

Why do some dietary migraine patients claim they get headaches from placebos?

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Summary

Background In six double-blind studies involving 182 tests of dietary migraine patients sensitive to tyramine and β -phenylethylamine, 18% reported headaches from placebos which were all concealed in gelatin capsules.

Objective The purpose of this research was to test a hypothesis: gelatin is partially hydrolysed animal protein; (partially) hydrolysed vegetable protein (PHVP) is known to cause migraine; perhaps the gelatin caused some of the headaches.

Method The author tested this hypothesis on himself because he suffers from dietary migraine. He proved this in a double-blind test with tyramine hydrochloride (TYH). The amount required for the test was so small (1 mg) that it was tasteless and capsules were unnecessary. The author then undertook tests with a capsule, PHVP, monosodium glutamate (MSG) aspartame (a dipeptide) and TYH, adjusting quantities to give a moderate headache. Samples were mixed with foods to simulate normal eating: the capsule with potato chips, aspartame with orange juice and the rest with cottage cheese or ricotta cheese. Times were measured from ingestion (1) to start of the headache and (2) to maximum headache intensity. Each experiment was repeated three times. The headaches were relieved with caffeine.

Results Of eight double-blind test samples, the author identified correctly the two placebos and five of the six samples containing tyramine. Quantities giving moderate headaches were: 1 gelatin capsule, 400 mg MSG, 118 mg PHVP, 4.0 mg aspartame and 1.0 mg TYH. Typical times for the three repetitions of the two time periods were 8, 9 and 11 and 17, 19 and 22 min.

Conclusions Capsules may give headaches to dietary migraine patients that are similar to those from foods. This would explain some of the headaches of patients from placebos. The double-blind test and the repeatability of the time measurements demonstrated the validity of the experiments.

Keywords: amines, auras, caffeine, capsule, dietary migraine, double-blind, food, gelatin, headache, placebo

Clinical and Experimental Allergy, Vol. 30, pp. 739–743. Submitted 13 January 1999; revised 18 March 1999; accepted 6 September 1999.

Introduction

The double-blind test

Since it was first proposed in 1937, the double-blind test has become an essential part of any test of the efficacy of a new drug [1]. Its purpose is to keep both the patient receiving the

test samples and the person administering them unaware of their composition so there is no influence that will affect the patient's judgement of the result. In studies of adverse food reactions there are similar concerns, and double-blind procedures are the norm there also.

Use of gelatin capsules in the double-blind test

It is sometimes possible to disguise the food or drug in samples given to the patient so that neither the patient nor

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This work was carried out in a laboratory at the author's home.

the person administering it can tell whether it is a real test sample or an inert substitute (a placebo). However, the most common procedure for concealing the identity of the sample is to enclose it in a gelatin capsule before it is consumed. If this were to be a questionable procedure, it would have a serious effect on the validity of the test.

The author as a subject

The author suffers from migraine-type headaches from various foods and food components. A characteristic of such headaches that I experience is seeing auras, averaging two per month of the type known as teichopsia [2]: beginning as a spot, forming an arc of short, brightly coloured, criss-crossing lines with an opaque centre, gradually expanding, then disappearing in about 25 min.

Included in the food components causing migraine for me are tyramine and β -phenylethylamine (BPEA). In tests on myself using gelatin capsules, I began to suspect that the capsule itself was causing me headaches.

Literature study

Wondering if headache from capsules might happen to other people subject to dietary migraine, I made a study of publications on patients with adverse reactions to tyramine and BPEA in which samples were contained in gelatin capsules. Table 1 summarizes results of 182 tests with placebos for 154 dietary migraine patients. Headaches resulted from 39 (21%) of the tests. I consider these patient reports to have significance although most of the authors did not. In his review of 'Tyramine sensitivity in dietary migraine' Kohlenberg tabulates headaches of dietary and non-dietary migraine patients [3]. Of 137 placebos given to dietary migraine patients, 34 resulted in headaches. Corresponding figures for non-dietary migraine patients were 179

and 33. He obviously considered these results to be significant, but attributed them to failure to be completely objective of the double-blind procedures used.

Since capsules are composed of partially hydrolysed protein, I made a list of related materials to include in some dietary migraine experiments to perform on myself: hydrolysed vegetable protein (HVP), monosodium glutamate (MSG), aspartame (a dipeptide) and tyramine (Table 2).

Little has been published about the composition of HVP. One expects it to be a mixture of amino acids. However, two papers have shown that hydrolysis is not complete. Aaslyng *et al.* [4] hydrolysed soy protein with acid (aHVP) and with enzymes (eHVP). They found that the degree of hydrolysis of aHVP was 78.2% and the eHVP 65.6%. Wang *et al.* [5] used acid to hydrolyse corn protein (the protein used for HVP in my experiments) and separated the oligopeptides formed by gel filtration chromatography. They found that 3% of the sample was peptides with molecular weight of 1000, 82% with molecular weights of 100–1000 and 15% free amino acids and other substances. Thus HVP is best described as partially hydrolysed vegetable protein (PHVP).

