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THE ADDITIVE EFFECT OF BANANA AND LOW-DOSE B-ADRENOCEPTOR BLOCKER PROPRANOLOL ON ENHANCED PHYSIOLOGIC TREMOR AND ESSENTIAL TREMOR

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ABSTRACT

Hypokalemia may pose deleterious effects in the various organ systems. Drug-induced hypokalemia may be associated with tremors especially enhanced physiologic tremors (EPT) and essential tremor (ET). In this study, the effect of banana intake (4-7 daily), propranolol (40 mg tablet daily) and their combination was compared in their ability to reverse hypokalemia, induce tremorlysis and enhance clinical function in 20 elderly patients with EPT and ET. Clinical function was assessed with Box and Block Test (BBT), 9-Hole Peg Test (9-HPT) and Activities of Daily Living-Total score 24 (ADL-T24). Low-dose propranolol, banana intake and their combination significantly ($P < 0.05$) attenuated the tremors of EPT/ET at 2, 4, 6 weeks and improved clinical function compared to controls. The banana intake and propranolol combination was most significant in reversing hypokalemia, attenuating tremors and improving scores in the ADL-T24. Order of significance (DMR) in reducing tremor severity was propranolol + banana > propranolol > banana intake. There was no rebound hyperkalemia with the banana intake, low-dose propranolol and their combination. In conclusion, banana intake may positively impact the peripheral and central mechanisms of tremorogenesis, may be additive with other tremorlytics, mitigates substance abuse and deserves further studies.

KEYWORDS: Enhanced physiologic tremor; Performance tremor; Potassium; Hypokalemia; Propranolol; Banana.

INTRODUCTION

Tremor is the most common movement disorder in the community and may negatively impact a significant fraction of the activities of daily living. Tremor is the involuntary, rhythmic oscillation of reciprocally innervated, antagonistic muscle groups, causing movement of a body part about a fixed plane in space.[1][2][3] Physiologic and essential tremors, which are postural tremors, occur when a limb is positioned against gravity.[1] Investigators have linked tremorogenesis to potassium and magnesium homeostasis. The ratio of intracellular to extracellular potassium ($K_I : K_e$) is the major determinant of resting membrane potential and excitability.[4] Hypokalemia and hypomagnesemia can be induced by the same mechanism and are often clinically correlated with one another.[5] Thus there may be inter-dependency in the roles of magnesium and potassium in tremor generation.

One medium-size banana contains about 422 mg of potassium or 9% of the reference daily intake (RDI) of 4,700 mg making it a good dietary source of potassium necessary to counter the effects of sodium in the body such as effect of salt on blood pressure and type 2 diabetes mellitus. Apart from decreasing blood pressure, arrhythmias and stroke risk, potassium has other protective mechanisms including inhibitory effects on free radical generation, smooth muscle proliferation and arterial thrombosis.[6] Banana is also an important source of magnesium; as well as of pyridoxine, dopamine, serotonin, gamma-amino butyric acid; and an important source of selenium for synthesis of selenoproteins. One large banana, which is comparatively a low- fructose fruit, gives 37 mg of magnesium or 9% of the RDI of 400 mg. Thus, about 8 medium-sized bananas, which contain minimal sodium, may provide the RDI of potassium and magnesium. Magnesium supplementation may be important in attenuating subjective anxiety,[7] insulin resistance,[8] cardiac electrophysiological remodelling,[9] and telomere attrition.[10]

Performance tremors may be associated with enhanced physiological tremors (EPTs) and also with essential tremors (ETs) amongst others. Unlike essential tremors, EPTs are not known presently to be related to neurologic disease but are more related to drug untoward effects.[11][12] Although mechanical, reflex and central mechanisms may be involved in tremor generation, most tremor size changes have a metabolic explanation.[11] It is now known that adequate dietary potassium may counter the tremor-inducing effects of hypokalemia (blood $K^+ < 3.5$ mmol/L). Increase in blood/interstitial potassium may be a peripheral mechanism to limit muscle excitability and increase muscle blood flow.[13] Tremors may be induced by

several common agents causing hypokalemia including coffee,[14] tea,[15] cola,[16] alcohol withdrawal,[17][18][19] lithium,[20] beta-adrenergic stimulants such as terbutaline and salbutamol,[21] glue sniffing (toluene abuse),[22] and topiramate.[23] Other conditions that may be associated with hypokalemia and tremors include vitamin B12 deficiency, essential hypertension, hyperthyroidism, Graves' disease, atrial fibrillation, pheochromocytoma, supraventricular tachycardia and chronic alcoholism (www.symptoma.cc). Hypokalemia-inducing agents, in addition to other side-effects, are tremorogenic for performance tremors commonly related to EPT and essential tremor,[24][25] who reported a direct relationship between muscle tremor and hypokalemic response.

