

Chapter 117

Headache Associated with Acute Substance Use or Exposure

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INTRODUCTION

Since Hippocrates (460 B.C.) and Cornelius Celsus (25–50 A.D.), we have known of substances that are able to induce headaches, especially in susceptible persons. The substances involved are many: drugs, chemical products, alcoholic drinks, vapors, and others. Drugs are the most widely cited, and their effects have been studied the most thoroughly. The descriptions of headaches induced by substances are generally not very precise. The headaches are often generalized, persistent, and at times throbbing, and increase in intensity with increased dosage of substances.

In particular, as noted in the first edition of the International Classification of Headache Disorders (ICHD) (27), “migraineurs are physiologically and perhaps psychologically hyper-responsive to a variety of internal and external stimuli. Alcohol, food and food additives, chemical and drug ingestion... have all been reported to provoke or activate migraine in susceptible individuals.” Headaches attributed to substances reflect the chemical sensitivity of the headache-prone brain, and migraine is a state of hypersensitivity to physical and chemical exposures.

In evaluating patients with headaches related to substance exposures, the first question is whether the headaches are primary or secondary. The ICHD-II (28) gives qualitative guidance on this issue: when a pre-existing headache disorder occurs in temporal relation to substance exposure, it may be coded as a primary or secondary headache. The factors in favor of secondary causation include close temporal association, marked worsening of pre-existing headache, “very good evidence” that the substance can aggravate the primary headache, and improvement of headache on termination of the substance.

EPIDEMIOLOGY

There are no population-based prospective epidemiologic data on the incidence of substance-induced headaches, but certain substances have been studied (4,23,62). The major study was the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring of 27 countries that gathered 10,506 reports of drug-induced headaches from 1972 to 1987. Of these headaches, 9733 were unclassified headaches, 611 were migraine-type headaches or worsening of a pre-existing migraine, and 162 were due to intracranial hypertension. The 10 most reported drugs associated with headaches were indomethacin, nifedipine, cimetidine, atenolol, trimethoprim-sulphamethoxazole, zimetidine, glyceryl trinitrate, isosorbide dinitrate, zomepirac, and ranitidine. The majority of the drugs were nonsteroidal antiinflammatory drugs (NSAIDs), peripheral vasodilators, calcium channel blockers, β -receptor blockers, histamine receptor blockers, or angiotensin-converting enzyme (ACE) inhibitors. Oral contraceptives were the most common cause of migraine. Other common precipitants of migraine-type headaches were atenolol, cimetidine, danazol, diclofenac, ethinylestradiol, indomethacin, nifedipine, and ranitidine. Tetracyclines, isotretinoin, and trimethoprim-sulphamethoxazole were the most frequently reported as causing intracranial hypertension (61,62,63).

PATHOPHYSIOLOGY

Substance-induced headache has variable mechanisms. Vasodilation is the oldest concept (77). Schumacher et al. (71) showed that intracranial vasodilation was responsible for headaches induced by histamine and that trigeminal

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nerve section blocked the occurrence of histaminic headache but only along the trigeminal nerve. Dhuna et al. described noradrenergic alteration in vessel tone due to cocaine (14); however, the drugs most frequently implicated in the origin of headaches do not penetrate the blood-brain barrier. Toth speculated that “cocaine- and amphetamine-induced headaches may relate to a rapid cocaine surge, leading to a rapid block of presynaptic norepinephrine reuptake with potent sympathomimetic effects and acute vasoconstriction. Prolonged cocaine use may lead to secondary presynaptic serotonin depletion, leading to increased severity of headache with cocaine use” (83).

Headaches also occur in situations associated with cerebral edema, such as hypertensive encephalopathy (75,79) and mountain sickness (38). Drugs that cause some degree of cerebral edema and intracranial hypertension include beclomethasone, cimetidine, indomethacin, isotretinoin, monocycline, methylprednisolone, nalidixic acid, nitrofurantoin, prednisolone, tamoxifen, tetracycline, and trimethoprim-sulphamethoxazole (4,23).

However, NSAIDs, hormones, and other substances do not have vascular effects and do not cause cerebral edema. Since medications such as cimetidine, indomethacin, and ranitidine can cause headache, some substance-induced headaches may be the result of a primary cerebral neuronal action, possibly triggering a vascular reaction, which by its nature or intensity may bring on the headache. The possibility of substance-use headaches as a result of direct chemically mediated irritative effects on trigeminal afferents has also been suggested (23).

