

Reappraisal of bovril as a source of arginine in the arginine stimulation test for growth hormone deficiency

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SUMMARY

The purpose of this case study is to report the use of oral Bovril (a food supplement which contains arginine) as an alternative test for growth hormone stimulation test. We performed oral Bovril test in 3 patients -- one with suspected growth hormone deficiency in whom insulin tolerance test could not be performed (subject A), one sex-matched control (subject B), and one with confirmed growth hormone deficiency (subject C). 14g/m² of oral Bovril was mixed with 150ml of warm water and was given to all three subjects. Blood for growth hormone was taken at baseline, and every 30 minutes till 150 minutes after ingestion of oral Bovril. The ingestion of oral Bovril showed a positive response in subjects A and B, with highest growth hormone levels of 28.4mIU/L and 42.0mIU/L respectively at 150 minutes. Subject C had suppressed growth hormone throughout the test. Oral Bovril is readily available and is a safe alternative for standard growth hormone stimulation test.

KEY WORDS:

Growth Hormone Deficiency, Growth Hormone Stimulation Test, Oral Bovril, Arginine

INTRODUCTION

Growth hormone deficiency is usually encountered in subjects who have pituitary macroadenoma or as a result of surgical or radiation therapy for the condition. The gold standard for diagnosis of growth hormone deficiency is the insulin tolerance test. However, this is contraindicated in some patients, especially in those with history of convulsion, severe hypopituitarism and ischemic heart disease. As an alternative, the GHRH-arginine test can be used but this is not widely available in developing countries. The other tests namely Glucagon stimulation test, Clonidine test and Exercise stimulation test have their own strengths and limitations. The administration of arginine has been shown to increase growth hormone in many previous reports. One of the known sources of arginine is the food supplement Bovril. We report the use of Bovril in place of arginine as a stimulation test for growth hormone.

SUBJECTS

A 16-year-old boy was referred with a 3 year history of short stature. In the past, he had been labelled with underlying mitochondrial disease which presented as frequent myoclonic jerks. Family history revealed a similar disease in his late

mother as well as elder sister but further details could not be obtained. He was delivered prematurely and had gross developmental delay. At presentation, his height was below the 3rd percentile, with mid parental height of 162cm (7 SD below). Bone age was delayed by 4 years. He was also noted to have hypogonadism with testicular sizes of 2ml (left) and 3ml (right) respectively, with stretched penile length of 4cm. Testosterone level was undetectable (<0.6nmol/L) and both gonadotrophs were low with LH 0.1IU/L (1.5-14.0), FSH 1.3IU/L (2.0-12.0). His early morning growth hormone was 3.24mIU/L; IGF-1 was 622nmol/L, which was normal for matched age and sex. The other anterior pituitary hormone levels were within normal range (prolactin 7.86ug/L, free T4 18.63pmol/L, TSH 1.74IU/L, random cortisol 622nmol/L). MRI of the brain and pituitary gland were reported as normal.

Following intramuscular testosterone, he attained 15cm in height over 3 years. However, growth hormone deficiency could not be ruled out and due to his underlying condition, insulin tolerance test was precluded while GHRH was not readily available. As he was wheelchair-bound due to the myopathy, exercise stimulation test was impractical. IGFBP-3, which is the main carrier of IGF-1 could have aided in diagnosing growth hormone deficiency, however it was not readily available in our center. Hence, oral Bovril test was selected in place of insulin tolerance test. As a comparison, a sex-matched male with normal height was taken as control. The test was also performed on a patient with confirmed growth hormone deficiency based on previous insulin tolerance test.

MATERIALS AND METHODS

The patient (subject A) was fasted overnight for 10 hours with only plain water allowed. The test was conducted the next morning, 30 minutes after arrival. The test was also performed in a same manner in a 28-year old healthy sex-matched male with normal height (subject B), as well as a 22-year old sex-matched patient with confirmed growth hormone deficiency based on previous insulin tolerance test (subject C). 14g/m² of oral Bovril was mixed with 150ml of warm water and was given to all three subjects. Blood for growth hormone was taken at baseline, and every 30 minutes till 150 minutes after ingestion of oral Bovril. Throughout the test, subject A rested in the wheelchair whereas subjects B and C maintained sedentary activities.