In consonance with the above, dietary banana due to its adequate potassium content may have similar role with agents which may attenuate hypokalemia and reverse the deleterious effects of hypokalemia in tremorogenesis.[26][27][28] These agents include potassium supplementation,[14][24] beta-blockers,[29] primidone,[30] benzodiazepines,[31] gabapentin (www.drugbank.ca) and THC-based cannabis,[32][33] and may effect hyperkalemia (K^+ > 5.0 mmol/L.[34] The magnesium in bananas also has a role similar to that of β-adrenergic blockers-induced inhibition of the integral membrane protein, the electrogenic Na^+-K^+-ATPase (sodium-potassium pump) with resultant increase in blood potassium concentration.[35][36][37] These agents which may induce relative hyperkalemia have proven beneficial for familial, drug-induced or age-induced EPTs and essential tremors.[38][39] Although patients with normal kidney function can adapt to increase in potassium intake,[4] it is recommended that potassium levels should be regularly monitored in patients on above agents.[34]

Performance tremors as a result of EPTs or ETs decrease quality of life. In contradistinction to essential tremor which greatly affects quality of life as the disease progresses,[40] EPTs such as writing tremor or golfer's tremor may be task-specific and patients with these perform better on functional tests of tremor and activities of daily living than patients with essential tremor. The implication is that efforts to provide a cure for the disease of EPTs and ET must continue, moreso that present remedies are known not to provide complete cure.[29][41] Presently, treatment for majority of tremor syndrome is similar regardless of the underlying aetiology.[42] Propranolol, clonazepam, primidone and gabapentin are used for limb tremors such as EPTs and ETs that need medication.[42] www.webd.com. Propranolol may also be second-line drug for tremor-predominant Parkinson's disease.[43] The

pathological essential tremor and EPT may represent two quantitatively different expressions of the same cortical process.[44]

The aim of the present report was to assess the effect of the beta-blocker propranolol and bananas, alone or in combination, on EPT/ET which may be responsible for performance tremor.

METHODS

Present work was carried out in Oseghale Oriaifo Medical Centre, Ekpoma. I8 male adults (aged 70-80 years) with EPT participated and were joined by 2 male adults (aged 65-80 years) with mild benign essential tremors. 7 of the subjects with EPTs were associated with coffee or tea beverages consumption; 2 were associated with pesticide use; 3 were associated with essential hypertension, 4 were associated with anti-asthmatics and 2 were associated with chronic alcoholism.

The study evaluated the severity, functional impairment, effect on activities of daily living (ADL) and blood potassium changes due to these enhanced physiological tremors and mild benign essential tremors. Ethical approval and patients' consent were obtained. Potassium levels were evaluated at 0 to 6 weeks in control subjects, subjects on propranolol (one tablet of 40 mg per day), subjects on bananas (at least 4-7 a day) and subjects on combination of propranolol and bananas. The tremor severity was assessed as follows: I) Mild: able to perform task without difficulty; 2): Moderate: able to perform task with little effort; 3): Severe: needs a lot of effort to perform task; 4): Incapacitating: Incapable of performing the activity by himself. Assessment of functional impairment was done by the modified 9-Hole Peg Test (9-HPT) and the Box and Block Test as previously described.[2][40] The 9-HPT is the time taken in seconds for placing and removing nine pegs in a modified pegboard. The BBT consists of moving the maximum number of blocks possible, one by one, from one compartment of a box to another of equal size within 60 seconds.

The Activities of Daily Living-T24 (ADL-T24) was tested by means of a questionnaire with a maximum score of 24 reflecting no problem (0), slight difficulty (I), important difficulty (2) and impossibility (3) on these 8 items of daily living: i) to move a glass of water; ii) to drink; iii) to eat (with fork and knives); iv) to shave unaided; v) to write words; vi) to read a book; vii) to drive a car; viii) to dress oneself. These activities are impaired in EPTs and ETs;

impairment which correlates positively with scores on the 9-HPT test but negatively with scores on the BBT test.

Inclusion criteria

Subjects with tremors of less than 2 years duration were included. Subjects with task tremors, postural, kinetic or intention tremors were included. Patients with BMI of < 30 Kg/M^2 and normal renal function tests were included.

Exclusion criteria

Patients with tremors of more than 2 years were excluded. Also subjects with moderate to severe heart, kidney or liver disease were excluded. Patients with rest tremors which may be characteristic of Parkinsonian tremor, rubral tremor or psychogenic tremor were excluded. Morbidly obese subjects and type 2 diabetics were excluded.

