J Headache Pain (2003) 4:18–23

REVIEW

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Pharmacological analysis of red-wine-induced migrainous headaches

Received: 17 September 2002
Accepted in revised form: 17 December 2002

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Abstract We describe a series of experiments designed to investigate the mechanisms by which headaches can be triggered by red wine in a small minority of migraine patients. Some red wines are particularly potent releasers of serotonin from platelet stores, but these are no more effective as triggers of headache in sensitive patients. Both the selective 5-HT_{2A} antagonist ketanserin and the non-selective 5-HT_{2ABC} antagonist pizotifen blocked the majority of headaches, and we then thought the antihistamine properties of these two drugs might be important. In a third experiment, however, the H_1 antagonist mepyramine did not convincingly antagonise the response to red wine. Plasma levels of the enzyme diamine oxidase, which metabolises histamine, were lower in all migraine patients, whether or not they were sensitive to red wine. The results reported here do not permit making firm conclusions; nevertheless it seems that different pharmacological receptors may be responsible in different patients.

Key words Headache • Food sensitivity • Wine • $5HT_2$ receptors • Histamine H1 receptors

Introduction

Cheese, chocolate and red wine are the most publicised triggers for migrainous headaches, at least in English speaking countries. Systematic surveys of patients attending the Princess Margaret Migraine Clinic at Charing Cross Hospital have established that about 18%–19% of patients report sensitivity to cheese or chocolate, and usually to both [1]. In a more recent epidemiological survey [2] the 18% of migrainous patients sensitive to all alcoholic drinks were distinguished from a further 12% sensitive only to red wine, but not to white wine or clear spirits. There was a statistically significant but by no means absolute correlation between red wine and food sensitivity, though it was extremely rare for a diet-sensitive patient to be tolerant of all forms of alcohol [2]. We also found very few patients with tension or cluster headache to be sensitive to food or

red wine, although many of the latter are sensitive to all forms of alcohol [2].

It has proved difficult to reproduce this epidemiological finding in an experimental context [3]. Data drawn from elimination diets, for example, are particularly open to suggestibility and bias. The first convincing provocation study was done by Hanington et al. [4] in which the authors administered tyramine and lactose capsules separately to a group of diet-sensitive migraine patients, and found that headache was induced on 78% of occasions by tyramine and 6% of occasions by lactose. It is now clear that tyramine cannot be the only responsible substance, as it is not found in sufficient quantity in many incriminated foods, such as red wine [5]. A blinded study of red wine compared with diluted vodka did show a significant association with headache ($p<0.001$; Fisher's exact test, two tailed) [6] and a smaller study of chocolate compared with placebo chocolate also demonstrated a convincing association with headache [7].

Red wine sensitivity

Our recent studies at the Princess Margaret Migraine Clinic have been largely concerned with alcoholic drinks, partly because their biochemistry seems a little easier to elucidate, and partly because of the wider implications in controlling alcohol consumption [8]. In all these studies we have deliberately selected patients who are not sensitive to alcohol as such: they can all drink white wine or clear spirits in social quantities, but not red wine or, sometimes, beer. It should be emphasised that such patients form a relatively small proportion of those attending the Princess Margaret Migraine Clinic with migrainous headaches fulfilling criteria of the International Headache Society (IHS). In the last ten years, only 128 red-wine-sensitive patients have been identified, and many of these have been unable or unwilling participate in clinical studies (Table 1).

The possible mechanisms of this response have been discussed in detail elsewhere [9]. Our finding of a lower activity of platelet phenol sulphotransferase P in susceptible subjects [10] has been confirmed by Launay et al. [11], whereas platelet monoamine oxidase is not lower in diet-sensitive patients [12]. Littlewood et al. [13] demonstrated an inhibition of phenol sulphotransferase in vitro by red wine, consistent with the consumption in vivo of a single glass. Jarman et al. [14] showed that serotonin could be released from pre-loaded platelets by red wine, which could also be demonstrated in vivo [15, 16]. Unfortunately, the platelets of migraine patients sensitive to red wine did not release more serotonin than those from non-diet-sensitive migraine patients when studied in vitro [17].

