 2
Bicarbonate (mmol/l)	23 ± 1	23 ± 2
Ionized Ca^{2+} (mg/dl)	4.8 ± 0.2	4.9 ± 0.2
Phosphate (mg/dl)	2.5 ± 0.7	2.4 ± 0.5
Glucose (mg/dl)	119 ± 18	121 ± 17
Urea nitrogen (mg/dl)	14 ± 3	12 ± 2
Creatinine (mg/dl)	0.6 ± 0.1	0.5 ± 0.2
Urine		
K^+/Cr (mmol/mmol)	1.2 ± 0.3	1.2 ± 0.2
FE_{Ca} (%)	3.6 ± 1.2	3.7 ± 1.5
FE_P (%)	2.3 ± 0.7	2.0 ± 1.1

* $P < 0.05$. Average blood pressure and heart rate in the first hour are shown.

(147 ± 15 vs 133 ± 8 mmHg, $P < 0.05$), heart rate (110 ± 11 vs 94 ± 9 beats/min, $P < 0.05$), and fT_4 level (4.4 ± 1.1 vs 3.1 ± 1.0 ng/dl, $P < 0.05$) than those without paradoxical hypokalemia. At a biochemical level, there was no significant difference in serum K^+ (2.1 ± 0.2 vs 2.2 ± 0.2 mmol/l), Na^+ , Cl^- , HCO_3^- , pH, Ca^{2+} , Mg^{2+} , phosphate, glucose, albumin, blood urea nitrogen (BUN), and creatinine between the two groups. However, serum phosphate concentration after recovery was significantly higher in patients with than those without paradoxical hypokalemia (5.1 ± 0.4 vs 4.4 ± 0.3 mg/dl, $P < 0.05$).

Discussion

KCl has been advocated for the treatment of paralysis and prevention of fatal cardiac arrhythmia in patients with TPP. Our previous case-controlled study in patients with TPP proved that intravenous KCl therapy is associated with a more rapid recovery of muscle strength (two times shorter) than controls without KCl supplementation (15). In this study, we observed that a paradoxical fall in serum K^+ concentrations developed in approximately one-fourth of patients with TPP during KCl supplementation. These patients had significantly higher levels of fT_4 associated with a more prominent sign of adrenergic activity on admission. They needed more KCl to restore muscle strength and developed more severe rebound hyperkalemia on recovery. In contrast, those who did not develop paradoxical hypokalemia only needed smaller doses to achieve faster recovery without severe hyperkalemia.

Although this observation with a paradoxical fall in serum K^+ concentrations has been described in some case reports (17, 18) and our retrospective analyses in TPP (9), it has not been well characterized. Patients with paradoxical hypokalemia may represent a much earlier stage of the disorder or a more profound stimulus to take up K^+ in cells. Because the lead time (time-to-therapy) and serum K^+ concentration on admission were comparable between TPP patients with and without paradoxical hypokalemia, a much stronger driving force caused K^+ in the extracellular fluid (ECF) and infused K^+ to move into cells, but not a much earlier stage was likely to be a primary contributor to this phenomenon.

The driving force behind K^+ shift into cells is a more negative voltage inside cells (19). The usual mechanism is the export of cations created by the electrogenic Na^+-K^+ -ATPase extruding three Na^+ ions for every two K^+ ions that enter the cells (20). Hyperthyroidism can induce an increase in the number and activity of the Na^+-K^+ pump (21) and also increase β -adrenergic sensitivity (22), further enhancing the activity of the Na^+-K^+ pump. Thyroid hormone *per se* increases cardiac contractility and output, and decreases systemic

vascular resistance, accounting for the increased systolic hypertension (23). Moreover, hyperthyroidism is also a hyperadrenergic state and β_1 -adrenergic stimulation of the heart causes tachycardia (24). The higher fT_4 concentration accompanied by higher systolic blood pressure and heart rate found in patients with TPP who had paradoxical hypokalemia suggests that severe hyperthyroidism and hyperadrenergic activity may contribute to the driving force behind intracellular K^+ during KCl therapy.