Differential diagnosis

a) Physiological tremor
b) Parkinson's disease (tremor-predominant)
c) Indeterminate tremor syndrome
d) Essential tremor or benign essential tremor
e) Dystonic tremor syndrome
f) Task specific tremor
g) Primary orthostatic tremor
h) Primary writing tremor
i) Neuropathic tremor
j) Holmes' tremor syndrome (rubral, mid-brain, thalamic, stroke-induced)
k) Cerebellar tremor
l) Drug-induced tremor
m) Psychogenic tremor

Statistical analysis

Statistical analysis was done with Unpaired t-test and one-way ANOVA using SSPS version 17 for analysis. Values were expressed as mean ± SD. Difference in means was considered significant if $P < 0.05$. DMR *post-hoc* test was used to calculate the order of significance. Pearson's correlation coefficient (r) is poor if $r < 0.3$ and strong if $r > 0.5$.

Table 1: Effect of Propranolol + Banana on Blood Potassium Levels, Tremor Severity and Function.

	Control			Propranolol				Banana				Propranolol+ Banana			
Weeks	0	4	6	0	2	4	6	0	2	4	6	0	2	4	6
Potassium level	2.98 ±0.16	3.02 ±0.15	3.06 ±0.17	3.32 ±0.12	3.43 ±0.14	3.71 ±0.18	4.20** ±0.12	3.24 ±0.19	3.26 ±0.22	3.56 ±0.12	3.91* ±0.18	3.12 ±0.19	4.16 ±0.22	4.20 ±0.12	4.22*** ±0.18
Tremor severity	Severe	Severe	Severe	Severe	Mild	Mild	Mild	Severe	Moderate	Moderate	Mild	Severe	None	None	None
BBT (number of blocks in 60 sec)	25.80 ±5.40	23.46 ±4.40	24.32 ±6.20	24.25 ±7.20	42.12 ±6.80	44.16 ±5.30	45.22** ±7.10	25.45 ±6.44	39.60 ±8.12	40.80 ±9.12	41.60* ±5.80	28.14 ±0.21	45.70 ±10.50	48.60 ±8.12	51.74*** ±12.22
9-HPT (seconds)	28.12 ±9.42	29.12 ±7.15	30.50 ±10.12	29.40 ±5.60	22.30 ±5.14	22.16 ±4.40	22.30** ±3.60	28.60 ±10.20	25.95 ±8.10	26.14 ±4.90	26.60* ±4.91	28.40 ±9.50	18.50 ±5.60	18.74 ±6.12	17.80*** ±5.40
ADL – T24	7.50 ±3.20	7.44 ±4.40	8.20 ±6.20	7.55 ±0.60	5.8 ±2.90	4.50 ±2.30	4.30** ±3.10	7.54 ±7.20	6.24 ±4.10	6.50 ±6.80	5.19* ±8.40	7.74 ±8.50	4.35 ±4.10	3.50 ±6.80	2.20*** ±5.16

Table 1: Control subjects had mild hypokalemia and severe tremors. Subjects on propranolol + bananas most significantly (***) had increase in potassium levels; and had no tremors. ADL-T24 was highest in controls and was most significantly reduced in the propranolol + banana group. ADL-T24 was positively correlated (r> 0.58) with the 9-HPT scores but negatively correlated (r > - 0.62) with the BBT scores. Order of significance in reducing tremor severity was propranolol + banana > propranolol > banana intake.

RESULTS

Table I shows mild hypokalemia was present in the control patients and at baseline in the test patients. The table shows that propranolol was more effective than banana intake in raising potassium levels at 6 weeks but that they both reversed the hypokalemia to induce normokalemia. Potassium absorption may be enhanced if there is hypokalemia. No hyperkalemia was observed during the period of observation in these series. The low dose of propranolol and the oral route of potassium supplementation with bananas prevent rebound hyperkalemia. Subjects on low-dose propranolol performed better (carried more blocks in 60 seconds) in the BBT than subjects on banana intake but the combination performed most significantly. With the 9-HPT test, subjects on banana took more time in seconds for placement of the pegs than subjects on propranolol. The combination of propranolol and banana intake gave the least time in seconds with placement of the pegs. Propranolol was more effective than banana intake in reducing the ADL-T24 scores but the combination of propranolol and banana intake was most significant in reducing disability and attendant ADL-T24 score at 6 weeks (DMR: banana intake + propranolol > propranolol > banana intake). ADL-T24 positively correlated with the 9-HPT test ($r > 0.58$) but negatively correlated with the BBT test ($r > -0.62$). 3 subjects who took only bananas reported decrease in their *wanting* for alcohol. 4 patients who were on propranolol and banana reduced their propranolol intake to half-tablet a day after 4 weeks.

