

Migraine

ABSTRACTS

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FEVERFEW (Tanacetum pathenium)

Visual evoked potentials and serum magnesium levels in juvenile migraine patients.

Aloisi P; Marrelli A; Porto C; Tozzi E; Cerone G Servizio di Neurofisiopatologia, University of L'Aquila, Italy.

Headache (United States) Jun 1997, 37 (6) p383-5

Changes in visual evoked potentials and decreased intracellular magnesium levels have been separately described in patients affected by migraine both during the attacks and in the interictal periods. An inverse correlation between increased P100 amplitude and lowered serum magnesium levels was found in children suffering from migraine with and without aura in a headache-free period. A 20-day treatment with oral magnesium pidolate seemed to normalize the magnesium balance in 90% of patients. After treatment, the reduced P100 amplitude confirmed the inverse correlation with the serum magnesium level. These data seem to suggest the hypothesis that higher visual evoked potential amplitude and low brain magnesium level can both be an expression of neuronal hyperexcitability of the visual pathways related to a lowered threshold for migraine attacks.

Nocturnal plasma melatonin profile and melatonin kinetics during infusion in status migrainosus

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Cephalalgia (Norway), 1997, 17/4 (511-517)

The plasma melatonin profile was significantly disturbed (phase-shift of the maximum melatonin level) in four out of six female sufferers from status migrainosus, compared with nine healthy controls. The number of secretion peaks was similar in both groups. A nocturnal 20 pg melatonin infusion (from 21.00 to 01.00 h) evoked plasma melatonin levels slightly higher than a physiological secretion peak. During infusion, the episodes of secretion were reinforced and the endogenous plasma profile was phase-advanced in two patients displaying a phase-delay. These data suggest impaired pineal function in migraine. In the absence of side effects of melatonin infusion, the relief of certain migraine symptoms described by our patients might support a controlled trial of melatonin in migraine.

Dentist Advocates Cold Gel for Migraines 2002.

Feig, C.

CNN Medical Unit/CNN.com Health

(www.cnn.com/2002/HEALTH/conditions/02/11/migraine.treatment/index.html).

An extract of Petasites hybridus is effective in the prophylaxis of migraine.

Grossman W, Schmidramsl H. Department of Neurology, Municipal Hospital, Munchen-Harlaching, Germany.

Altern Med Rev 2001 Jun;6(3):303-10

OBJECTIVE: Migraine is still an unsolved problem. This clinical trial investigates the efficacy and tolerance of Petasites hybridus in the prophylaxis of migraine.

METHODS: A randomized, group-parallel, placebo-controlled, double-blind clinical study was carried out with a special CO₂ extract from the rhizome of Petasites hybridus. Following a four-week run-in phase, 60 patients received either the special Petasites hybridus extract Petadolex or placebo at a dosage of two capsules (each capsule contains 25 mg) twice daily over 12 weeks. Outcome variables included the frequency, intensity and duration of migraine attacks as well as any accompanying symptoms.

RESULTS: The frequency of migraine attacks decreased by a maximum of 60 percent compared to the baseline. This reduction in migraine attacks with Petadolex was significant ($p < 0.05$) compared to placebo. No adverse events were reported. Petasites was exceptionally well tolerated.

CONCLUSIONS: The results suggest that migraine patients can benefit from prophylactic treatment with this special extract. The

combination of high efficacy and excellent tolerance emphasizes the particular value that *Petasites hybridus* has for the prophylactic treatment of migraine.

The results of pycamilon therapy in patients with hemicrania.

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Efficiency of pycamilon in patients with hemicrania was studied. Indications for pycamilon application in response to the clinical form of hemicrania and to the course of disease were defined more exactly. It was been established that pycamilon has a pronounced effect on painful hemicrania access both decreasing its intensity and mitigating or absolute ceasing of accompanying symptoms. Pycamilon is most effective for simple forms of hemicrania with preferential left sided topoalgia in patients without pronounced depressive hypochondria.

Results of a 5 years prospective study of estriol succinate treatment in patients with climacteric complaints.

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Horm Metab Res 1987 Nov;19(11):579-84

In a prospective study 911 patients were treated over a period of 5 years (M = 2.2) or a total of 2007 treatment years with estriol succinate oral (Synapause, 2-12 mg per day). The treatment was very effective in the removal of all typical climacteric complaints and of the atrophic genital changes caused by estrogen deficiency. Subjective side effects were seldom seen and without practical importance for the treatment. Objective, grave side effects were only few: one superficial phlebo-thrombosis, 2 cases of thrombophlebitis, one carcinoma in situ of the portio vaginalis uteri and 2 mammary cancers were seen. The carcinoma had probably no causal relationship to the treatment. Embolies, myocardial infarctions, cerebrovascular and liver-gall bladder complications did not occur during treatment. The rate of uterine bleedings was low. The incidence of all complications was not increased by estriol succinate; but was even lower than expected. Endometrial and ovarian cancers were not seen. Estriol succinate is accordingly a very effective and well tolerated preparation against climacteric complaints, exerting no significant side effects. It is remarkable that it does not proliferate the endometrium when given in one dose a day. Estriol succinate can therefore be characterized as the estrogen to be favoured for the treatment of postclimacteric women, who do not want to have uterine bleedings any longer.

Role of magnesium in the pathogenesis and treatment of migraines.

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Clin Neurosci 1998;5(1):24-7

The importance of magnesium in the pathogenesis of migraine headaches is clearly established by a large number of clinical and experimental studies. However, the precise role of various effects of low magnesium levels in the development of migraines remains to be discovered. Magnesium concentration has an effect on serotonin receptors, nitric oxide synthesis and release, NMDA receptors, and a variety of other migraine related receptors and neurotransmitters. The available evidence suggests that up to 50% of patients during an acute migraine attack have lowered levels of ionized magnesium. Infusion of magnesium results in a rapid and sustained relief of an acute migraine in such patients. Two double-blind studies suggest that chronic oral magnesium supplementation may also reduce the frequency of migraine headaches. Because of an excellent safety profile and low cost and despite the lack of definitive studies, we feel that a trial of oral magnesium supplementation can be recommended to a majority of migraine sufferers. Refractory patients can sometimes benefit from intravenous infusions of magnesium sulfate.

[The new cerebrovascular preparation pikamilon]

Mirzoian RS; Gan'shina TS

Farmakol Toksikol (USSR) Jan Feb 1989, 52 (1) p23 6,

Picamilon, a sodium salt of N nicotinoyl gamma aminobutyric acid, was shown to induce a significant increase of cerebral blood flow in conscious cats. Picamilon was found to inhibit neurogenic spasms of cerebral vessels that was followed by suppression of tonic activity and reflectory discharges in sympathetic nerves. Picamilon led to restoration of the initial condition of cerebral hemodynamics disturbed by a previous administration of serotonin.

Randomised double-blind placebo-controlled trial of feverfew in migraine prevention.

Murphy JJ, Heptinstall S, Mitchell JR. Department of Medicine, University Hospital, Nottingham.

Lancet 1988 Jul 23;2(8604):189-92

The use of feverfew (*Tanacetum parthenium*) for migraine prophylaxis was assessed in a randomised, double-blind, placebo-controlled crossover study. After a one-month single-blind placebo run-in, 72 volunteers were randomly allocated to receive either one capsule of dried feverfew leaves a day or matching placebo for four months and then transferred to the other treatment limb for a further four months. Frequency and severity of attacks were determined from diary cards which were issued every two months; efficacy of each treatment was also assessed by visual analogue scores. 60 patients completed the study and full information was available in 59. Treatment with feverfew was associated with a reduction in the mean number and severity of attacks in each two-month period, and in the degree of vomiting; duration of individual attacks was unaltered. Visual analogue scores also indicated a significant improvement with feverfew. There were no serious side-effects.

Feverfew (*Tanacetum parthenium*) as a prophylactic treatment for migraine: A double-blind placebo-controlled study

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Phytotherapy Research (United Kingdom) 1997, 11/7 (508-511)

To assess the effectiveness of feverfew as a prophylactic therapy for migraine, a double-blind placebo controlled cross-over trial was conducted for a period of 4 months. Fifty seven patients who attended an outpatient pain clinic were selected at random and divided into two groups. Both groups were treated with feverfew in the preliminary phase (phase 1), which lasted 2 months, in the second and third phases, which continued for an additional 2 months, a double-blind placebo controlled cross-over study was conducted. The results showed that feverfew caused a significant reduction in pain intensity compared with the placebo treatment. Moreover, a profound reduction was recorded concerning the severity of the typical symptoms that are usually linked to migraine attacks, such as vomiting, nausea, sensitivity to noise and sensitivity to light. Transferring the feverfew -treated group to the placebo treatment resulted in an augmentation of the pain intensity as well as an increase in the severity of the linked symptoms, in contrast, shifting the placebo group to feverfew therapy resulted in a reduction of the pain intensity as well as in the severity of the linked symptoms.

Open label trial of coenzyme Q10 as a migraine preventive.