Methods

Double-blind test

When the author proposed doing experiments on himself, he knew it would be imperative to authenticate his headaches first by undergoing an independent, double-blind test. Samples containing 1 mg of tyramine hydrochloride (TYH) in 1 mL of water were prepared and coded at the Wilson Testing Laboratories in Shamokin, PA, USA. They were then mailed to a referee in Lewisburg who administered them to him at random in 20 mL of water, a quantity and concentration so small that he could not detect the tyramine by taste, so capsules were unnecessary. The codes and his

No. and type of patients	DB?	H	No H	Authors' comments	Ref.
17 dietary migraine	DB	2	24	none	11
8 dietary headache	DB	5	3	*	12
46 dietary migraine [†]	‡	10	36	none	13
27 dietary migraine	DB	14	17	§	14
6 dietary migraine [†]	‡	2	4	¶	15
50 dietary migraine	DB	6	60	none	16

Table 1. Reports of headaches (H) from placebos in capsules during double-blind (DB) tests

* Excess of neuroticism, introversion and obsessionality. [†] Dietary patients sensitive to BPEA, others sensitive to tyramine. [‡] Unidentified samples sent to patients. [§] 'Power of suggestion plays a large role in the aetiology of migraine'. [¶] The two patients who developed attacks when on placebo had raised blood ketone-body concentrations that would be in keeping with increased fat metabolism in migraine'.

Table 2. Food test materials, relationships and preparation methods

Food materials	Raw materials	Process	Ref.
1. HVP partially hydrolysed vegetable protein	Soy or corn protein water	Hydrolysis by dil HCl and/or enzymes	17
2. Monosodium L-glutamate (MSG)	Molasses, sugar, ferrous, potassium ions, oxygen	Aerobic fermentation by <i>Corynebacterium glutamicum</i> and crystallization	18
3. Aspartame, a sweetener and a dipeptide	Aspartic acid and phenylalanine	Combination of the two amino acids with elimination of water	19
4. Tyramine $\text{NH}_2(\text{CH}_2)_2\text{C}_6\text{H}_4\text{OH}$	Amino acid tyrosine in cheese	Ageing of cheese with loss of CO_2 from tyrosine	20
5. Gelatin	Collagen from hides or bones water	Partial hydrolysis with heat and pressure	21

reactions were recorded and mailed back to the Wilson Laboratories, where they were summarized.

Food challenge experiments

Since these experiments could not be repeated by anyone but me, I planned to demonstrate their validity by performing them three times and showing that the measurements were repeatable. The measurements were (1) the time for the headache to start, and (2) the time for it to reach maximum intensity. Quantities of samples were adjusted to give a moderate headache. The substances tested were: MSG, PHVP, aspartame, TYH and gelatin capsules. All samples were taken with food to simulate normal eating and to provide a carrier, then followed by water. The capsule was ingested with potato chips, aspartame with

orange juice, the other samples with cottage cheese or ricotta cheese.

Analgesics

Since all the experiments involved giving myself a headache, it was necessary to find an efficient analgesic. After testing all non-prescription headache remedies on the market and carrying out some experimentation, I found caffeine (100 mg) to be the only effective non-prescription analgesic [6].

Results

It is shown in Table 3 that both placebos and five of the six tyramine samples were identified correctly. Results for the food challenges are shown in Table 4.

Table 3. Double-blind test with tyramine hydrochloride (TYH). Samples of 1.00 mg TYH in 1.00 mL water, or placebo, added to 20 mL water, stirred and consumed, followed by 50 mL water

Code	Contents	Headache?	Started	Moderate	Correct?
6257	1.00 mg TYH	yes	14 min	25 min	yes
1424	Placebo	no	yes		
7418	1.00 mg TYH	yes	10 min	15 min	yes
9415	1.00 mg TYH	yes	10 min	20 min	yes
3989	1.00 mg TYH	yes	9 min	20 min	yes
5723	Placebo	no	yes		
2662	1.00 mg TYH	yes	13 min	20 min	yes
8910	1.00 mg TYH	no	no		

Table 4. Results of ingesting samples of food materials related to gelatin; sample weights and times for headaches to start and to reach a maximum (moderate) intensity for three repetitions of each experiment

Food materials	MSG	PHVP	Aspartame	Tyramine*	Capsule†
Weight, mg	400	118	4.00	1.00	123
Taken with	15 g CC‡	15 g RC‡	100 mL or juice	15 g RC‡	8 g PC‡
followed by	50 mL water	50 mL water	–	50 mL water	100 mL water
H started, min	9, 9, 10	9, 10, 11	8, 9, 11	8, 13, 13	13, 15, 20
H moderate, min	16, 19, 22	17, 19, 22	17, 19, 22	18, 21, 25	28, 33, 34

* As hydrochloride. † Libby Gelcap, no. 00. ‡ CC, cottage cheese; R, ricotta cheese; PC, potato chips.

Discussion

The result of the double-blind test was not perfect, but results with human subjects seldom are. The complete test was performed a second time and still had one error, so the test was stopped. As can be seen in Table 4, the times for headache to start and to reach maximum intensity were repeatable. The quantity of PHVP required to give a moderate headache and the capsule weight were comparable. These results support the hypothesis that capsule gelatin causes headaches.

Although the author has had practice in experimenting with foods to which he is sensitive, he does not recommend that others with the same ailment do so. It is dangerous when one does not know what the effect of deliberately ingesting something will be. Writing about physicians performing such food challenges on patients, Atkins [7] also warns of the possibility of severe reaction. When the dangers of monoamine oxidase inhibitors were not well understood, there were patients who died from brain haemorrhage after ingesting foods containing amines. A 1964 editorial in *Headache* [8] cites two such cases [9,10].

Acknowledgements

The following people were very helpful: chemists Timothy and Thomas Barwick of the Wilson Testing Laboratories who prepared the double-blind samples, Mrs Helen Richards who administered them, Mr Harry Gadhvi of Royal Foods and Flavors who provided samples of PHVP, David P. Roeltgen, MD for assistance and comments and Dr Jeddeo Paul, who reviewed the manuscript.

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