Toth speculated that “peripheral sensitization with altered neurotransmitter sensitivity may play a role, as central sensitization may occur due to certain substances” (83). Post and Silberstein noted that c-fos is immediately expressed after medication delivery, which may be a signal of altered pain modulation (65).

CAUSATION

Headaches can be induced by acute or delayed exposure to a substance, or from its withdrawal. The immediate headache is closely temporally related to the exposure, while the delayed headache occurs many hours to days after the immediate headache has resolved (Table 117-1).

A causal relationship between headache and acute use or exposure to a specific substance often is difficult to determine and requires well-conducted controlled studies.

It has been stated that “a diagnosis of *Headache attributed to a substance* usually becomes definite only when the headache resolves or greatly improves after termination of exposure to the substance... The fact that these stimuli are associated with headache does not prove causation or eliminate the need to consider other aetiologies... Because common events happen commonly, the association between a headache and an exposure to a substance

TABLE 117-1 2004 International Classification of Headache Disorders (ICHD-II) Classification of Headache Attributed to a Substance or Its Withdrawal

8.1 Headache induced by acute substance use or exposure
8.1.1 Nitric oxide (NO) donor-induced headache
8.1.1.1 Immediate NO donor-induced headache
8.1.1.2 Delayed NO donor-induced headache
8.1.2 Phosphodiesterase (PDE) inhibitor-induced headache
8.1.3 Carbon monoxide-induced headache
8.1.4 Alcohol-induced headache
8.1.4.1 Immediate alcohol-induced headache
8.1.4.2 Delayed alcohol-induced headache
8.1.5 Headache induced by food components and additives
8.1.5.1 Monosodium glutamate-induced headache
8.1.6 Cocaine-induced headache
8.1.7 Cannabis-induced headache
8.1.8 Histamine-induced headache
8.1.8.1 Immediate histamine-induced headache
8.1.8.2 Delayed histamine-induced headache
8.1.9 Calcitonin gene-related peptide (CGRP)-induced headache
8.1.9.1 Immediate CGRP-induced headache
8.1.9.2 Delayed CGRP-induced headache
8.1.10 Headache as an acute adverse event attributed to medication used for other indications
8.1.11 Headache induced by other acute substance use or exposure
8.2 Medication-overuse headache (not covered in this chapter)
8.3 Headache as an adverse event attributed to chronic medication (not covered in this chapter)
8.4 Headache attributed to substance withdrawal (not covered in this chapter)

From ref. 22: Giuseffi V, Michel W, Siegel PZ, et al. Symptoms and disease associations in idiopathic intracranial hypertension (pseudo-tumor cerebri) a case-control study. *Neurology* 1991;41:239-244.

may be mere coincidence. Headache can occur just on the basis of chance.” (62).

The ICHD-II lists the following as contributing to headache after acute exposure (28) (Table 117-2). *Immediate* acute substance-induced headaches (Table 117-3) and *delayed* substance-induced headaches (Table 117-4) often are different. Therefore, they are described separately.

TABLE 117-2 Substances Causing Headache After Acute Exposure

8.1.1 Nitric oxide (NO) donor (immediate and delayed)
8.1.2 Phosphodiesterase (PDE) inhibitor
8.1.3 Carbon monoxide
8.1.4 Alcohol (immediate and delayed)
8.1.5 Food components and additives (e.g., monosodium glutamate [MSG])
8.1.6 Cocaine
8.1.7 Cannabis
8.1.8 Histamine-induced (immediate and delayed)
8.1.9 Calcitonin gene-related peptide (CGRP) (immediate and delayed)

TABLE 117-3 Immediate Headaches Induced by Acute Substance Use or Exposure (8.1)