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Cephalalgia. 2002 Mar;22(2):137-41

The objective was to assess the efficacy of coenzyme Q10 as a preventive treatment for migraine headaches. Thirty-two patients (26 women, 6 men) with a history of episodic migraine with or without aura were treated with coenzyme Q10 at a dose of 150 mg per day. Thirty-one of 32 patients completed the study; 61.3% of patients had a greater than 50% reduction in number of days with migraine headache. The average number of days with migraine during the baseline period was 7.34 and this decreased to 2.95 after 3 months of therapy, which was a statistically significant response ($P < 0.0001$). Mean reduction in migraine frequency after 1 month of treatment was 13.1% and this increased to 55.3% by the end of 3 months. Mean migraine attack frequency was 4.85 during the baseline period and this decreased to 2.81 attacks by the end of the study period, which was a statistically significant response ($P < 0.001$). There were no side-effects noted with coenzyme Q10. From this open label investigation coenzyme Q10 appears to be a good migraine preventive. Placebo-controlled trials are now necessary to determine the true efficacy of coenzyme Q10 in migraine prevention.

Glucosamine for migraine prophylaxis?

Russell AL, McCarty MF. Brampton Pain Clinic, Bramalea, Ontario, Canada.

Med Hypotheses 2000 Sep;55(3):195-8

Following a fortuitous observation that migraine headaches ceased in a patient receiving glucosamine therapy for osteoarthritis, a further ten patients with migraine or migraine-like vascular headaches, refractory to established preventive or abortive therapies, have been treated with daily oral glucosamine. After a lag of 4-6 weeks, a substantial reduction in headache frequency and/or intensity has been noted; in some cases, the benefit appears to be dose-dependent. Since glucosamine can be a rate-limiting precursor for mucopolysaccharide synthesis, it is germane to note previous reports that heparin and pentosan polysulfate may have migraine-preventive activity. There is reason to suspect that mast cells are central mediators of the neurogenic inflammation associated with

migraine and cluster headaches. The heparin produced by mast cells may function to provide feedback down-regulation of mast cell activation, and exerts a range of other anti-inflammatory effects. We postulate that supplemental glucosamine can boost mast cell heparin synthesis - perhaps correcting a functional heparin deficiency - thereby preventing or ameliorating the neurogenic inflammation that mediates pain in vascular headache. Whether or not this idea has validity, a controlled study of glucosamine for migraine prophylaxis appears to be warranted.

Prophylactic treatment of migraine with beta-blockers and riboflavin: differential effects on the intensity dependence of auditory evoked cortical potentials.

Sandor PS, Afra J, Ambrosini A, Schoenen J. Neurology Department, CHR Citadelle, University of Liege, Belgium.

Headache 2000 Jan;40(1):30-5

OBJECTIVE: To investigate the influence of different pharmacological treatments on the intensity dependence of auditory evoked cortical potentials in migraineurs.

BACKGROUND: Between attacks, patients with migraine show abnormalities in cortical information processing and decreased brain mitochondrial energy reserve. Both are most probably relevant for migraine pathogenesis, and they could be differentially modified by prophylactic drug therapy. Design.-The intensity dependence of the auditory evoked cortical potentials is, on average, increased in migraine. We have studied this intensity dependence in 26 patients before and after a 4-month period of prophylaxis with beta-blockers (n = 11, all migraine without aura; metoprolol or bisoprolol) or riboflavin (n = 15, migraine without aura: 13, migraine with aura: 2). Recordings were performed at least 3 days before or after an attack.

RESULTS: After the treatment with beta-blockers, the intensity dependence of the auditory evoked cortical potentials was significantly decreased (before: 1.66±1.02 microV/10 dB; after: 0.79±1.06 microV/10 dB, P=.02). The decrease in intensity dependence was correlated significantly with clinical improvement (r = .69, P = .02). There was no change in intensity dependence after riboflavin treatment (before: 1.80±0.81 microV/10 dB; after: 1.56±0.83 microV/10 dB, P = .39), although the majority of patients showed improvement.

CONCLUSIONS: These results confirm that beta-blockers and riboflavin act on two distinct pathophysiological mechanisms. Combining both treatments might enhance their efficacy without increasing central nervous system side effects.

High-dose riboflavin as a prophylactic treatment of migraine: Results of an open pilot study

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Cephalalgia (Norway), 1994, 14/5 (328-329)

If the brain of migraineurs is characterized between attacks by a reduction of mitochondrial phosphorylation potential, riboflavin, which has the potential of increasing mitochondrial energy efficiency, might have prophylactic effects in migraine. In this preliminary open pilot study, 49 patients suffering from migraine (45 without aura, 4 with aura) were treated with 400 mg of riboflavin as a single oral dose for at least 3 months. Twenty-three patients received in addition 75 mg of aspirin. Mean global improvement after therapy was 68.2% and there was no difference between the two groups of patients. With the exception of one patient in the riboflavin plus aspirin group who withdrew because of gastric intolerance, no drug-related side effects were reported. High-dose riboflavin could thus be an effective, low-cost prophylactic treatment of migraine devoid of short-term side effects. A placebo-controlled trial of its efficacy seems worthwhile.

Pathogenesis of migraine.

Welch KM Department of Neurology, Henry Ford Hospital and Health Sciences Center, Detroit, Michigan 48202, USA.

Semin Neurol (United States) 1997, 17 (4) p335-41

Prevailing hypotheses for the mechanisms of migraine are reviewed. Models of aura mechanisms include transient cerebral ischemia and spreading depression. Models of headache involve trigeminovascular and brainstem mechanisms. The ability to trigger an attack may depend on a threshold of brain excitability. Mitochondrial disorder, magnesium deficiency, and abnormality of presynaptic calcium channels may be responsible for neuronal hyperexcitability between attacks. It remains to be determined whether cortical or brainstem centers generate the attack. (64 Refs.)

Suggested Reading

Feverfew and vascular smooth muscle: extracts from fresh and dried plants show opposing pharmacological profiles, dependent upon sesquiterpene lactone content.

Barsby RW; Salan U; Knight DW; Houlst JR Pharmacology Group, King's College London, U.K.

Planta Med (Germany) Feb 1993, 59 (1) p20-5

Preparations of fresh or dried feverfew (*Chrysanthemum parthenium*) are widely consumed in the U.K. as a remedy for arthritis and migraine, but the pharmacological basis for this has not been established. We have, therefore, compared the properties of extracts of fresh plants with those of dried powdered leaves available commercially from health food shops. The two extracts differed radically in their content of alpha-methylbutyrolactones and in their pharmacological profile when tested in vitro on the rabbit aortic ring and rat anococcygeus preparations. Extracts of fresh leaves caused dose- and time-dependent inhibition of the contractile responses of aortic rings to all receptor-acting agonists so far tested; the effects were irreversible and may represent a toxic modification of post-receptor contractile function in the smooth muscle. The presence of potentially -SH reactive parthenolide and other sesquiterpene aliphatic butyrolactones in these extracts, and the close parallelism of the actions of pure parthenolide, suggest that the inhibitory effects are due to these compounds. In contrast, chloroform extracts of dried powdered leaves were not inhibitory but themselves elicited potent and sustained contractions of aortic smooth muscle that were not antagonised by ketanserin (5-HT₂ receptor antagonist). These extracts did not contain parthenolide or butyrolactones according to a chemical-HPLC assay. We conclude that there are marked differences in the pharmacological potency and profiles between preparations from fresh and dried feverfew and that this may relate to their lactone content. As the effects of the lactones are potentially toxic, it will be necessary to compare the clinical profiles and side effects of preparations obtained from the two sources.

Inhibition of 5-lipoxygenase and cyclo-oxygenase in leukocytes by feverfew. Involvement of sesquiterpene lactones and other components.

Sumner H; Salan U; Knight DW; Houlst JR Pharmacology Group, King's College London, U.K.

Biochem Pharmacol (England) Jun 9 1992, 43 (11) p2313-20

Leaves or infusions of feverfew, *Tanacetum parthenium*, have long been used as a folk remedy for fever, arthritis and migraine, and derived products are widely available in U.K. health food shops. Previous reports have suggested interactions with arachidonate metabolism. Crude chloroform extracts of fresh feverfew leaves (rich in sesquiterpene lactones) and of commercially available powdered leaves (lactone-free) produced dose-dependent inhibition of the generation of thromboxane B₂ (TXB₂) and leukotriene B₄ (LTB₄) by ionophore- and chemoattractant-stimulated rat peritoneal leukocytes and human polymorphonuclear leukocytes. Approximate IC₅₀ values were in the range 5-50 micrograms/mL, and inhibition of TXB₂ and LTB₄ occurred in parallel. Isolated lactones (parthenolide, epoxyartemisinin) treated with cysteine (to neutralize reactive alpha-methylene butyrolactone functions of the sesquiterpenes). Inhibition of eicosanoid generation appeared to be irreversible but not time-dependent. We conclude that feverfew contains a complex mixture of sesquiterpene lactone and non-sesquiterpene lactone inhibitors of eicosanoid synthesis of high potency, and that these biochemical actions may be relevant to the claimed therapeutic actions of the herb.