Table 1 Patients seen in the Princess Margaret Migraine Clinic, London, in the period 1989-1997, by headache characteristics and willingness to participate in clinical studies. Mepyramine experiment

Characteristic	Patients, n (%)
All patients	2173 (100)
Migraine patients	1606 (74)
Red-wine-sensitive migraineurs	128 (6)
Considered for study	72 (3.3)
Excluded	
Too far	13
Refused	19
Not sensitive in a second interview	4
Taking medication	7
Unobtainable	11
Pregnant	2
In other trials	1
Incidental illness	2
Available for study	13 (0.6)

A study comparing IgE and IgG_4 levels in diet-sensitive and non-diet-sensitive migraine patients [18] did not support an immunological mechanism for this phenomenon, and indeed the disparate nature of the foods implicated would militate against any single trigger for an antibody; we feel the balance of evidence favours a chemical mechanism which may relate to the processes of fermentation which are common to many, but by no means all the implicated foodstuffs. As well as tyramine, there is evidence that the flavinoid substances which contribute to the pigment of red wine have complicated pharmacological properties in vivo [9].

In a now classic paper, Brewerton et al. [19] found that the trazadone metabolite metachlorophenylpiperazine (mCPP) would trigger headaches in some patients with a previous history of migraine, though it is unclear from this report whether this applies to only a proportion of migrainous subjects. There is increasing evidence that this substance has significant agonist pharmacological activity at $5HT_2$ receptor sub-types, particularly as the response is blocked by the serotonin antagonist metergoline [20]. In addition, a number of drugs effective in migraine prophylaxis, such as propranolol, pizotifen and methysergide, may also act as antagonists at one or more of the receptors in this group [21].

Serotonin binding or reuptake?

Although the in vitro study of Jarman et al. [17] suggested that red-wine-sensitive migraine patients' platelets were not more likely to release stored serotonin than those from non-diet-sensitive patients, it remained possible that serotonin release from neuronal or platelet stores plays a major role in

Table 2 Wine challenge experiments performed in 13 red-wine-sensitive migraineurs. Values are headache ratings according to the Glaxo scale [22] in which a value of 3 represents severe headache and 1 represents mild headache

Patient	First challenge [9][a]		Sangiovese (5 ml/kg) [26]		Sangiovese (5 ml/kg)		Plasma DAO, U/l[b]
	Chianti (5 mg/kg)	Valpolicella (5 mg/kg)	Pizotifen (3 mg)	Ketanserin (20 mg)	Mepyramine (100 mg)	Placebo	
1	2	3	–	–	–	–	–
2	1	2	–	–	–	–	–
3	3	2	–	–	–	–	–
4	3	3	–	–	–	–	–
5	1	NH	3; L, N, A	NH	1	2	4.5
6	NH	2	–	–	–	–	–
7	–	–	NH	NH	NH	NH	8.0
8	–	–	NH	NH	2; L, N	NH	7.0
9	–	–	NH	3; N, A	2; N	1.5; L, N	8.8
10	–	–	NH	1	–	–	–
11	–	–	1; L, N, A	NH	–	–	–
12	–	–	–	–	NH	NH	3.5
13	–	–	–	–	NH	2; L	0

[a] Information regarding lateralisation of pain, nausea, vomiting or aura was not collected; [b] DAO was measured by colourimetric analysis after it had been allowed to act in vitro for 60 min
NH, no headache experienced; *L*, lateralised pain; *N*, nausea or vomiting; *A*, aura; *DAO*, diamine oxidase

the induction of headache. For this reason we performed a challenge experiment comparing two Italian red wines: a Chianti which is a potent releaser of platelet serotonin, and a Valpolicella (made from the same grape variety) which is a relatively poor releaser [15]. In the experimental study [9] six patients consumed 5 mg/kg of each of the wines on two separate occasions at least two weeks apart, with two dry biscuits (Table 2). The development of symptoms was recorded on a questionnaire that was returned the following day. A headache developed on 10 of 12 possible occasions, and was graded according to the well established criteria used in recent drug trials [22]. Three patients reported that the Valpolicella produced a worse headache, two that the Chianti produced a worse headache, and in one the headache was severe in both cases (Table 2). This in vivo study, therefore, supported the view of the earlier Jarman et al. [17] experiment that serotonin release from platelet stores is unlikely to be a major mechanism of the phenomenon.

Serotonin receptors types 2B and 2C

If red wine had a direct pharmacological effect on a receptor, the obvious candidate would be one of the $5HT_2$ receptors. Previous genetic studies [23, 24] had shown no evidence of polymorphisms at $5HT_{2A}$ and $5HT_{2C}$ receptors. Chabriat et al. [25] used positron emission tomography (PET) to show that cerebral $5HT_{2A}$ receptors are unchanged in migraine patients. $5HT_{2A}$ receptor agonists are believed to be hallucinogenic, so an action at $5HT_{2B}$ and $5HT_{2C}$ receptors seemed more plausible, particular as mCPP is ten-fold more selective for these sub-types.

