Longitudinal open label prospective study to assess the efficacy and tolerance of daily usage of the wake promoting beverage "WakeUp®" following lunch on vigilance and function of healthy volunteers

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ABSTRACT

Post-lunch dip is a very well-established phenomenon which results in substantial deterioration of function and productivity following lunch, between the hours of 12:00 and 4:00 pm. The newly developed WakeUp® drink (Inno-Bev Ltd, Tel Aviv, Israel) is a wake-promoting drink based on herbal ingredients consisting of extracts of Ginkgo biloba, Guarana, Elderberry plus the naturally derived Carob sweetener. In a double-blind, placebo and active controlled (caffeine) study, we previously showed that a single intake of WakeUp beverage (100 ml) after lunch improved vigilance and performance. (CITATION) The current study sought to assess effects over a 30-day period of daily use after lunch. Ninety-five healthy volunteers underwent performance and subjective scaling of vigilance and effectiveness on three different days: Day 1 (first day of drink), Day 30 (last day of drink) and Day 31 (one day after the study, without drink). On every study day, they underwent tests before lunch and again 1 hour following lunch (and WakeUp beverage after lunch in days 1 and 30). WakeUp beverage resulted in improvement of both objective performance and subjective assessment of vigilance, focus and work effectiveness similarly on Day 1 and Day 30 without adverse effects on hemodynamic measures. WakeUp is an effective way to counteract the fatigue and reduced performance from a post-lunch dip.

BACKGROUND

Post-lunch dip is a very well-established phenomenon which results in substantial deterioration of function and productivity following lunch, between 12:00 and 4:00 pm (CITATION). Indeed, in several places around the world it is common to take a nap ("siesta") between 1:00-3:00 or 2:00-4:00 pm. The reason for this midday post-lunch sleep propensity is complex, and consists of hormonal, circadian, and nutritional/gastrointestinal mechanisms (CITATION). Temperature changes decreased cortisone levels, and re-distribution of blood following lunch contribute to this sleepiness (CITATION). It has been shown that the post-lunch dip during these 2-3 hours has a substantial impact on work performance (CITATION). Productivity and quality of work decrease while errors and work accidents increase. A recent study with 28,902 adults aged 18 to 65 found fatigue results in lost productive time that costs employers $136.4 billion dollars annually, an excess of $101 billion dollars annually compared with workers without fatigue (CITATION).

A wake-promoting drink may reduce this phenomenon and result in significant improvement of vigilance, productivity and achievements at work. Coffee and other caffeine-containing drinks improve vigilance and function by blocking adenosine receptors and by inhibiting phospho-di-esterase (PDE) which results in increased cAMP and adrenergic activity (CITATION). However, caffeine has a short half-life and potential side effects, such as increased pulse rate and blood pressure (CITATION). In addition, regular coffee drinking results in tolerance and substantial reduction of the effect of caffeine (CITATION).

WakeUp is a newly developed wake-promoting drink based on Ginkgo biloba, Guarana, Elderberry and Carobs sweetener.

Guarana (*Paullinia cupana*) seeds have a long history of use as a stimulant by Amazonian tribes (CITATION). Caffeine provides the stimulant properties, although it comprises only 2.5–5% of the extracts' dry weight (CITATION). The psychoactive properties of Guarana may also be attributable to the relatively high content of saponins and tannins (CITATION). It has been previously shown that Guarana improves memory performance and mood, and increases alertness, even in relatively low doses (CITATION).

Ginkgo biloba is a unique tree native to China. Ginkgo extracts are used in herbal medicine for asthma, bronchitis, fatigue, and tinnitus (CITATION). It promotes vigilance and has been shown to improve memory (CITATION). It is currently being used as a preventive treatment for Alzheimer's disease and other types of dementia in Asia (CITATION).

Carobs sweetener predominantly adds flavor to WakeUp, although its glucose content may also improve alertness. It has a relatively low glycemic index.

In a double-blind, placebo- and active-controlled study, we previously showed a single serving of WakeUp (100 ml) after lunch improved vigilance and performance 30 min following drinking, similar to caffeine and significantly better than placebo (STATS) (CITATION). Performance and vigilance were significantly higher with WakeUp compared to both placebo and caffeine 120 minutes after drinking WakeUp (STATS). While caffeine was associated with an increased pulse and blood pressure at the 30-minute time point, in the WakeUp group, there were no hemodynamic differences compared with placebo at 30 minutes or 120 minutes following consumption (STATS).