Efficacy of feverfew as prophylactic treatment of migraine.

Johnson ES; Kadam NP; Hylands DM; Hylands PJ

Br Med J (Clin Res Ed) (England) Aug 31 1985, 291 (6495) p569-73

Seventeen patients who ate fresh leaves of feverfew daily as prophylaxis against migraine participated in a double blind placebo controlled trial of the herb: eight patients received capsules containing freeze dried feverfew powder and nine placebo. Those who received placebo had a significant increase in the frequency and severity of headache, nausea, and vomiting with the emergence of untoward effects during the early months of treatment. The group given capsules of feverfew showed no change in the frequency or severity of symptoms of migraine. This provides evidence that feverfew taken prophylactically prevents attacks of migraine, and confirmatory studies are now indicated, preferably with a formulation controlled for sesquiterpene lactone content, in migraine sufferers who have never treated themselves with this herb.

Herbal therapy for migraine: An unconventional approach

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Postgraduate Medicine (United States) 1987, 82/1 (197-198)

A pilot study was conducted at the City of London Migraine Clinic to establish whether feverfew 's efficacy could be shown through orthodox clinical evaluation and also to demonstrate any adverse effects on cellular and chemical elements of the blood. Because of possible ethical objections, only patients who had previously consumed feverfew leaves were included in the study.

Platelet ionized magnesium, cyclic AMP, and cyclic GMP levels in migraine and tension-type headache.

Mishima K; Takeshima T; Shimomura T; Okada H; Kitano A; Takahashi K; Nakashima K Division of Neurology, Tottori University Faculty of Medicine, Yonago, Japan.

Headache (United States) Oct 1997, 37 (9) p561-4

Decreased serum and intracellular levels of magnesium have been reported in patients with migraine . It has been suggested that magnesium may play an important role in the attacks and pathogenesis of headaches. We measured ionized magnesium, cyclic AMP (adenosine monophosphate), and cyclic GMP (guanosine monophosphate) in platelets of patients with migraine, in patients with tension-type headache, and in healthy controls. The platelet level of ionized magnesium from patients with tension-type headache was significantly lower than the levels from the other two groups. The platelet level of cyclic AMP from patients with migraine was higher than those from the other groups. We found no significant differences in the platelet cyclic GMP levels among the three groups. It is suggested that reduced platelet ionized magnesium in patients with tension-type headache is related to abnormal platelet function, and that increased platelet cyclic AMP in patients with migraine is related to alteration of neurotransmitters in the platelet.

Omega- 3: Essential for good health

Pelton R.

American Druggist (United States) 1997, 214/7 (52-53)

Supplements of omega -3 fatty acids may be needed to maintain a careful balance with omega-6 and regulate the production of prostaglandins and their effects.

Pathophysiology of the migraine aura

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Bollettino - Lega Italiana contro l'Epilessia (Italy) 1997, -/99 (359-362)

Modern techniques have improved our knowledge of the pathophysiology of the migraine . In general two approaches have been taken, modeling the mechanisms of the attack and modeling the true cause of migraine , in other word, the mechanisms through which the attacks are triggered. From animal experiments it is known that there are two possible explanation for the migraine aura. Aura symptoms could arise from spreading depression or from the oligoemia due to changes in diameter of small cerebral vessels. Preliminary data obtained by functional imaging techniques such as PET and f- MR indicates that the spreading depression model appears the most plausible to account for the migraine aura. Neurophysiological, CBF and brain metabolic measures have suggested neuronal and neurovascular instability between migraine attacks. A mitochondrial defect or a disturbance in magnesium metabolism could account, alone or in combination, for neuronal hyperexcitability especially in the occipital cerebral cortex. In families linked to chromosome 19, familial hemiplegic migraine is caused by point mutations in the CACNL1A4 gene coding for a P/Q type brain specific $\alpha 1$ subunit calcium channel. This will open a new window on the understanding the pathophysiology of the migraine .

Food and headache

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Headache Quarterly (United States) 1997, 8/4 (319-329)

Objective: To review the significant literature relating to food and headache. Data sources study selection and data extraction: Medline review and extraction. Synthesis was done by selecting the more recant 'hard science' articles.

Conclusion: Red wine can be a trigger for migraine attacks in susceptible patients. Susceptibility may be related to the low level of phenosulphotransferase P, the enzyme that detoxicates flavonoid phenols found in red wine. Other types of alcohol drinks can also precipitate migraine but their mechanism is different. Chocolate may precipitate attacks because of its phenolic content. Other dietary triggers are probably multifactorial, ie they trigger attacks only under certain circumstances. Fasting is a well- authenticated

trigger but not because of hypoglycemia . More research needs to be done in this field as dietary triggers can throw light on the pathogenesis of headache.

Migraine treatment

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Seminars in Neurology (United States) 1997, 17/4 (325-333)

Migraine is a primary headache disorder characterized by recurring attacks of pain and associated symptoms. Migraine sufferers require a continuum of clinical care that depends on their disability and response to treatment. Treatment consists of: (1) prevention of attacks by avoidance of triggers; (2) the use of nonpharmacologic treatments; (3) treatment of the acute attack; and (4) long-term prophylactic therapy. Migraine is comorbid for affective disorders, epilepsy, stroke, and mitral valve prolapse. The therapy selected depends on the headache severity and frequency, the pattern of associated symptoms, comorbid illnesses, and the patient's treatment response profile. Acute treatment can be symptomatic or specific, using drugs such as dihydroergotamine (DHE) or sumatriptan. Preventive treatment can be episodic, subacute, or chronic. The major drug groups include beta- adrenergic blockers, antidepressants, calcium channel blockers, serotonin antagonists, anticonvulsants, and nonsteroidal anti-inflammatory drugs (NSAIDs). These can be divided into two major categories and second-line choices.

In search of the ideal treatment for migraine headache.

Bic Z; Blix GG; Hopp HP; Leslie FM School of Public Health, Loma Linda University, CA 92350-0001, USA.

Med Hypotheses (England) Jan 1998, 50 (1) p1-7

Migraine headache is a common syndrome, afflicting millions, that has so far defied a definitive cure. Experimental research studies of the syndrome tend to describe the triggering factors separately. We propose a common denominator--namely, high levels of blood lipids and free fatty acids--as underlying factor in the development of migraine headaches. Biological states that may cause increases in free fatty acids and blood lipids include: high dietary fat intake, obesity, insulin resistance, vigorous exercise, hunger, consumption of alcohol, coffee, and other caffeinated beverages, oral contraceptives, smoking, and stress. Elevated blood lipids and free fatty acids are associated with increased platelet aggregability, decreased serotonin, and heightened prostaglandin levels. These changes lead to the vasodilatation that precedes migraine headache. We suggest that migraine headache should not be seen as an isolated symptom, but as a first signal of potential biochemical imbalances in the body, which can lead to development of chronic disease. (69 Refs.)

Diet and migraine

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Rev Neurol (Spain) May 1996, 24 (129) p534-8

Some foods in our diet can spark off migraine attacks in susceptible individuals. Some foods can bring an attack on through an allergic reaction. A certain number such as citrus fruits, tea, coffee, pork, chocolate, milk, nuts, vegetables and cola drinks have been cited as possible allergens associated with migraine . This mechanism has however been criticized: an improvement in symptoms by eliminating some food(s) from our diet does not necessarily mean an immunologically based allergic reaction. The high IgE incidence rate is not greater in such patients than in the population at large. Other allergic reactions unrelated to diet may also be associated with migraine attacks. On the other hand substances in food may be the cause of modifications in vascular tone and bring migraine on in those so prone. Among such substances are tyramine, phenylalanine, phenolic flavonoids, alcohol, food additives (sodium nitrate, monosodium glutamate, aspartame) and caffeine. Another recognized trigger for migraine is hypoglycemia. Such foods as chocolate, cheese, citrus fruits, bananas, nuts, 'cured' meats, dairy products, cereals, beans, hot dogs, pizza, food additives (sodium nitrate, monosodium glutamate in Chinese restaurant food, aspartame as a sweetener), coffee, tea, cola drinks, alcoholic drinks such as red wine, beer or whisky distilled in copper stills, all may bring on a migraine attack. For every patient we have to assess which foodstuffs are involved in the attack (not necessarily produced by consuming the product concerned) in order to try to avoid their consumptions as a means of prophylaxis for migraine . (46 Refs.)