A paired feature of hypokalemia, hypophosphatemia resulting from acute shift of phosphate into cells, was also frequently observed during attacks of TPP (12, 14, 25, 26). Likewise, normal to increased serum phosphate concentration was found during the recovery phase of TPP, consistent with previous reports in patients with TPP on recovery and untreated hyperthyroidism (14, 27). The mechanisms for normal to increased serum phosphate concentration are primarily related to increased bone resorption and renal tubular reabsorption of phosphate by direct action of thyroid hormone (28). It has been shown that serum phosphate concentration was associated with the level of fT_4 in patients with untreated hyperthyroidism (29). We found that serum phosphate concentration on recovery was significantly higher in TPP patients with paradoxical hypokalemia, supporting that they had significantly higher fT_4 and severe hyperthyroidism.

In terms of the dose of KCl therapy and development of rebound hyperkalemia, we found that those who did not develop paradoxical hypokalemia needed smaller doses of KCl to achieve muscle recovery with less risk of rebound hyperkalemia. In contrast, TPP patients who had paradoxical hypokalemia needed twofold higher KCl dose to achieve recovery and developed more severe rebound hyperkalemia. The maximal renal K^+ excretion rate is ~ 10 – 15 mmol/h (250–400 mmol/day) in normal subjects on a very high K^+ diet (30), but declines substantially to 1 mmol/h (15–20 mmol/day) when hypokalemia is induced (31). Therefore, hyperkalemia is expected to result when the rate of K^+ entry into the ECF upon recovery from TPP exceeds the rate of renal K^+ elimination. A positive correlation between the dose of KCl administered and Δ serum K^+ in this study also supports that severe rebound hyperkalemia is caused by excessive K^+ administration.

When faced with falling serum K^+ concentrations, physicians may be inclined to administer more K^+ supplementation, which only increases the risk of rebound hyperkalemia and life-threatening ventricular arrhythmias upon recovery (14, 18). Because total body K^+ stores are normal in patients with TPP, the treatment should be directed at blocking a further intracellular shift of K^+ . Nonselective β -blockers impair net cellular K^+ uptake in animals (32) and humans (33), and has been increasingly reported to prevent and terminate acute attacks of TPP via the suppression of

β -adrenergic activity and inhibition of insulin secretion (34, 35). Some reports show that intravenous propranolol promptly terminated paralytic symptoms in patients with TPP refractory to KCl supplementation (17, 36). Our previous experience suggests that some cases of TPP can be rapidly reversed with high-dose oral propranolol (3–4 mg/kg) alone without rebound hyperkalemia (37, 38). TPP patients who have paradoxical hypokalemia associated with evidence of hyperadrenergic activity and prolonged recovery time may be candidates for the use of nonselective β -blockers. However, this hypothesis merits further investigation.

There are some limitations to this study. First, because the dose of KCl given was fixed at the same rate, it was not possible to demonstrate the correlation between the dose of KCl administered and recovery time. Secondly, we only found a relatively small number of patients with paradoxical hypokalemia; more cases are needed to specifically characterize their clinical and therapeutic courses. Thirdly, one may question the validity of the definition of paradoxical hypokalemia as a further fall in serum K^+ concentration of at least 0.1 mmol/l during KCl therapy. However, modern laboratory technique and rigorous IQC can discriminate this difference (~ 5 – 6%) on continual K^+ analysis. Fourthly, K^+ exit from muscle owing to contraction and K^+ reabsorbed quickly after the stomach contracted could raise the serum K^+ concentration. However, we could not determine some factors such as motor activity in the upper limbs and K^+ absorption in the gastrointestinal tract that may influence the venous K^+ concentration (39). Finally, acute hypokalemia with increased K^+ shift into cells may be present for some time prior to the paralytic attack. We could not evaluate the period of time from weakness to paralysis in this study.

In conclusion, KCl administration must be cautiously exercised in patients with TPP. TPP patients who have not developed a paradoxical hypokalemia only need a small dose to achieve recovery. For TPP patients who develop paradoxical hypokalemia associated with more severe hyperthyroidism and hyperadrenergic activity, the blockade of intracellular K^+ shift with nonselective β blockers may be an alternate option. Close monitoring of serum K^+ concentration is mandatory to managing the therapeutic options and avoiding complications during KCl therapy.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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