WakeUp seemed to be an effective drink to counteract somnolence and reduced performance during the post-lunch hours without hemodynamic side effects. But this assumption was based on a single use. The present study assesses the wake-promoting and hemodynamic effects associated with a daily use of WakeUp over a 30-day time period. Potential habituation/tolerance or cumulative effects are included in the study.

AIM

The goal of this trial is to study the effects of daily usage of the wake-promoting beverage WakeUp on vigilance, function and hemodynamic measures.

We hypothesized that drinking WakeUp following lunch on a daily basis for 30 days would not induce tolerance and the effects will be similar on Day 1 and Day 30 of usage.

METHODS

Ninety-five healthy volunteers were studied on 3 different days: The first day of usage (Day 1); after 30 days of drinking WakeUp® every day (Day 30); and one day after 30 days of usage, without drinking the beverage ("day 31"). On Day 1 and Day 30 of the study, volunteers reported to the hospital at 11:45 am and had a standard and consistent lunch. Right after lunch they underwent a battery of functional tests and hemodynamic measurements (see below), and then drank one bottle of WakeUp (100 ml). After one hour (at 1:00 pm) they underwent another battery of the same tests. On days 2-29 of the study, the participants were instructed to drink one bottle of WakeUp in their home every day after lunch. On day 31 of the study, the participants underwent the same regimen with lunch at 11:45 and tests at 12:00 and 1:00, except that they did not drink WakeUp after lunch.

The battery of tests conducted at the hospital on days 1, 30 and 31 included measurements of vital signs and administration of validated, commonly used standard function and vigilance tests such as an immediate word recall test (IWRT; short term memory), digit symbol substitution test (DSST; concentration), and subjective rating using a visual analogue scale (VAS) of their vigilance, ability to focus and effectiveness at work. Test results at 12:00 and 1:00 were compared to each other. In addition, the results on Days 1, 30 and 31 were compared using a paired t-test or one-way analysis of variance (ANOVA), with $p<0.05$ considered statistically significant.

The study was approved by the institutional review board (IRB, Helsinki committee) of Rambam Medical Center and all participants signed an informed consent prior to participation.

A linear mixed model was used to analyze the data, as it is designed for multiple measurements on the same subjects over time. It resolves the non-independence from having multiple responses by the same subject. We used R (R Core Team, 2012) and lme4 (Bates, Maechler & Bolker, 2012) to perform a linear mixed effects analysis of the relationship between intake (before or after WakeUp consumption) and day of study (1, 30, and 31). The fixed effects were intake and day. The random effect was subject. Residual plots did not reveal any obvious deviations from homoscedasticity or normality. However, there was one outlier removed, presumably from a data error entry (subject #98 systolic blood pressure reported as 11 on day 31, 12:00). Likelihood ratio tests of the full model with the effect in question compared to the model without the effect in question gave Chi squared and p values, where $p<0.05$ was considered statistically significant. A slope of the fixed effects was used to show whether the effect increased or decreased over time.

RESULTS

Overall, 95 volunteers (40 males and 55 females) participated with an average age of 37±11 years (range 19-63 years), and average BMI 24.5 ± 1.7 Kg/m2 (range 19.7-34.7).

Effect of intake (12:00 vs 1:00)

This study did not have a placebo or no-treatment group. Therefore, the test results before WakeUp consumption (12:00) were compared to after WakeUp consumption (1:00), with the 12:00 measurement acting as the no-treatment control. Results (Tables 1 and 2) show that DSST ($p<0.001$), vigilance ($p<0.01$), and concentration all improved significantly after WakeUp consumption (all $p<0.05$). In addition, the three hemodynamic parameters of pulse ($p=0.01$), systolic ($p<0.01$) and diastolic blood ($p<0.001$) pressure were significantly reduced after WakeUp consumption.