Dietary factors in migraine precipitation: The physicians' view

Blau J.N.; Diamond S. The National Hospital for Nervous Diseases, City of London Migraine Clinic, London United Kingdom

Headache (United States) 1985, 25/4 (184-187)

Five hundred and fifty questionnaires were sent to members of the American Association for the Study of Headache as well as to British physicians with a known interest in migraine. Of the 327 that replied, only 21% favored the term 'dietary migraine'. To determine the presence of food sensitivity in their patients 71% relied on information from the patient's history alone. However, 21% employed special tests in addition to the history. Estimates of the percentage of patients in whom dietary factors were operative ranged from 0-80%. Seventy-four percent were in the 0-20% range (some indicating an incidence nearer 1-5% or less). Sixteen percent estimated the range of their patients in whom diet provoked migraine was between 20-40%, three percent estimated 40-60%, and two percent 60-80%. The foods most commonly cited as triggering agents are presented in descending rate of frequency: chocolate, alcohol, cheese, monosodium glutamate, nuts, citrus fruit, meat, coffee, nitrates, fish, dairy products, onions, hot dogs, pizza, wheat products, bananas, tomatoes, apples, and various vegetables. Individual comments invited on the questionnaire are described. The consensus is that foods or alcohol can provoke occasional attacks in some patients. They conclude that the appropriate term is 'dietary precipitated migraine'.

Pathogenesis of posttraumatic headache and migraine: a common headache pathway?

Packard RC; Ham LP Headache Management and Neurology, Pensacola, FL 32503, USA.

Headache (United States) Mar 1997, 37 (3) p142-52

In recent years, research implicating biochemical abnormalities in various pathological conditions has spiralled. Headache is an area in which numerous research studies have been conducted examining biochemical alterations. We have noticed several similarities in biochemical changes reported to occur in migraine and in experimental traumatic brain injury. The most common symptom in mild head injury or mild traumatic brain injury is headache which, in many instances, resembles migraine but has a poorly understood pathophysiology. Biochemical mechanisms believed to be similar in both conditions include: increased extracellular potassium and intracellular sodium, calcium, and chloride; excessive release of excitatory amino acids; alterations in serotonin; abnormalities in catecholamines and endogenous opioids; decline in magnesium levels and increase in intracellular calcium; impaired glucose utilization; abnormalities in nitric oxide formation and function; and alterations in neuropeptides. In this paper, these proposed biochemical alterations will be reviewed and compared. Very similar alterations suggest posttraumatic headache associated with mild head injury and migraine may share a common headache pathway. (114 Refs.)

[Migraine--diagnosis, differential diagnosis and therapy]

Diener HC Klinik und Poliklinik für Neurologie, Universität Essen.

Ther Umsch (Switzerland) Feb 1997, 54 (2) p64-70

Migraine is caused by intermittent brain dysfunction. Attacks result in severe unilateral headache with nausea, vomiting, photophobia, phonophobia and general weakness. The prevalence of migraine is 12 to 20% in women and 8 to 12% in man. Treatment of an acute attack is done by antiemetics in combination with analgesics. Severe migraine attacks are treated with ergotamine or sumatriptan. Parenteral treatment is performed most efficiently and safely with i.v. ASA. Frequent and severe attacks require prophylaxis. Drugs of first choice are metoprolol, propranolol, flunarizine and cyclandelate. Substances of second choice are valproic acid, DHE, pizotifen, methysergide and magnesium. Homeopathic remedies are not superior to placebo. Nonpharmacological treatment consists of sport therapy and muscle relaxation techniques.

Magnesium taurate and fish oil for prevention of migraine.

McCarty MF Nutrition 21, San Diego, CA 92109, USA.

Med Hypotheses (England) Dec 1996, 47 (6) p461-6

Although the pathogenesis of migraine is still poorly understood, various clinical investigations, as well as consideration of the characteristic activities of the wide range of drugs known to reduce migraine incidence, suggest that such phenomena as neuronal hyperexcitation, cortical spreading depression, vasospasm, platelet activation and sympathetic hyperactivity often play a part in this syndrome. Increased tissue levels of taurine, as well as increased extracellular magnesium, could be expected to dampen neuronal hyperexcitation, counteract vasospasm, increase tolerance to focal hypoxia and stabilize platelets; taurine may also lessen sympathetic outflow. Thus it is reasonable to speculate that supplemental magnesium taurate will have preventive value in the treatment of migraine. Fish oil, owing to its platelet-stabilizing and antivasospastic actions, may also be useful in this regard, as suggested by a few clinical reports. Although many drugs have value for migraine prophylaxis, the two nutritional measures suggested here may have particular merit owing to the versatility of their actions, their safety and lack of side-effects and their long-term favorable impact on vascular health. (94 Refs.)

Prophylaxis of migraine with oral magnesium: results from a prospective, multi-center, placebo-controlled and double-

blind randomized study.

Peikert A; Wilimzig C; Kohne-Volland R Department of Neurology and Clinical Neurophysiology, Munich-Harlaching Clinic, Germany.

Cephalalgia (Norway) Jun 1996, 16 (4) p257-63

In order to evaluate the prophylactic effect of oral magnesium, 81 patients aged 18-65 years with migraine according to the International Headache Society (IHS) criteria (mean attack frequency 3.6 per month) were examined. After a prospective baseline period of 4 weeks they received oral 600 mg (24 mmol) magnesium (trimagnesium dicitrate) daily for 12 weeks or placebo. In weeks 9-12 the attack frequency was reduced by 41.6% in the magnesium group and by 15.8% in the placebo group compared to the baseline ($p < 0.05$). The number of days with migraine and the drug consumption for symptomatic treatment per patient also decreased significantly in the magnesium group. Duration and intensity of the attacks and the drug consumption per attack also tended to decrease compared to placebo but failed to be significant. Adverse events were diarrhea (18.6%) and gastric irritation (4.7%). High-dose oral magnesium appears to be effective in migraine prophylaxis.

Electromyographical ischemic test and intracellular and extracellular magnesium concentration in migraine and tension-type headache patients.

Mazzotta G; Sarchielli P; Alberti A; Gallai V Interuniversity (Perugia-Rome-Sassari-Bari) Centre for the Study of Headache and Neurotransmitter Disorders of the CNS, Italy.

Headache (United States) Jun 1996, 36 (6) p357-61

Headache has often been described in the hyperexcitability syndrome which recognizes an alteration of calcium and magnesium status in its etiopathogenesis. Moreover, in migraine patients magnesium has been shown to play an important role as a regulator of neuronal excitability and, therefore hypothetically, of headache. The present research involves a neurophysiological evaluation and magnesium status assessment of a group of headache patients. Nineteen patients (15 women and 4 men) with episodic tension-type headache and 30 patients (27 women and 3 men) with migraine without aura were examined. An ischemic test was carried out on the right arm with electromyographic (EMG) recording of motor unit potential activity during the interictal period. The determination of extracellular (serum and saliva) and intracellular (red and mononuclear blood cells) magnesium was also performed. The EMG test was positive in 25 of 30 migraine patients and in 2 of 19 tension-type headache patients. Between the two patient groups, there were no significant variations in the concentration of extracellular and white blood cell magnesium, while the red blood cell concentration of this mineral in the group of migraineurs was significantly reduced with respect to that in the group of tension-type headache patients ($P < 0.05$). The positive EMG test was significantly associated with a low concentration of red blood cell magnesium ($P < 0.0001$). These results confirm previous findings by demonstrating different etiopathogenic mechanisms as the basis of migraine and tension-type headache. Migraine seems to be related to an altered magnesium status, which manifests itself by a neuromuscular hyperexcitability and a reduced concentration in red blood cells.

Long-time efficacy of cyclandelate and propranolol in prophylaxis of migraine following four months of treatment

Schellenberg R.; Schwarz A.; Niederberger U.; Bolsche F.; Schindler M.; Gerber W.-D.; Wedekind W.; Soyka D. Dr. R. Schellenberg, Talstrasse 29, D-35625 Huttenberg Germany

Nervenheilkunde (Germany), 1997, 16/3 (183-187)

After a 4 months randomized double-blind study with cyclandelate versus propranolol all patients kept a miniaturized headache diary for one more year. Both duration of migraine attacks in hours and the number of additional analgetic medication were recorded monthly. Reduction of the duration of migraine attacks in the clinical responders of the cyclandelate treated patients remained nearly unchanged. In the propranolol responders the duration of migraine attacks in hours increased from the third month after finishing the medication and reached values comparable to those at the beginning of the active treatment. Intake of additional analgetic medication during the 1-year-follow-up was lower in the cyclandelate responders than in the propranolol-responders. Cyclandelate can be described as an effective long-lasting drug in migraine prophylaxis.

Nocturnal melatonin excretion is decreased in patients with migraine without aura attacks associated with menses

Brun J.; Claustrat B.; Saddier P.; Chazot G.

Cephalalgia (Norway), 1995, 15/2 (136-139)

Nocturnal melatonin excretion was studied throughout a complete menstrual cycle in 10 women with migraine without aura attacks

associated with menses and 9 women controls. Urine melatonin was determined by radioimmunoassay. The mean nocturnal melatonin excretion throughout the cycle was significantly lower in the migraine patients than in controls. In the control group, melatonin excretion increased significantly from the follicular to the luteal phase, whereas no difference was observed in the migraine group. Results are discussed in view of the role of the pineal gland in the organization of biological rhythms and homeostasis in relation to environmental conditions.