IHS Diagnosis	8.1.1	8.1.2	8.1.3	8.1.4.1	8.1.5	8.1.6	8.1.7	8.1.8.1	8.1.9.1
Headache-associated substance	NO donor	PDE inhibitors	Carbon monoxide	Alcohol	Food additives	Cocaine	Cannabis	Histamine	CGRP
Headache onset	Within 10 minutes	Within 5 hours	Within 12 hours	Within 3 hours	Within 12 hours (MSG 1 hour)	Within 1 hour	Within 12 hours	Within 10 minutes	Within 10 minutes
Headache postexposure resolution	Within 1 hour	Within 72 hours	Within 72 hours	Within 72 hours	Within 72 hours	Within 72 hours	Within 72 hours	Within 1 hour	Within 1 hour
Headache features	<ul style="list-style-type: none"> ▶ Bilateral ▶ Frontotemporal ▶ Pulsating ▶ ↑with activity 	<ul style="list-style-type: none"> ▶ Bilateral ▶ Frontotemporal ▶ Pulsating ▶ ↑with activity 	<ul style="list-style-type: none"> ▶ Depends on extent of exposure 	<ul style="list-style-type: none"> ▶ Bilateral ▶ Frontotemporal ▶ Pulsating ▶ ↑with activity 	<ul style="list-style-type: none"> ▶ Bilateral ▶ Frontotemporal ▶ Pulsating ▶ ↑with activity 	<ul style="list-style-type: none"> ▶ Bilateral ▶ Stabbing or pulsating ▶ "Pressure" 	<ul style="list-style-type: none"> ▶ Bilateral ▶ Frontotemporal ▶ Pulsating ▶ ↑with activity 	<ul style="list-style-type: none"> ▶ Bilateral ▶ Frontotemporal ▶ Pulsating ▶ ↑with activity 	

CGRP = calcitonin gene-related peptide; MSG, monosodium glutamate; NO, nitric oxide; PDE, phosphodiesterase. From ref. 22: Giuseffi V, Michel W, Siegel PZ, et al. Symptoms and disease associations in idiopathic intracranial hypertension (pseudo-tumor cerebri) a case-control study. *Neurology* 1991;41:239-244.

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TABLE 117-4 Delayed Headaches Induced by Acute Substance Use or Exposure

<i>IHS</i> Diagnosis	8.1.1.2	8.1.4.2	8.1.8.2	8.1.9.2
Headache-associated substance	NO donor	Alcohol	Histamine	CGRP
Headache onset postexposure	▶Migraineurs and tension-type HA: 5–6 hours ▶Cluster HA: 1–2 hours	After alcohol cleared from the blood	▶Migraineurs and tension-type HA: 5–6 hours ▶Cluster HA: 1–2 hours	▶Migraineurs and tension-type HA: 5–6 hours ▶Cluster HA: 1–2 hours
Headache resolution postexposure	Within 72 hours	Within 72 hours	Within 72 hours	Within 72 hours
Headache features	▶Migraineurs: migraine without aura ▶Tension-type HA: tension-type HA ▶Cluster HA: cluster HA	▶Bilateral ▶Frontotemporal ▶Pulsating ▶↑with activity	▶Migraineurs: migraine without aura ▶Tension-type HA: tension-type HA ▶Cluster HA: cluster HA	▶Migraineurs: migraine without aura ▶Tension-type HA: tension-type HA ▶Cluster HA: cluster HA

CGRP, calcitonin gene-related peptide; HA, headache.
 From ref. 22: Giuseffi V, Michel W, Siegel PZ, et al. Symptoms and disease associations in idiopathic intracranial hypertension (pseudo-tumor cerebri) a case-control study. *Neurology* 1991;41:239–244.

IMMEDIATE HEADACHES INDUCED BY SUBSTANCES

Nitric Oxide Donor

International Headache Society (IHS) code and diagnosis: 8.1.1.1 Immediate nitric oxide donor-induced headache

WHO code: G44.400

This type of headache includes those associated with the contact or use of nitroglycerine (NTG), (nitroglycerine headache or dynamite headache) and nitrates or nitrites (hot-dog headache).

Nitroglycerine

Nitroglycerine serves as a nitric oxide (NO) donor and its ingestion causes immediate headache in most people. The headaches are nonspecific and may be due to cyclic guanine monophosphate (cGMP) activation (74,82).

NTG was first recognized to induce headache after observing complaints of workers in factories manufacturing explosives (e.g., dynamite) (72). It was later noted that the minimum dose of NTG needed to bring on a headache could be rapidly reduced while simultaneously consuming alcohol (72). Also, migraine sufferers are known to be more susceptible to NTG, as are cluster headache sufferers during cluster episodes (16).