Table 1. Summary of averaged data collected on days 1, 30, and 31, ± standard error

	Day 1			Day 30			Day 31		
	12:00	13:00	Change (%)	12:00	13:00	Change (%)	12:00	13:00	Change (%)
Pulse	74±11	73±10	-1.4	77±10	75±11	-2.6	76±11	73±11	-4.0
Systolic BP	122±12	120±13	-1.6	121±13	119±12	-1.7	119±14	118±14	-0.8
Diastolic BP	76±10	74±9	-2.6	74±9	73±9	-1.4	75±9	72±9	-4.0
iWRT	9.1±3.7	9.8±3.4	+7.7	9.6±3.9	10.3±3.9	+7.3	10.0±3.8	8.9±3.3	-11.0
DSST	79±14	86±15	+8.9	87±15	93±16	+6.9	93±17	90±19	-3.2
Vigilance	5.9±2.1	6.9±1.9	+17.0	6.3±2.0	7.9±1.8	+25.4	6.7±1.8	6.0±2.0	-10.5
Concentration	6.0±1.9	6.9±1.8	+15.0	6.3±2.0	7.1±1.9	+12.7	6.8±1.7	6.0±2.0	-11.8
Work	6.4±1.9	7.3±1.3	+14.0	6.7±2.0	7.4±1.8	+10.5	7.1±1.6	6.3±2.0	-11.3

iWRT = immediate Word Recall Test; DSST = Digit Symbol Substitution Test.

Table 2. Statistical analysis of WakeUp acute effects (12:00 vs. 1:00)

	Slope	SE	Chi squared	p Chi
Pulse	-1.604	0.621	6.623	0.010
Systolic	-1.884	0.708	7.028	0.008
Diastolic	-1.891	0.523	12.912	3.265E-04
Words recalled	0.091	0.181	0.254	0.614
DSST	3.575	0.601	34.099	5.239E-09
Vigilance	0.314	0.119	6.844	0.009
Concentration	0.269	0.120	5.003	0.025
Work	0.218	0.117	3.485	0.062

SE = standard error; p Chi = likelihood ratio test using ANOVA function

Effect of study day

Study participants consumed WakeUp for 30 days to see if there was any tolerance to long term consumption. Effects were measured on day 1, 30, and 31 of the study (Table 1). There were no statistically significant changes in iWRT, vigilance, concentration or work performance over the course of the study (Table 3). DSST is the only performance parameter that significantly changed over the course of the study DSST, improving from Day 1 to Day 31 ($p<0.001$) (Table 3). Blood pressure (systolic and diastolic) dropped over the course of the study (Table 1), but the results were only significant ($p<0.05$) for systolic blood pressure (Table 3).

Table 3. Chronic effects of WakeUp consumption (day 1-31)

	Slope	SE	Chi squared	p Chi
Pulse	0.037	0.022	2.731	0.098
Systolic	-0.055	0.029	4.271	0.039
Diastolic	-0.037	0.019	3.810	0.051
Words recalled	0.009	0.007	1.816	0.178
DSST	0.278	0.022	142.190	2.200E-16
Vigilance	0.004	0.004	0.753	0.386
Concentration	0.002	0.004	0.229	0.632
Work	-4.586E-04	0.004	0.012	0.913

SE = standard error; p Chi = likelihood ratio test using ANOVA function

Interaction of day and intake

The interaction of study day and intake was calculated to determine if the effect of day of the study (and its corresponding conditions) and intake (before or after WakeUp consumption) were interdependent.

The interaction of day and intake was only significant for systolic blood pressure out of the three hemodynamic measurements. This means the acute reduction in systolic blood pressure was significantly dependent on the day of the study. Looking at Table 1, systolic blood pressure dropped after consuming WakeUp on Days 1 and 30 but did not drop as much on Day 31 when no WakeUp was consumed.

On the other hand, performance parameters were all significantly dependent on whether or not WakeUp had been recently consumed (Table 4). The general trend was an increase in performance parameters over 30 days, with a better response after WakeUp at 1:00 than before WakeUp at 12:00. But on Day 31, performance scores did not improve as they had on Day 1 or Day 30 at 1:00. Rather, the scores went down, indicating poorer overall performance outcomes (Table 1).

Table 4. Interaction of acute and chronic consumption of WakeUp

	Chi squared	p Chi
Pulse	2.200	0.138
Systolic	0.197	0.657
Diastolic	2.00E-04	0.990

Words recalled	6.783	9.20E-03
DSST	18.541	1.66E-05
Vigilance	12.873	3.33E-04
Concentration	14.812	1.19E-04
Work	14.109	1.73E-04

p Chi = likelihood ratio test using ANOVA function

CONCLUSIONS

Looking at the data and considering statistical analysis, WakeUp improved vigilance, concentration and performance on the DSST test one hour after consumption of WakeUp (days 1 and 30). There did not appear to be any tolerance effect due to consumption of WakeUp, since the acute effects of WakeUp consumption on day 30 were similar to or better than the effects on Day 1.