Urinary melatonin excretion throughout the ovarian cycle in menstrually related migraine

Murialdo G.; Fonzi S.; Costelli P.; Solinas G.P.; Parodi C.; Marabini S.; Fanciullacci M.; Polleri A. Endocrinological/Metabol. Sci. Dept., Viale Benedetto XV, 6, I-16132 Genoa Italy

Cephalalgia 1994 Jun;14(3):205-9

Nocturnal urinary melatonin excretion was significantly decreased throughout an ovarian cycle in 12 migraine without aura patients compared to 8 healthy controls. Normal increases in urinary melatonin excretion during the luteal phase was less pronounced in the migraine patients. Melatonin excretion was further decreased during headache. The data indicate impaired pineal function in migraine.

Nocturnal plasma melatonin levels in migraine: A preliminary report

Claustrat B, Loisy C, Brun J, Beorchia S, Arnaud JL, Chazot G

Headache (United States) Apr 1989, 29 (4) p242-5

We determined by radioimmunoassay plasma melatonin levels on blood samples drawn at 11 p.m. in migraine patients and control subjects. Ninety-three cephalalgic outpatients (75 females, 18 males) were compared to a control group (24 females, 22 males) matched according to age. Patients were divided into subgroups presenting common migraine (n = 38); ophthalmic migraine (n = 12); and tension headache associated with ophthalmic or common migraine (n = 24), and associated depressive status (n = 19). Statistical analysis revealed a decrease in plasma melatonin levels for the entire migraine population, compared to the control one, and a heterogeneity in both controls and patients; this heterogeneity was found mainly in the depressive and tension headache subgroups. When the migraine population - from which the depressive patients were excluded - was divided into male and female subgroups, a decrease in plasma melatonin levels was observed only for the female subgroups. Results are discussed with reference to the role of the pineal gland in the synchronization of the organism with the environmental conditions.

The influence of the pineal gland on migraine and cluster headaches and effects of treatment with picoTesla magnetic fields.

Sandyk R

Int J Neurosci (England) Nov-Dec 1992, 67 (1-4) p145-71

For over half a century the generally accepted views on the pathogenesis of migraine were based on the theories of Harold Wolff implicating changes in cerebral vascular tone in the development of migraine. Recent studies, which are based on Leao's concept of spreading depression, favor primary neuronal injury with secondary involvement of the cerebral circulation. In contrast to migraine, the pathogenesis of cluster headache (CH) remains entirely elusive. Both migraine and CH are cyclical disorders which are characterised by spontaneous exacerbations and remissions, seasonal variability of symptoms, and a relationship to a variety of environmental trigger factors. CH in particular has a strong circadian and seasonal regularity. It is now well established that the pineal gland is an adaptive organ which maintains and regulates cerebral homeostasis by "fine tuning" biological rhythms through the mediation of melatonin. Since migraine and CH reflect abnormal adaptive responses to environmental influences resulting in heightened neurovascular reactivity, I propose that the pineal gland is a critical mediator in their pathogenesis. This novel hypothesis provides a framework for future research and development of new therapeutic modalities for these chronic headache syndromes. The successful treatment of a patient with an acute migraine attack with external magnetic fields, which acutely inhibit melatonin secretion in animals and humans, attests to the importance of the pineal gland in the pathogenesis of migraine headache. (242 Refs.)

Is migraine due to a deficiency of pineal melatonin?

Toglia JU

Ital J Neurol Sci (Italy) Jun 1986, 7 (3) p319-23

Recent clinical observations favor the theory that migraine is caused by a primary injury of cerebral neurons with secondary involvement of intracranial and extracranial blood vessels. The primary injury is attributed to disruption of cerebral neurotransmitters and particularly the neuroadrenergic and serotonergic systems. These theories have not explained the importance of environmental factors, which so frequently trigger migraine. The author suggests that the pineal gland, which is outside the CNS unprotected by blood brain barrier and sensitive to external stimuli, could act as the intermediate causative factor of migraine, via a derangement of melatonin. (47 Refs.)

FEVERFEW (*Tanacetum parthenium*):

Feverfew appears to work in the treatment and prevention of migraine headaches by inhibiting the release of blood vessel dilating substances from platelets (serotonin and histamine), inhibiting the production of inflammatory substances (leukotrienes, serine proteases, etc.), and re-establishing proper blood vessel tone. Commercial sources providing assurance of botanical identity and minimum required level of parthenolides are needed (Awang DVC. Feverfew. *Can Pharm J* 122:266-70, 1989).

In vitro Study: Feverfew was found to contain a factor that inhibits prostaglandin synthesis, but differs from salicylates by not inhibiting cyclo-oxygenase by prostaglandin (PG) synthase. "The ability of feverfew to inhibit PG production may account for its effectiveness as a herbal remedy in conditions responding to acetylsalicylate and like-acting drugs" (Collier HOJ, Butt NM, McDonald-Gibson WJ, Saeed SA. Extract of feverfew inhibits prostaglandin biosynthesis. *Lancet* October 25, 1980).

The dosage of feverfew used in one double-blind study was one capsule containing 25 mg of the freeze-dried pulverized leaves twice daily; in another double-blind study it was one capsule containing 82 mg of dried powdered leaves once daily. While these low dosages may be effective in preventing an attack, a higher dose (1 to 2 grams) may be necessary during an acute attack.

Note: The efficacy of feverfew is dependent upon adequate levels of parthenolide, the active ingredient. (The preparations used in successful clinical trials have a parthenolide content of 0.4-0.66%.)

Animal Ex vivo Study: Extracts of fresh feverfew caused a dose- and time dependent, irreversible inhibition of the contractile response of rabbit aortic rings to all receptor-acting agonists tested. The presence of potentially SH reacting parthenolide and other sesquiterpene alpha-methylenebutyrolactones in, these extracts, and the close parallelism of pure parthenolide, suggest that the inhibitory effects are due to these compounds. Extracts of the dry leaves were not inhibitory and actually caused potent and sustained contractions of aortic smooth muscle; these extracts were found to be devoid of parthenolide or butyrolactones (Barsby RWJ, Salan U, Knight BW, Houlst JRS. Feverfew and vascular smooth muscle: Extracts from fresh and dried plants show opposing pharmacological profiles, dependent upon sesquiterpene lactone content. *Planta Medica* 59:20-5, 1993).

Chemical Analysis: The parthenolide content of over 35 different commercial preparations of feverfew was determined by bioassay, 2 HPLC methods, and NMR. The results indicate a wide variation in the amts. of parthenolide in commercial preparations. The majority of products contained no parthenolide or only traces (Heptinstall S et al. Parthenolide content and bioactivity of feverfew (*Tanacetum parthenium* (L.) Schultz-Bip.). Estimation of commercial and authenticated feverfew products. *J Pharm Pharmacol* 44:391-5, 1992).

WARNING: No long-term toxicity studies have been conducted. While feverfew is extremely well-tolerated and no serious side effects have ever been reported, chewing the leaves can result in small ulcerations in the mouth and swelling of the lips and tongue in about 10% of users (Awang DVC. Feverfew. *Can Pharm J* 122:266-70, 1989).

MIGRAINE (Page 2)

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- > In vivo administration of propranolol decreases exaggerated amounts of serum TNF-alpha in patients with migraine without aura. Possible mechanism of action.
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 - > The co-occurrence of multiple sclerosis and migraine headache: the serotonergic link.
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 - > Is migraine due to a deficiency of pineal melatonin?
 - > Melatonin in humans physiological and clinical studies.
-

Nocturnal plasma melatonin profile and melatonin kinetics during infusion in status migrainosus

Claustrat B.; Brun J.; Geoffriau M.; Zaidan R.; Mallo C.; Chazot G.
B. Claustrat, Serv. Radiopharmacie/Radioanalyse, Hopital Neurologique, 59 Boulevard Pinel, 69003 Lyon France
Cephalalgia (Norway), 1997, 17/4 (511-517)

The plasma melatonin profile was significantly disturbed (phase-shift of the maximum melatonin level) in four out of six female sufferers from status migrainosus, compared with nine healthy controls. The number of secretion peaks was similar in both groups. A nocturnal 20 pg melatonin infusion (from 21.00 to 01.00 h) evoked plasma melatonin levels slightly higher than a physiological secretion peak. During infusion, the episodes of secretion were reinforced and the endogenous plasma profile was phase-advanced in two patients displaying a phase-delay. These data suggest impaired pineal function in migraine. In the absence of side effects of melatonin infusion, the relief of certain migraine symptoms described by our patients might support a controlled trial of melatonin in migraine.