Nitrates and Nitrites

Some people describe variable intensity headaches minutes or hours after eating sausages or other cured meats and fish such as frankfurters, bacon, ham, salami, pepperoni, corned beef, pastrami, and lox. This type of head-

ache has become known as the “hot-dog headache” and is related to the nitrates or nitrites that are added to foods for food coloring, to impart a cured flavor, and to prevent botulism (30). Nitrates normally become toxic only under conditions in which they are, or may be, reduced to nitrites (56). Toxicity of nitrites is due primarily to their interaction with blood pigment to produce methemoglobinemia (3).

Authorities limit the use of nitrites in cured meat (to 200 mg/kg), and the storing and cooking of the food further reduces the nitrite content (to 50 to 130 mg/kg) (30,56). Other substances in the same group, such as cyclandelate, dipyridamole, erythryl tetranitrate, isosorbide dinitrate, mannitol hexanitrate, nimodipine, papaverine hydrochloride, pentaerythritol tetranitrate, tolazoline hydrochloride, and trolnitrate phosphate, can also bring on nitrite headaches, particularly in susceptible patients (56).

Immediate NO donor-induced headache diagnostic criteria (ICHD-II) are as follows:

- A.** Headache with at least one of the following characteristics and fulfilling criteria C and D:
 1. Bilateral
 2. Frontotemporal location
 3. Pulsating quality
 4. Aggravated by physical activity
- B.** Absorption of NO donor
- C.** Headache develops within 10 minutes after absorption of NO donor.
- D.** Headache resolves within 1 hour after release of NO has ended.

Phosphodiesterase Inhibitor

IHS code and diagnosis: 8.1.2 Phosphodiesterase (PDE) inhibitor-induced headache

WHO code: G44.40

PDE-induced headache is migrainous in quality, except for being bilateral, and monophasic in temporal sequence, unlike NO donor headache. PDEs are enzymes that metabolize cGMP and cyclic adenosine monophosphate (cAMP), and the erectile dysfunction medications such as sildenafil, vardenafil, and tadalafil are examples. They inhibit cGMP-specific PDE5, thereby increasing levels of cGMP. Since cGMP likely mediates the nonspecific immediate headaches post-NTG, and because PDE-induced headache is more common in migraine similar to NO-induced headache, it is plausible that PDE-induced headache is NO-mediated. According to prescribing information, headache occurs in between 11% and 15% of patients treated with tadalafil, and in 16% of sildenafil patients, compared to about 5% with placebo (64). PDE-induced headache occurs in 14% of migraine patients.

PDE inhibitor-induced headache diagnostic criteria (ICHD-II) are as follows:

- A. Headache with at least one of the following characteristics and fulfilling criteria C and D:
 1. Bilateral
 2. Frontotemporal location
 3. Pulsating quality
 4. Aggravated by physical activity
- B. A single dose of a PDE inhibitor has been given.
- C. Headache develops within 5 hours of PDE inhibitor intake.
- D. Headache resolves within 72 hours.

Carbon Monoxide

IHS code and diagnosis: 8.1.3 Carbon monoxide-induced headache

WHO code: G44.401

Previously used term: warehouse workers' headache

Headache caused by carbon monoxide (CO) is often a dull, continuous bilateral discomfort, with character and intensity related to the severity of CO intoxication (Table 117-5). Slight headache or dizziness may occur in heavy smokers or those using gas for cooking food or exposed to car exhaust (29,50,55,86,88).

CO-induced headache diagnostic criteria (ICHD-II) are as follows:

- A. Bilateral and/or continuous headache, with quality and intensity that may be related to severity of carbon monoxide intoxication, fulfilling criteria C and D.
- B. Exposure to CO.
- C. Headache develops within 12 hours of exposure
- D. Headache resolves within 72 hours after elimination of CO.

Alcohol

IHS code and diagnosis: 8.1.4.1 Immediate alcohol-induced headache

TABLE 117-5 Relationship Between Carbon Monoxide (CO) Blood Levels, Headache Type and Severity, and Emergence of Associated Symptoms

CO level (%)	Headache Type and Severity	Associated Symptoms
10–20	Dull, mild	None
>20–30	Moderate, pounding	Irritability
>30–40	Severe, pounding	Nausea, vomiting, blurred vision
>40–50		Confusion
>50–60		Coma
80		Death

CO, Carbon monoxide.