On Day 31, when no WakeUp was consumed, test scores went down, providing additional evidence that WakeUp is responsible for the improved performance. These data, along with the Day 31 hemodynamic data (Table 1), corroborate the “post-lunch dip” phenomenon. Interestingly, DSST significantly improved over the course of 30 days without a large reduction on day 31. This could suggest consistent ingestion of WakeUp may improve brain function (processing speed) over time. Alternatively, it could be an artifact of the participants learning how to master the DSST test over time.

WakeUp significantly improved hemodynamic parameters one hour after consumption on Days 1 and 30. Over time, systolic blood pressure was statistically significantly improved, with a trend toward improvement for pulse and diastolic blood pressure.

Given the observed results, WakeUp appears to be an effective way to combat post-lunch dip, increasing mental performance without adversely affecting hemodynamic parameters.

Fig 1: Effect of WakeUp® beverage after lunch on immediate word recall test.

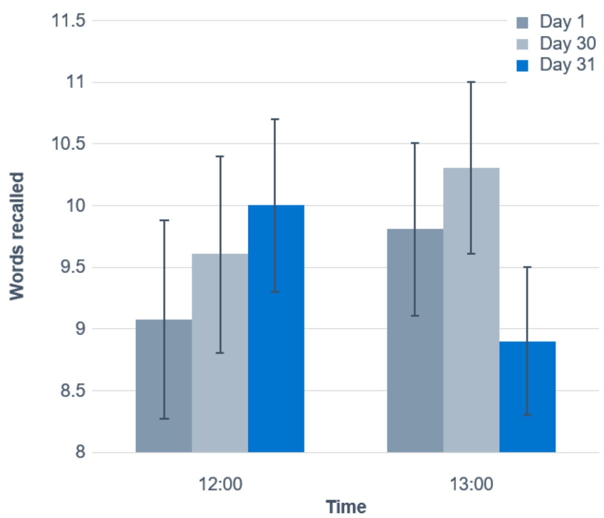

Fig 2: Effect of WakeUp® beverage after lunch on Digit Symbol Substitution Test.

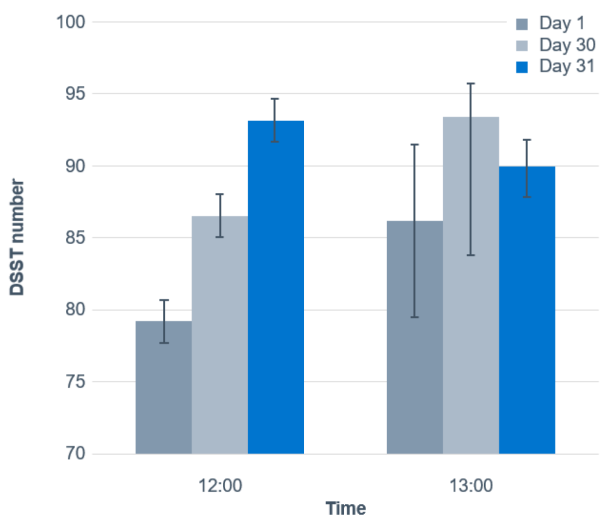

Fig 3: Effect of WakeUp® beverage after lunch on subjective vigilance (visual analog scale).

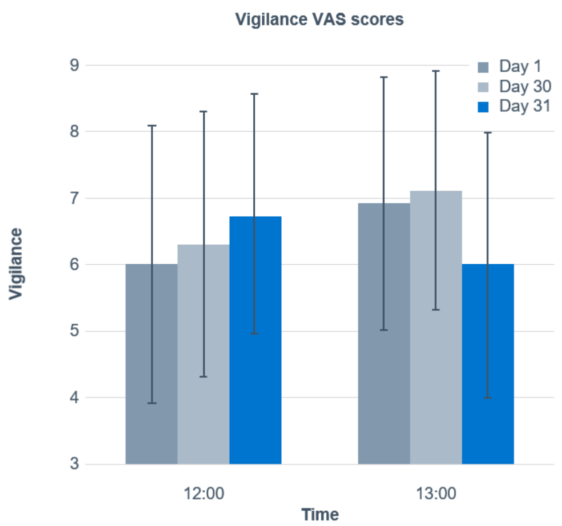

Fig 4: Effect of WakeUp® beverage after lunch on subjective effectiveness (visual analog scale).