We obtained a new wine (Sangiovese di Toscana, 1995 from Cecchi, Tuscany, Italy), and Dr. Martyn Wood (SmithKline Beecham) kindly undertook some in vitro pharmacological studies of a freeze-dried sample of this wine. The wine yielded approximately 30 mg freeze-dried extract per millilitre. Thus drinking 5 ml wine per kilogram bodyweight equates to approximately 150 mg extract per kilogram body weight and, if absorbed fully, not destroyed in the gut and then distributed in all the body water, leads to a body concentration of 120 µg/ml. Table 3 shows the in vitro binding characteristics of the red wine to a variety of serotonin receptors: 50% saturation of binding sites was achieved for most receptor sub-types at concentrations of around 5 µg/ml, which seems entirely realistic in vivo.

In a further challenge experiment [26] six red-wine-sensitive patients, including one used in the earlier survey, again drank 5 ml/kg wine, two hours after being treated with either 3 mg pizotifen or 20 mg ketanserin (Table 2). Pizotifen is a non-selective $5HT_2$ receptor antagonist, whereas ketanserin is a selective antagonist of $5HT_{2A}$ receptors (Table 4). It was, of course, hypothesised that ketanserin would be ineffective and would thus function as a positive control, and that the effect of pizotifen on the

Table 3 Binding properties of freeze-dried wine extract (Sangiovese di Toscana) at 5HT receptors in vitro

Receptor sub-type	pKi	Equivalent concentration, µg/ml [a]
1B	<6.0	>6.6
1D	6.15	4.7
2A	<6.08	>5.5
2B	6.19	4.3
2C	6.18	4.4
7	6.28	3.7

[a] Assuming a molecular weight of wine extract equal to 660

Table 4 Binding affinities (pKa) of $5HT_2$ receptor agonists and antagonists

	$5HT_{2A}$	$5HT_{2B/2C}$	Reference
Agonists			
mCPP	6.7	7.7	[33]
Red wine	<6.08	6.19	
Antagonists			
Ketanserin	8.5	<5.2	[21, 34]
Pizotifen	8.6	8.54	[21, 34]
Metergoline	9.0	9.2	[34]

Table 5 Binding affinities (pKa) of receptor agonists

	Pizotifen	Ketanserin	Mepyramine
$5HT_{2A}$	8.6[a]	8.5[a]	6.18[b]
Histamine H1	9.45[c]	8.83[d]	9.097[e]

[a] From [34]; [b] From [35]; [c] From [36]; [d] From [37]; [e] From [38]

$5HT_{2B}$ and $5HT_{2C}$ receptors would antagonise the effect of the wine. However, the results were inconclusive. Two patients did not develop a headache on either test; two patients developed mild pain, one of them after ketanserin and the other after pizotifen, with no headache on the other occasions; and two patients developed severe prostrating pain on one occasion each, again one after ketanserin and one after pizotifen (Table 2). Although the in vitro studies suggested that the wine was likely to have some effect on most serotonin receptors in vivo, certainly in the gut and probably systemically, each drug appears to have inhibited the development of 4 of 6 headaches, and probably ameliorating one further headache each, which suggested that a pharmacological property common to both these drugs was more likely to be relevant. We had already felt that the $5HT_{2A}$ receptor was unlikely, and it was then suggested that histamine might be responsible, particularly as both pizotifen and ketanserin are potent antagonists of the histamine H_1 receptor (Table 5).

The role of histamine

Krabbe and Olesen [27] infused histamine intravenously into a group of headache patients, finding that those susceptible to migraine, but not muscle contraction headache, developed a headache (controls did not develop headache). This reached its maximum intensity within 2–3 minutes of infusion and ceased within 4–5 minutes of stopping the infusion. The H_1 receptor antagonist mepyramine, also administered intravenously, greatly decreased or stopped the headaches in virtually all the patients within 1–2 minutes, while cimetidine had a lower, though still significant, effect. In contrast, mepyramine did not antagonise the similar headache induced by glyceryl trinitrate infusion [28], which suggests that this is not mediated by the liberation of histamine. These authors speculated that histamine, acting via an H_1 receptor, stimulated endothelial nitric oxide synthase rather than interacting directly within the smooth muscle cells. It has, of course, been appreciated since the studies of Anthony et al. [29] that both the H_1 antagonist chlorpheniramine and the H_2 antagonist cimetidine are ineffective as migraine prophylactics.

There is ample evidence of the presence of histamine in wines. Achilli et al. [30], for example, found 10.7 mg/l in some Italian Borolo, with 1.9 mg/l in Chianti and 2.2 mg/l in red Bordeaux. In contrast Champagne contained 0.67 mg/l and still white wine no more than 0.12 mg/l. A bioassay, using guinea-pig ileum, of the same batch of Sangiovese di Toscana performed by Dr. Keith Rhodes showed that it had histamine-like activity equivalent to a concentration of 5.7 mg/l, and the response was blocked by mepyramine (10 nM).

