Analysis of Resting Metabolic Rate in a Latin Square Design With Repeated Measures

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Background

- **Metabolism is the process by which our bodies convert food into energy. Even when we are sleeping (resting) our bodies need energy for ongoing functions such as breathing, circulating blood, adjusting hormone levels and growing and repairing cells.**
- **The amount of energy a person daily uses to carry out these basic functions is known as that persons resting metabolic rate (RMR).**

Background

- **RMR is usually reported as an estimate of the number of kilocalories per day a given person uses that is attributable to energy required for basic ongoing body functions.**
- **A kilocalorie is the amount of energy needed to raise the temperature of one kilogram of water by one degree Celsius (Metric System).**
- **One kilocalorie is approximately 4.2 kilojoules (International System of Units).**

Background

- Different tissues of the body contribute different amounts to a person's RMR. A gram of lean mass (muscle) contributes more than a gram of fat mass.
- Men generally have higher RMR's than women because they tend to have more muscle tissue.
- RMR decreases about 5% each decade in people over age 40 years, partly because of decreases in muscle mass.
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Background

- If a person is trying to lose weight, he or she can do so by increasing their RMR while maintaining their food intake at a constant level of caloric consumption.
- RMR can be increased by aerobic (walking, jogging) and resistance (weight lifting) physical activity training.
- Pharmaceuticals and dietary supplements.

Specific Aim

- **A study was designed to evaluate efficacy for increasing RMR in adults using combination of one of two doses of drug A with one of two doses of drug B instead of a single dose of only one of the drugs.**
- **In separate studies, each of the two drugs had previously been shown to increase RMR.**

Drug Delivery

- **Participants were give 2 pills to swallow for each treatment administration.**
- **One pill was either a dose of drug A or Placebo.**
- **The other pill was either a dose of drug B or Placebo.**
- **The two pills could not be double Placebo.**

Treatment Doses

- **Study doses for drug A:**
  1. A_0 --- placebo
  2. A_2 --- 2 mg of drug A
  3. A_4 --- 4 mg of drug A

- **Study doses for drug B:**
  1. B_{000} --- placebo
  2. B_{100} --- 100 mg of drug B
  3. B_{200} --- 200 mg of drug B

Treatment Combinations

A_0B_{000} -- **Placebo, Placebo (not used)**

A_0B_{100} -- **Placebo, 100 mg drug B**

A_0B_{200} -- **Placebo, 200 mg drug B**

A_2B_{000} -- **2 mg drug A, Placebo**

A_2B_{100} -- **2 mg drug A, 100 mg drug B**

A_2B_{200} -- **2 mg drug A, 200 mg drug B**

A_4B_{000} -- **4 mg drug A, Placebo**

A_4B_{100} -- **4 mg drug A, 100 mg drug B**

A_4B_{200} -- **4 mg drug A, 200 mg drug B**

Study Design

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Inclusions

- **Healthy males or females between the ages of 18 and 50 years.**
- **Body mass index between 19 and 40 kg/m^2, inclusive.**

Exclusions

- **Females who are pregnant or nursing.**
- **Women of childbearing potential who do not agree to use an effective method of contraception during the trial.**
- **Smokers and nicotine users.**
- **Regular medication use.**
- **Use of medications known to alter metabolic rate (some asthma medications).**

Study Design

- **A pilot study was conducted to obtain variance estimates for a power/sample size analysis prior to conducting a definitive study.**
- **8 treatment combinations were investigated over an 8 week period during which 8 participants received each of 8 treatment combinations in random order using a Latin Square design.**
- **Participants reported to the clinic metabolic laboratory on 8 occasions separated by 7 ± 2 days.**

End Points

1. **Primary**
   Resting Metabolic Rate

2. **Secondary**
   Respiratory quotient
   Pulse rate
   Systolic blood pressure
   Diastolic blood pressure
   Temperature

3. **Safety Assessments**
   Lab
   Adverse events
   Physical exams
   Electrocardiograms

Participant Visit Plan

Assessments	Screen 1	Screen 2	Test Day**
Consent	x		
Medical History		x	
Physical Exam		x	
Chemistry Panel	x		
CBC	x		
Pregnancy Test	x		
Electrocardiogram		x	
Metabolic Rate			x
Temperature			x
Blood Pressure			x
Pulse Rate			x
Respiratory Quotient			x

**Weekly for 8 weeks

Test Day Plan

	0	30	60	90	120	150	180	210
Rest	x		x		x		x	
Take Medication			x					
Metabolic Rate		x		x		x		x
Respiratory Quotient		x		x		x		x
Temperature	x		x		x		x	
Blood Pressure	x		x		x		x	
Pulse Rate	x		x		x		x	

30 min RMR

Dose (mg)			
Drug A	Drug B	Mean (kcal/day)	Std Err (kcal/day)
0	100	1393	33.6
0	200	1396	33.6
2	0	1340	33.6
2	100	1364	33.6
2	200	1339 (low)	33.6
4	0	1361	33.6
4	100	1356	33.6
4	200	1398 (high)	33.6

Overall: Mean = 1368 kcal/day SD = 153 kcal/day

30 min RMR

Analysis of Variance for 30 min RMR

Source	DF	SS	MS	p-value
Week	7	76490.2	10927.1	0.9569
Subject	7	1053196.5	150456.6	<0.0001
Treatment	7	32937.9	4705.4	0.8145
Residual Error	42	380242.1	9053.4	
Corrected Tot	63	1484335.9		

ANOVA for Δ RMR

Analysis of Variance for Post-treatment ΔRMR

Source	DF	SS	MS	p-value
Week	7	111387.0	15912.4	0.0034
Subject	7	142448.4	20349.8	0.0004
Treatment	7	398644.8	56949.3	<0.0001
Test Time	2	11741.9	5870.9	0.3115
Residual Error	168	839866.6	4999.2	
Corrected Tot	191	1492769.9		

Study Design

Trt Num	Trt Combo	ΔRMR**	Contrast	p-value	Contrast	p-value	
1	A0B100	36.5					
2	A0B200	90.7					
3	A2B000	96.4					
4	A2B100	104.7	4 v 1	0.0010	4 v 3	0.6851	???
5	A2B200	178.6	5 v 2	<0.0001	5 v 3	<0.0001	***
6	A4B000	130.2					
7	A4B100	175.2	7 v 1	<0.0001	7 v 6	0.0291	***
8	A4B200	157.8	8 v 2	0.0010	8 v 6	0.1790	???

**kcal

Conclusions

- **A2B100 is not clearly better than either A2 or B100 alone**
- **A2B200 is significantly better than either A2 or B200 alone**
- **A4B100 is significantly better than either A4 or B100 alone**
- **A4B200 is not clearly better than either A4 or B100 alone**
- **Combined therapy is better than monotherapy in some dose combinations.**

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