Pharmacology of serotonin as related to anesthesia

Gyermek L.
Department of Anesthesiology, Harbor-UCLA Medical Center, 1000 West Carson Street, Torrance, CA 90509 USA
Journal of Clinical Anesthesia (USA), 1996, 8/5 (402-425)

Serotonin (5-hydroxytryptamine) is an important biogenic amine that fulfills the role of neurotransmitter and neuromodulator. It has been a focus of interest during the last decade. Its diversity of pharmacologic actions is related to a wide variety of receptors and effector mechanisms. Serum serotonin receptor families have been identified thus far. They are genetically different transmembrane proteins composed of several hundred amino acids. The majority of these are G-protein-coupled, except the 5-HT₃ receptors, which are directly ligand gated to fast ion channels. Serotonin is widely distributed in the body within the central and peripheral nervous systems, smooth muscles, and platelets, in particular. Consequently, its effects manifest mainly in these organs and influence a wide variety of neural, vascular, smooth muscle, and platelet functions. (Melatonin, a physiologically active metabolite of serotonin, is also instrumental in affecting many neural and hormonal functions.) Several selective agonists and particularly many selective antagonists have been developed for serotonin, which helped the serotonin receptor subtype classification. Some of these drugs are also used therapeutically in the treatment of migraine (eg, sumatriptan, which is a 5-HT₁ receptor agonist), vascular disorders (5-HT₂ antagonists), and nausea and vomiting (5-HT₃ antagonists, eg, dolasetron, granisetron, ondansetron, and tropisetron), and have been investigated in gastrointestinal motility disorders (5-HT₄ antagonists) and behavioral psychopathologies (5-HT₁ agonists and 5-HT₂₋₄ antagonists). Serotonin reuptake inhibitors are of particular clinical importance in

the treatment of psychological illnesses. Future use of these drugs is also envisioned in the treatment of certain types of pain syndromes. Awareness of the serotonergic drugs and the recognition of possible drug interactions among drugs that influence serotonergic mechanisms in humans are becoming increasingly important in the practice of anesthesiology.

Pathogenesis of posttraumatic headache and migraine: a common headache pathway?

Packard RC; Ham LP

Headache Management and Neurology, Pensacola, FL 32503, USA.

Headache (United States) Mar 1997, 37 (3) p142-52

In recent years, research implicating biochemical abnormalities in various pathological conditions has spiralled. Headache is an area in which numerous research studies have been conducted examining biochemical alterations. We have noticed several similarities in biochemical changes reported to occur in migraine and in experimental traumatic brain injury. The most common symptom in mild head injury or mild traumatic brain injury is headache which, in many instances, resembles migraine but has a poorly understood pathophysiology. Biochemical mechanisms believed to be similar in both conditions include: increased extracellular potassium and intracellular sodium, calcium, and chloride; excessive release of excitatory amino acids; alterations in serotonin; abnormalities in catecholamines and endogenous opioids; decline in magnesium levels and increase in intracellular calcium; impaired glucose utilization; abnormalities in nitric oxide formation and function; and alterations in neuropeptides. In this paper, these proposed biochemical alterations will be reviewed and compared. Very similar alterations suggest posttraumatic headache associated with mild head injury and migraine may share a common headache pathway. (114 Refs.)

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Diener HC

Klinik und Poliklinik für Neurologie, Universität Essen.

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Migraine is caused by intermittent brain dysfunction. Attacks result in severe unilateral headache with nausea, vomiting, photophobia, phonophobia and general weakness. The prevalence of migraine is 12 to 20% in women and 8 to 12% in men. Treatment of an acute attack is done by antiemetics in combination with analgesics. Severe migraine attacks are treated with ergotamine or sumatriptan. Parenteral treatment is performed most efficiently and safely with i.v. ASA. Frequent and severe attacks require prophylaxis. Drugs of first choice are metoprolol, propranolol, flunarizine and cyclandelate. Substances of second choice are valproic acid, DHE, pizotifen, methysergide and magnesium. Homeopathic remedies are not superior to placebo. Nonpharmacological treatment consists of sport therapy and muscle relaxation techniques.

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McCarty MF

Nutrition 21, San Diego, CA 92109, USA.

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Peikert A; Wilimzig C; Kohne-Volland R
Department of Neurology and Clinical Neurophysiology, Munich-Harlaching Clinic, Germany.
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Interuniversity (Perugia-Rome-Sassari-Bari) Centre for the Study of Headache and Neurotransmitter Disorders of the CNS, Italy.
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Efficacy and tolerability of subcutaneous sumatriptan administered using the IMITREX STATdose System.

Mushet GR; Cady RK; Baker CC; Clements B; Gutterman DL; Davis R
Georgia Headache Treatment Center, Augusta, USA.
Clin Ther (United States) Jul-Aug 1996, 18 (4) p687-99

The efficacy and tolerability of subcutaneous (SC) sumatriptan administered with the IMITREX (sumatriptan succinate) STATdose System, which circumvents the need for patients or health care professionals to handle a syringe, were evaluated in two randomized, double-masked, parallel-group, placebo-controlled, multicenter studies. In the clinic, 158 adults with migraine diagnosed according to International Headache Society criteria received SC sumatriptan (6 mg) or placebo delivered with the IMITREX STATdose System for treatment of a migraine attack. By 120 minutes after SC dosing, 73% and 79% of sumatriptan-treated patients, compared with 28% and 37% of placebo-treated patients in studies 1 and 2, respectively, experienced headache relief (a statistically significant difference). Clinical disability scores 120 minutes after dosing showed that 75% and 85% of sumatriptan-treated patients, compared with 30% and 42% of placebo-treated patients, were normal or only mildly impaired (a statistically significant difference). Similar efficacy rates were observed for nausea, phonophobia, and photophobia. No serious or unusual adverse events occurred, and no clinically relevant abnormalities in laboratory test values were reported. Based on these results, we concluded that SC sumatriptan (6 mg) administered using the IMITREX STATdose System is effective for the treatment of migraine. The efficacy and tolerability profiles of SC sumatriptan administered with this device are similar to those reported for SC sumatriptan administered with a conventional syringe.

A double-blind study of subcutaneous dihydroergotamine vs subcutaneous sumatriptan in the treatment of acute

migraine.

Winner P; Ricalde O; Le Force B; Saper J; Margul B
Palm Beach Headache Center, Fla, USA.
Arch Neurol (United States) Feb 1996, 53 (2) p180-4

OBJECTIVE: To assess the efficacy and tolerability of subcutaneous dihydroergotamine mesylate (DHE-45) vs subcutaneous sumatriptan succinate (Imitrex) for the treatment of acute migraine with or without aura.

DESIGN: Double-blind, randomized trial with parallel treatment arms.

SETTING: Clinics and private neurology practices.

SUBJECTS: Patients of either sex, with migraine with or without aura, between the ages of 18 and 65 years.

INTERVENTIONS: Patients with moderate or severe head pain were randomized to receive either 1 mg of subcutaneous dihydroergotamine mesylate or 6 mg of subcutaneous sumatriptan succinate. Patients rated head pain, functional ability, nausea, and vomiting at baseline and at 0.5, 1, 2, 4, and 24 hours after the injection. Presence or absence of headache at 3 hours was calculated from collected data. If pain persisted after 2 hours, a second injection of the same study medication was allowed, and self-ratings were repeated 30 and 60 minutes later. Follow-up data were collected at 24 hours.

MAIN OUTCOME MEASURES: Relief of head pain and recurrence of successfully treated headache.

RESULTS: There were 295 evaluable patients. At 2 hours, 73.1% of the patients treated with dihydroergotamine and 85.3% of those treated with sumatriptan had relief ($P = .002$). There was no statistical difference in headache relief between the groups at 3 or 4 hours. Headache relief was achieved by 85.5% of those treated with dihydroergotamine and by 83.3% of those treated with sumatriptan by 4 hours. By 24 hours 89.7% of dihydroergotamine-treated patients and 76.7% of sumatriptan-treated patients had relief ($P = .004$). Headache recurred within 24 hours after treatment in 45% of the sumatriptan-treated patients and in 17.7% of the dihydroergotamine-treated patients ($P < \text{or} = .001$).

CONCLUSIONS: Both sumatriptan and dihydroergotamine were effective in aborting migraine headaches. Headache recurrence was two and a half time as likely with sumatriptan as with dihydroergotamine.

Herbal products begin to attract the attention of brand-name drug companies.

Cottrell K
Can Med Assoc J (Canada) Jul 15 1996, 155 (2) p216-9

Many Canadians are interested in alternative medicine, and burgeoning public interest in herbal remedies has not gone unnoticed by Canada's drug companies. McNeil Consumer Products recently began selling a migraine prophylaxis made from the plant feverfew. Physicians who would like to see herbal medications subjected to outcome studies and quality-control standards, with evidence of risks and benefits being made available to consumers, welcome the interest the companies are showing. Meanwhile, physicians and pharmacists are trying to respond to consumer demand by increasing their own knowledge about herbal medications.