Histamine experiments

We therefore assessed the effect of mepyramine in a further group of six red-wine-sensitive patients including one studied in both the earlier experiments, three studied in the second experiment and two further patients (unpublished observations). Each was again given 5 ml/kg Sangiovese di Toscana on two occasions at least a fortnight apart, on each occasion two hours after being administered mepyramine (100 mg) or placebo, on a double-blind randomised basis. The patients were again asked to record the maximal intensity of their headache using the Glaxo rating scale [22], returning a questionnaire the following morning. Two pa-

tients did not develop a headache on either occasion, two patients developed a moderate headache on one occasion and none on the other, one of them after mepyramine and the other after placebo, and two further patients developed a headache on both occasions, which was worse after placebo in one and after mepyramine in the other (Table 2).

By analogy with the studies of platelet monoamine oxidase undertaken by Glover et al. [12], we also speculated that histamine metabolism might be impaired in the red-wine-sensitive patients. Dietary histamine is largely metabolised by diamine oxidase (DAO) in the gut wall, and traces of this can be assayed within the plasma, correlating reasonably with gut levels in experimental animals [31]. Using the colorimetric method described by Takagi et al. [32], we measured diamine oxidase in blood samples taken from the 6 red-wine-sensitive patients who participated in the mepyramine study, and in 6 migraine patients not sensitive to red wine drawn from the hospital clinic, as well as in six controls (unpublished observations). The individual values obtained in the red-wine-sensitive patients are shown in Table 2, while the overall study results are summarised in Table 6. Plasma DAO levels were marginally, though not significantly *higher* in the red-wine-sensitive patients than in the non-sensitive migraine patients, but both groups had significantly lower levels than the control group. There seemed to be no correlation between diamine oxidase levels and either the development of headache after drinking red wine, or its antagonism by mepyramine.

Table 6 Plasma concentration of diamine oxidase (DAO) in migraineurs and controls. Values are mean (SEM)

	DAO, U/l
Red-wine-sensitive migraineurs (n=6)	5.29 (1.34)**
Migraneurs not sensitive to red wine (n=6)	3.42 (2.44)*
All migraineurs (n=12)	4.45 (1.36)**
Control subjects (n=6)	18.54 (3.21)

*p=0.052 vs. controls; **p=0.002 vs. controls on Mann-Whitney U test

Discussion

Challenge experiments of this type are extremely difficult to undertake. Patients genuinely sensitive to red but not white wine are unusual, a number have travelled a long way to the clinic and it is unrealistic to expect them to return for experimental studies, particularly as they may leave the hospital with a headache. A number are on medication and more are unwilling to volunteer. The experiments, therefore, have been done on a small group of loyal volunteers whose goodwill cannot be stretched indefinitely.

Several of the volunteers did not develop a headache at all even in the absence of any realistic antagonist. The reliability of the patient's own description of trigger factors must therefore be questioned, as well as such other variables as the time since the last headache. In addition, clean pharmacological effects are difficult to achieve with agents currently available for use in man, as the relatively broad spectrum of receptor antagonism shown by both ketanserin and pizotifen suggests. The Sangiovese di Toscana may, in addition, be less potent at inducing headaches.

Our studies have not addressed the role of the H_2 receptor, either alone or in association with H_1 receptors. A response to $5HT_{2A}$ and $5HT_{2C}$ receptors together has not been excluded. Diamine oxidase does not seem associated with red-wine-induced headaches, but the apparent deficiency in migraine patients as a whole clearly needs confirmation.

We are forced to conclude that the supply of patients is too small, and the consistency of responses in these experimental studies is too unreliable to offer definitive results. It remains most probable that the response is indeed to a chemical constituent of the wine, but the extent to which deficient metabolism of this agent and thus excessive supply to the neurovascular system, or altered receptor affinity to one or more agents may be relevant is unclear. The receptors involved may vary from patient to patient. It does seem likely, however, that the mechanism by which headache is produced by small quantities of red wine is independent of the mechanism of spontaneous headache which does not, for example, respond to an anti-histamine, though it often does to pizotifen.

Acknowledgements We thank Dr. Vivette Glover and colleagues at Queen Charlotte's Hospital, Dr. Martyn Wood and Dr. Andrew Parsons (Smithkline Beecham), and Prof. M.E. Parsons (University of Hertfordshire). We also thank Dr. Nick Deaney (Merck Sharp Dohme) for financial support. Mr. I.M. Gardiner died in August 2002.

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