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Table I: Growth hormone levels post ingestion of oral Bovril

| Growth hormone (mIU/L) | 0 min | 30 min | 60 min | 90 min | 120 min | 150 min |
|------------------------|-------|--------|--------|--------|---------|---------|
| Subject A | 19.4 | 5.58 | 3.30 | 2.70 | 22.0 | 28.4 |
| Subject B | 3.06 | 4.08 | 1.49 | 1.53 | 16.9 | 42.0 |
| Subject C | <0.15 | <0.15 | <0.15 | <0.15 | <0.15 | <0.15 |

RESULTS

The ingestion of oral Bovril showed a positive response in subjects A and B, with sharp rise of growth hormone levels at 120 minutes and showed highest growth hormone levels of 28.4mIU/L and 42.0mIU/L respectively at 150 minutes. The growth hormone level for subject A showed a sharp dip at 30 minutes which was also seen for subject B at 60 minutes. Subject C had suppressed growth hormone throughout the test, which was similar to his previous insulin tolerance test results. The results are as shown in Table I.

DISCUSSION

Somatotropes secrete growth hormone from the anterior pituitary gland in a pulsatile manner, as a result of the interaction between growth hormone-releasing hormone and somatostatin. Growth hormone deficiency leads to short stature in prepubertal children. A normal IGF-1 does not rule out growth hormone deficiency. Dynamic testing is mandatory after replacement of other deficient hormones, like testosterone as seen in Subject A. Insulin tolerance test is the most extensively validated gold standard test.¹ However, as it induces hypoglycemia, it is contraindicated in patients at risk of seizure attacks. GHRH-arginine test also has sufficient sensitivity and specificity for diagnosis of growth hormone deficiency.¹ However, it is not widely available in many parts of the world. Other tests such as clonidine test, exercise stimulation test, as well as arginine-levodopa stimulation test have low sensitivity. Glucagon stimulation test is lengthy and requires half hourly blood measurements for at least 4 hours.

Oral Bovril, a health supplement readily available in Asian countries, contains arginine. It was used in 1960s as an alternative for growth hormone stimulation test as it is cheap, readily available, has no side effects, does not require intravenous infusion and has fairly good performance. Jackson et al compared the response of growth hormone secretion with Oral Bovril test in groups of children and found those with normal height, small normal children, and children with short stature with low birth weight could mount a normal response to oral Bovril. Of those who underwent both Bovril test as well as insulin tolerance test, the results were similar for both tests,² as reflected in subject C. The reliability of oral Bovril test was further assessed in a larger scale population and showed similar results.³ Although the patients who underwent oral Bovril test showed peak responses at different time points, a cut-off value of >10mIU/L (5mcg/L) is considered a positive response to oral Bovril test. The test was only performed for a total of 150 minutes post ingestion of oral Bovril, similar to previous studies. Future studies could increase the period of growth hormone assessment post oral Bovril ingestion to determine the subsequent growth hormone profile. As Subject A could mount a positive response to the oral Bovril test as shown

above, growth hormone deficiency was ruled out. Hence we felt that the cause of short stature in our patient is most likely secondary to his underlying chronic illness.

Arginine increases growth hormone release by suppressing endogenous somatostatin secretion. This response is more attenuated in younger subjects and the magnitude reduces with increasing age.⁴ Females also show greater increases in GH with less variability compared to males of similar age. This is believed to be due to enhancement of GH release by estrogen. However, false positive result in adults may be as high as 59% for arginine test in some reports.⁵

The initial fall of growth hormone with ingestion of oral Bovril in our subjects were not seen in previous literature. This could be due to the diurnal variation seen in patients of younger age group.⁵ The other possible reason is that the initial cannulation at baseline resulted in substantial stress response. The low amount of carbohydrate content in oral Bovril (1g of carbohydrate in 12g of oral Bovril) is unlikely to be responsible for the initial fall of growth hormone seen.² The delayed rise in growth hormone in both subjects A and B could probably be explained by digestion and absorption of oral Bovril. Previous studies showed a rise in GH between 30-150 minutes after Bovril,^{2,3} hence blood sampling for growth hormone may need to be prolonged till at least 150 minutes post Bovril ingestion. Larger scale studies need to be conducted to further elucidate the growth hormone trends post ingestion of oral Bovril.

CONCLUSION

We aim to highlight an alternative test for growth hormone stimulation test when the usual recommended tests are beyond the means of the practitioner. The oral Bovril test is safe, cheap and can be easily performed. It may serve as an alternative to standard growth hormone stimulation test.

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