Long-time efficacy of cyclandelate and propranolol in prophylaxis of migraine following four months of treatment

Schellenberg R.; Schwarz A.; Niederberger U.; Bolsche F.; Schindler M.; Gerber W.-D.; Wedekind W.; Soyka D.
Dr. R. Schellenberg, Talstrasse 29, D-35625 Huttenberg Germany
Nervenheilkunde (Germany), 1997, 16/3 (183-187)

After a 4 months randomized double-blind study with cyclandelate versus propranolol all patients kept a miniaturized headache diary for one more year. Both duration of migraine attacks in hours and the number of additional analgetic medication were recorded monthly. Reduction of the duration of migraine attacks in the clinical responders of the cyclandelate treated patients remained nearly unchanged. In the propranolol responders the duration of migraine attacks in hours increased from the third month after finishing the medication and reached values comparable to those at the beginning of the active treatment. Intake of additional analgetic medication during the 1-year-follow-up was lower in the cyclandelate responders than in the propranolol-responders.

Cyclandelate can be described as an effective long-lasting drug in migraine prophylaxis.

Sumatriptan use in a large group-model health maintenance organization

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American Journal of Health-System Pharmacy (USA), 1996, 53/6 (633-638)

The outcomes of sumatriptan use at a health maintenance organization (HMO) were studied. The study was conducted during one year beginning immediately after sumatriptan was added to the formulary of a large group-model HMO. Subjects were included on the basis of drug-use evaluation criteria, a positive response to the first dose of sumatriptan (administered at the HMO by a nurse), and ability to participate in a telephone survey. Responders to the first dose were eligible to receive up to six doses of sumatriptan for home use. The telephone survey was designed to assess sumatriptan's effects on migraine headache and to capture data on quality of life, perceived problems with sumatriptan, and patient satisfaction. Patients who received sumatriptan between April and September 1993 were interviewed in late September 1993; patients who received sumatriptan between September and April 1994 were interviewed in late April 1994. Of 180 patients surveyed, 160 (89%) had evaluable responses. Migraine headache improved in two thirds of the patients. Sumatriptan was more effective than previously used agents in three fourths. The mean number of migraine headaches per patient per month decreased from 7.4 to 4.2. Quality-of-life indicators, such as time spent with friends, improved in three fourths. Eighty-three percent reported missing fewer days from work. Ninety percent said they would continue to take the drug, despite a 44% incidence of drug-related problems. There were no unexpected problems. A retrospective review showed that utilization of the HMO's resources was reduced with sumatriptan. Placing sumatriptan on an HMO's formulary led to favorable effects on the frequency and severity of migraine headache, patient quality-of-life indicators and productivity, and resource utilization by the organization.

The effect of sumatriptan on brain monoamines in rats

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Headache (USA), 1996, 36/1 (29-31)

Clinical data suggests that sumatriptan is effective in the acute treatment of migraine. The vascular effects of the drug have been invoked to explain this antimigraine efficacy. However, the effect of sumatriptan on brain monoamines has not previously been investigated. In order to study these hypothetical effects, we administered the drug to 24 male rats, subcutaneously, at three doses (0.3, 0.6, and 0.9 mg/kg of body weight), and 30 minutes later, all animals were decapitated. Dopamine, serotonin, and their metabolites 3,4 dihydroxyphenylacetic acid, 5-hydroxyindoleacetic acid, and homovanillic acid concentrations were measured in the frontal cortex, hypothalamus, striatum, and hippocampus, by high performance liquid chromatography. Plasma concentrations of the drug were also determined. The control group was treated with NaCl 0.9%, given subcutaneously. Sumatriptan, at the dose of 0.3 mg/kg did not alter the brain monoamine concentrations; however, at the dose of 0.6 mg/kg, sumatriptan decreased serotonin concentration in the hypothalamus and increased the turnover of dopamine and serotonin in the hypothalamus and striatum, while at the dose of 0.9 mg/kg, it augmented only the turnover of serotonin in the hypothalamus. No dose-dependent effect of the drug was found. This subcortical antidopaminergic and antiserotonergic effect of sumatriptan may be involved in its antimigraine action.

In vivo administration of propranolol decreases exaggerated amounts of serum TNF-alpha in patients with migraine without aura. Possible mechanism of action.

Covelli V; Munno I; Pellegrino NM; Marinaro MR; Gesario A; Massari F; Savastano S; Jirillo E

Acta Neurol (Napoli); 14(4-6):313-9 1992

Patients with migraine without aura (MWA) display elevated amounts of Tumor Necrosis Factor (TNF)-alpha in their sera. In this study in 18 patients with MWA the in vivo effect of propranolol, a beta blocker agent, was evaluated with regard to the TNF serum levels before and after treatment. Results show that in 9 out of 11 patients exaggerated serum concentrations of TNF reverted to normality after three months of therapy. Some hypotheses on the mechanisms of action of propranolol in terms of modulation of the immune response are formulated.

Concurrent use of antidepressants and propranolol: case report and theoretical considerations

Nemeroff CB; Evans DL
Biol Psychiatry; 18(2):237-41 1983

The therapeutic indications for propranolol have been steadily increasing in recent years. Propranolol and other beta-adrenergic blocking agents are now generally acknowledged to be helpful in the management of hypertension, certain cardiac arrhythmias, migraine, essential tremor, angina pectoris, and most recently, immediately after myocardial infarction (Frishman, 1981; Norwegian Multicenter Study Group, 1982). Because of the myriad clinical settings in which propranolol has been found to be of benefit, the interactions of these drugs with other commonly utilized pharmacological agents is of great pragmatic interest. In this report we describe the successful concomitant clinical use of propranolol and an antidepressant drug. This finding is also of interest because of recent theories concerning the mechanism of action of antidepressant drugs. Because propranolol readily penetrates into the CNS, it blocks beta-adrenergic receptors in both the periphery and the CNS (Weiner, 1980). Much attention has been focused recently on the effects of long-term antidepressant therapy on central beta-adrenergic receptors in the brain as a possible mechanism of action of these drugs. The concurrent use of propranolol and an antidepressant drug in the patient described in this report did not attenuate the therapeutic effects of the antidepressant.

Nocturnal melatonin excretion is decreased in patients with migraine without aura attacks associated with menses

Brun J.; Claustrat B.; Saddier P.; Chazot G.
Cephalalgia (Norway), 1995, 15/2 (136-139)

Nocturnal melatonin excretion was studied throughout a complete menstrual cycle in 10 women with migraine without aura attacks associated with menses and 9 women controls. Urine melatonin was determined by radioimmunoassay. The mean nocturnal melatonin excretion throughout the cycle was significantly lower in the migraine patients than in controls. In the control group, melatonin excretion increased significantly from the follicular to the luteal phase, whereas no difference was observed in the migraine group. Results are discussed in view of the role of the pineal gland in the organization of biological rhythms and homeostasis in relation to environmental conditions.

Urinary melatonin excretion throughout the ovarian cycle in menstrually related migraine

Murialdo G.; Fonzi S.; Costelli P.; Solinas G.P.; Parodi C.; Marabini S.; Fanciullacci M.; Polleri A.
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Cephalalgia 1994 Jun;14(3):205-9

Nocturnal urinary melatonin excretion was significantly decreased throughout an ovarian cycle in 12 migraine without aura patients compared to 8 healthy controls. Normal increases in urinary melatonin excretion during the luteal phase was less pronounced in the migraine patients. Melatonin excretion was further decreased during headache. The data indicate impaired pineal function in migraine.

Nocturnal plasma melatonin levels in migraine: A preliminary report

Claustrat B, Loisy C, Brun J, Beorchia S, Arnaud JL, Chazot G
Headache (United States) Apr 1989, 29 (4) p242-5

We determined by radioimmunoassay plasma melatonin levels on blood samples drawn at 11 p.m. in migraine patients and control subjects. Ninety-three cephalalgic outpatients (75 females, 18 males) were compared to a control group (24 females, 22 males) matched according to age. Patients were divided into subgroups presenting common migraine (n = 38); ophthalmic migraine (n = 12); and tension headache associated with ophthalmic or common migraine (n = 24), and associated depressive status (n = 19). Statistical analysis revealed a decrease in plasma melatonin levels for the entire migraine population, compared to the control one, and a heterogeneity in both controls and patients; this heterogeneity was found mainly in the depressive and tension headache subgroups. When the migraine population - from which the depressive patients were excluded - was divided into male and female subgroups, a decrease in plasma melatonin levels was observed only for the female subgroups. Results are discussed with reference to the role of the pineal gland in the synchronization of the organism with the environmental conditions.

Octopamine and some related noncatecholic amines in invertebrate nervous systems

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Int. Rev. Neurobiol. (USA), 1976, Vol.19 (173-224)

In addition to the major monoamines (dopamine, noradrenaline, serotonin) there exists in the nervous tissue of all species examined a group of monoamines described as exotic amines, trace amines or microamines. Among the endogenous microamines found in the mammalian brain are beta phenylethylamine, phenylethanolamine, m and p tyramine, octopamine and tryptamine. Despite their very low concentrations, microamines are interesting for several reasons: they are heterogeneously distributed within the brain; they are present in the same subcellular fraction as catecholamines and 5 HT; they have a high turnover rate; they release and/or replace catecholamines from storage sites and block reuptake; they may be excreted abnormally in the urine of patients with migraine, Parkinson's disease, schizophrenia and depression; some of them are behaviorally active. Analytical procedures for micramines are described and their biosynthesis and catabolism discussed. Out of them octopamine proved to be the most prospective candidate as a transmitter in the invertebrate nervous system as it fulfilled six of the seven criteria for identification of chemical transmitters (it has been shown to be present in neurons; presence of synthetic enzymes as well as precursors and intermediates has been demonstrated; it was released during nerve stimulation; exogeneous octopamine mimics the effect of the released transmitter; pharmacological agents interact with both the synaptically released transmitter and octopamine in an identical manner. The physiological means of inactivation and/or removal from the synapse, however, remain unknown). Among the other microamines, there is little evidence for a role in invertebrates.