DISCUSSION

Study supports previous evidence that after dietary potassium loading, rate of potassium excretion is increased by the large intestine and distal nephron of the kidneys in order to prevent hyperkalemia. Gut sensing of potassium intake may help in colonic excretion, renal excretion and cell uptake to maintain homeostasis and prevent rebound hyperkalemia after oral potassium loading.[45][46] Putative potassium receptors in the gut may mediate a kaliuretic reflex to increase potassium excretion after dietary intake.[47] Also, there is the co-ordinated actions of potassium (with or without aldosterone), alkalemia (alkalosis), glucose-induced insulin release, β_2-adrenoceptor agonists in activating the sodium-potassium-ATPase for enhanced cell uptake of potassium into extra-renal sites (especially muscle). This is responsible for the acute clearance of potassium from blood in the first 4-6 hours after a dietary potassium load.[13][48] This chorus, later amplified by renal mechanisms, contributes to the potassium homeostatic mechanism (potassium adaptation) that prevents surges in blood potassium levels or rebound hyperkalemia after potassium loading in individuals without

diabetes. Above all, dietary potassium, where the potassium is bound to phosphate, may not pose high risk for hyperkalemia.[49] Present results also confirm the report of previous investigation that there is a direct relationship between muscle tremors and hypokalemic response.[25] This association may be more pertinent in the elderly who tend to have a significant large prevalence of potassium and magnesium deficiency.[50] Also subjects who take beverages may be more susceptible because of caffeine-induced diuresis causing hypokalemia. Present study also indicate that performance and essential tremors cause great disability in daily activities of life.

Present work shows that propranolol and banana intake cause significant reversal of the hypokalemia to attenuate the tremors. The significant positive change in the kalemic response may be more important in the extenuation of the tremors. The increase in the potassium concentration blunts the response of muscle and reduces its fusion frequency.[24] Bromelain in banana may be additive with potassium and magnesium contained therein in enhancing vasodilation of skeletal muscle.[51] The propranolol and banana intake did cause the most significant increase in the kalemic response at 6 weeks. Magnesium in bananas may also be critical in attenuating tremorogenesis.[5] Magnesium in bananas; and also propranolol cause inhibition of the sodium-potassium transporter (activated by hypokalemia-inducing drugs such as salbutamol) which could also affect the normokalemic response. Hypomagnesemia may induce inappropriate kaliuresis.[19] Magnesium, and dietary restriction which it enhances, have been reported to protect against not only intractable hypokalemia and calcium-induced arrhythmogenesis but also against movement disturbances and parkinsonian tremors.[6][52][53] In this study, blood magnesium determinations which are not reliable indicators of magnesium deficiency were not done.[54]

Banana is also a good source of dopamine (from the phenylanine and tyrosine contained therein) and serotonin (from the tryptophan) which may be associated with a normokalemic response to cause tremorlysis. Dopamine regulates the sodium-potassium-ATPase in the neuraxis, inhibiting it in the neostriatum.[55] Normal levels of serotonin and dopamine require magnesium and there are dopaminergic deficits in essential tremor with or without parkinsonian features.[56] In Parkinson's disease where hypomagnesemia may be associated with parkinsonism-dementia complex,[57] bananas may be a preventive and treatment means due to its high magnesium content which decrease the products of dopamine oxidation, inhibits the sodium-potassium-ATPase and may be additive with dopamine in the

neostriatum. Judicious intake of banana may help reduce the dose of propranolol needed for control of performance tremors, thus obviating propranolol dependence. Regular banana intake may also reduce alcohol craving and vulnerability to drug-seeking behaviour.[58] Magnesium as well as bromelain in banana attenuate NF-kappaβ upregulation that has been incriminated in drug addiction and relapse.[59] It should be noted, however, that obsession-induced banana intoxication has been reported (20 bananas a day for more than 2 years raised potassium level in blood from 4.7 to 6.I meq/L) to induce hyperkalemia and hyperdopaminemia.[26] Banana-derived serotonin, dopamine, niacinamide (from the kynurenine pathway of tryptophan metabolism) and gamma-amino butyric acid (from glutamate decarboxylation) may also be important centrally in attenuating tremorogenesis/anxiogenesis associated with EPT.[56][60][61]

Additionally, the resistant starch present especially in green bananas may be a source of increase in the short chain fatty acid, butyrate. Butyrate is a histone deacetylase inhibitor (HDACi) with growing therapeutic implications in clinical practice.[62] Butyrate may correct hypokalemia,[62] is anxiolytic for chronic mild stress,[63] and decreases inflammation to protect dopaminergic neurons. It also increases mitochondrial function and the synthesis of dopamine.[64]

In conclusion, present results indicate that banana intake may positively impact the peripheral and central mechanisms of tremorogenesis; may be additive with other tremorlytics, mitigates substance abuse and deserves further studies.

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