The co-occurrence of multiple sclerosis and migraine headache: the serotonergic link.

Sandyk R; Awerbuch GI

Int J Neurosci (England) Jun 1994, 76 (3-4) p249-57

The occurrence of migraine headaches in patients with multiple sclerosis (MS) has been recognized for quite some time but the significance of this association to the pathogenesis of MS largely has been ignored. Several reports have documented that migraine headaches may occur during exacerbation of symptoms and may even herald the onset of relapse in MS. We present three MS patients in whom migraine headaches developed during a period of relapse. As migraine has been linked to changes in serotonin (5-HT) functions, the emergence of migraine headaches coincident with the onset of relapse implicates dysregulation of the 5-HT system in the pathophysiology of MS. This hypothesis is plausible considering the evidence that MS patients are serotonergically depleted and that 5-HT is involved in maintaining the integrity of the blood brain barrier, disruption of which is believed to occur in the initial stages of exacerbation of MS symptoms. Furthermore, this hypothesis may have potential therapeutic implications in the treatment of exacerbations of MS and possibly in the prevention of relapse in the disease.

Urinary melatonin excretion throughout the ovarian cycle in menstrually related migraine

Murialdo G; Fonzi S; Costelli P; Solinas GP; Parodi C; Marabini S; Fanciullacci M; Polleri A

Cephalalgia (Norway) Jun 1994, 14 (3) p205-9

Nocturnal urinary melatonin excretion was significantly decreased throughout an ovarian cycle in 12 migraine without aura patients compared to 8 healthy controls. Normal increases in urinary melatonin excretion during the luteal phase was less pronounced in the migraine patients. Melatonin excretion was further decreased during headache. The data indicate impaired pineal function in migraine.

The influence of the pineal gland on migraine and cluster headaches and effects of treatment with picoTesla magnetic fields.

Sandyk R

Int J Neurosci (England) Nov-Dec 1992, 67 (1-4) p145-71

For over half a century the generally accepted views on the pathogenesis of migraine were based on the theories of Harold Wolff implicating changes in cerebral vascular tone in the development of migraine. Recent studies, which are based on Leao's concept of spreading depression, favor primary neuronal injury with secondary involvement of the cerebral circulation. In contrast to

migraine, the pathogenesis of cluster headache (CH) remains entirely elusive. Both migraine and CH are cyclical disorders which are characterised by spontaneous exacerbations and remissions, seasonal variability of symptoms, and a relationship to a variety of environmental trigger factors. CH in particular has a strong circadian and seasonal regularity. It is now well established that the pineal gland is an adaptive organ which maintains and regulates cerebral homeostasis by "fine tuning" biological rhythms through the mediation of melatonin. Since migraine and CH reflect abnormal adaptive responses to environmental influences resulting in heightened neurovascular reactivity, I propose that the pineal gland is a critical mediator in their pathogenesis. This novel hypothesis provides a framework for future research and development of new therapeutic modalities for these chronic headache syndromes. The successful treatment of a patient with an acute migraine attack with external magnetic fields, which acutely inhibit melatonin secretion in animals and humans, attests to the importance of the pineal gland in the pathogenesis of migraine headache. (242 Refs.)

Is migraine due to a deficiency of pineal melatonin?

Toglia JU
Ital J Neurol Sci (Italy) Jun 1986, 7 (3) p319-23

Recent clinical observations favor the theory that migraine is caused by a primary injury of cerebral neurons with secondary involvement of intracranial and extracranial blood vessels. The primary injury is attributed to disruption of cerebral neurotransmitters and particularly the neuroadrenergic and serotonergic systems. These theories have not explained the importance of environmental factors, which so frequently trigger migraine. The author suggests that the pineal gland, which is outside the CNS unprotected by blood brain barrier and sensitive to external stimuli, could act as the intermediate causative factor of migraine, via a derangement of melatonin. (47 Refs.)

Melatonin in humans physiological and clinical studies.

Wetterberg L
J Neural Transm Suppl (Austria) 1978, (13) p289-310

Studies are reported of the variation of melatonin in serum, plasma urine and cerebrospinal fluid in normal subjects and in patients with various diseases. The diurnal variation of plasma and urine melatonin found in healthy controls on a regular dark-sleep pattern persisted when the subjects slept in light. The effect of sleep deprivation and of rapid light exposure at night is reported. There was a correlation between melatonin in morning urine and plasma at 2 a.m. Four hours of extended darkness in the morning as well as a 9-hour shift of sleep and activity cycles following travel affected the melatonin rhythm. The night increase in plasma melatonin preceded both the cortisol and prolactin rise. A single oral dose of 4.3×10^5 nmol of melatonin given to a 44-year-old healthy male gave a peak plasma value of 624 nmol/l after 30 min. Plasma melatonin was not affected by electroconvulsive therapy, TRH-injection, L-Dopa or bromoergocryptine orally. Patients with alcoholism, migraine, postoperative pinealoma, panhypopituitarism, hereditary dystonia and schizophrenics on propranolol exhibited a decreased amplitude of their diurnal rhythm of melatonin. Two patients with pituitary tumors had occasional high levels of plasma melatonin. The change in melatonin secretion in human is apparently controlled by a mechanism which is at least partly influenced by environmental lighting conditions, drugs and different disease states. (27 refs.)

FEVERFEW (Tanacetum pathenium):

Feverfew appears to work in the treatment and prevention of migraine headaches by inhibiting the release of blood vessel dilating substances from platelets (serotonin and histamine), inhibiting the production of inflammatory substances (leukotrienes, serine proteases, etc.), and re-establishing proper blood vessel tone. Commercial sources providing assurance of botanical identity and minimum required level of parthenolides are needed (Awang DVC. Feverfew. Car Pharm J 122:266-70, 1989).

In vitro Study: Feverfew was found to contain a factor that inhibits prostaglandin synthesis, but differs from salicylates by not inhibiting cyclo-oxygenase by prostaglandin (PG) synthase. "The ability of feverfew to inhibit PG production may account for its effectiveness as a herbal remedy in conditions responding to acetylsalicylate and like-acting drugs" (Collier HOJ, Butt NM, McDonald-Gibson WJ, Saeed SA. Extract of feverfew inhibits prostaglandin biosynthesis. Letter. Lancet October 25, 1980).

The dosage of feverfew used in one double-blind study was one capsule containing 25 mg of the freeze-dried pulverized leaves twice daily; in another double-blind study it was one capsule containing 82 mg of dried powdered leaves once daily. While these low dosages may be effective in preventing an attack, a higher dose (1 to 2 grams) may be necessary during an acute attack.

Note: The efficacy of feverfew is dependent upon adequate levels of parthenolide, the active ingredient. (The preparations used in

successful clinical trials have a parthenolide content of 0.4-0.66%.)

Animal Ex vivo Study: Extracts of fresh feverfew caused a dose- and time dependent, irreversible inhibition of the contractile response of rabbit aortic rings to all receptor-acting agonists tested. The presence of potentially SH reacting parthenolide and other sesquiterpene alpha-methylenebutyrolactones in, these extracts, and the close parallelism of pure parthenolide, suggest that the inhibitory effects are due to these compounds. Extracts of the dry leaves were not inhibitory and actually caused potent and sustained contractions of aortic smooth muscle; these extracts were found to be devoid of parthenolide or butyrolactones (Barsby RWJ, Salan U, Knight BW, Hoult JRS. Feverfew and vascular smooth muscle: Extracts from fresh and dried plants show opposing pharmacological profiles, dependent upon sesquiterpene lactone content. *Planta Medica* 59:20-5, 1993).

Chemical Analysis: The parthenolide content of over 35 different commercial preparations of feverfew was determined by bioassay, 2 HPLC methods, and NMR. The results indicate a wide variation in the amts. of parthenolide in commercial preparations. The majority of products contained no parthenolide or only traces (Heptinstall S et al. Parthenolide content and bioactivity of feverfew (*Tanacetum parthenium* (L.) Schultz-Bip.). Estimation of commercial and authenticated feverfew products. *J Pharm Pharmacol* 44:391-5, 1992).

WARNING: No long-term toxicity studies have been conducted. While feverfew is extremely well-tolerated and no serious side effects have ever been reported, chewing the leaves can result in small ulcerations in the mouth and swelling of the lips and tongue in about 10% of users (Awang DVC. Feverfew. *Can Pharm J* 122:266-70, 1989).

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