From ref. 22: Giuseffi V, Michel W, Siegel PZ, et al. Symptoms and disease associations in idiopathic intracranial hypertension (pseudo-tumor cerebri) a case-control study. *Neurology* 1991;41:239–244.

WHO code: G44.83

Short description: It is the immediate headache associated with the single ingestion of alcohol-containing drinks, foods, or drugs.

Immediate alcohol-induced headache, or cocktail headache, generally occurs 30 to 45 minutes after the consumption of alcohol, which corresponds to the time needed for the alcohol to be fully absorbed (13,21,57) (Table 117-3). It is rarer than the delayed headache (Table 117-4).

Alcohol has little or no effect on vascular smooth muscle or cerebral blood flow (62), so that the headache is probably not brought on by intra- or extracranial vasodilation. Instead, alcohol impairs cerebral autoregulation (1) and depresses cerebral serotonin turnover, which may be an underlying mechanism for the headache (53,54). Also, hypomagnesemia or alcohol additives may participate in inducing the headache. Combining alcohol with other substances such as monoamine oxidase inhibitors, tyramine, disulfiram, metronidazole, furazolidone, chloramphenicol and moxalactam disodium, tolbutamide, or chlorpropamide may cause headache (62,87).

Food Components and Additives

IHS code and diagnosis: 8.1.5 Headache induced by food components and additives

WHO code: G44.4

Previously used term: Dietary headache

The diagnostic criteria for headache induced by food components and additives (ICHD-II) are as follows:

- A. Headache with at least one of the following characteristics and fulfilling criteria C and D:
 1. Bilateral
 2. Frontotemporal location
 3. Pulsating quality
 4. Aggravated by physical activity

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- B. Ingestion of a minimum dose of food component or additive.
- C. Headache develops within 12 hours after substance intake.
- D. Headache resolves within 72 hours after single intake.

Monosodium Glutamate

IHS code and diagnosis: 8.1.5.1 Monosodium Glutamate Induced Headache

WHO code: G44.401

Previously used term: Chinese restaurant syndrome

Monosodium glutamate (MSG) is a substance that is used as a flavor enhancer in Chinese cooking, especially in soy sauce (36,52,89). Also, capsules used in placebo studies contain MSG-like substances and may cause headache (80).

Susceptible people describe a hot flush in the chest, neck, and shoulders, abdominal discomfort associated with tightening of the chest and face, and a bifrontal or bitemporal dull or burning (occasionally pulsating) headache that occurs 20 to 25 minutes after consumption of Chinese food (25,36,37,52,69). MSG has become far more prevalent in canned, packaged, and prepared foods under the labels of flavor, natural flavor, or hydrolyzed vegetable protein (HVP) additives (69,70,73). The Chinese restaurant syndrome was studied in a general population in which a 12.8% prevalence of one or more symptoms of this syndrome was found (5,25,68).

Kenny concluded that large doses (>150 mL) or high concentrations (3.33%) of MSG will provoke a variety of sensations in 32% of a tested population compared with placebo (36), but at a level of 1.5% only a few individuals will be affected (81). Oral MSG can produce symptoms in approximately 20 minutes with a dosage of 3 g or less, the MSG content of 200 mL of wonton soup. The consumption of food with MSG delays its absorption, while simultaneous consumption of alcohol may exacerbate symptoms.

Glutamate from MSG is present in high concentrations throughout the whole body and is synthesized in the brain and retina. The exact mechanism of MSG-induced headache is unclear, but Merritt and Williams (52) found that a direct vasoconstrictor effect was obtained with high doses. Another possible mechanism of action of MSG is the activation of the NO-mediated neurotransmission pathway with NO release in endothelial cells, which in turn act on neighboring vascular smooth muscle cells to induce vasodilation (52). Administration of MSG in rodents caused degeneration of neurons in the retina and hypothalamus, suggesting that MSG-delivered glutamate is a neurotoxic substance (31,56,69). Since glutamate has been implicated in migraine, and AMPA-kainate glutamate receptor antagonists have been found to be effective in terminating

migraine in proof of concept studies, the glutamate link seems most plausible (52).

MSG-induced headache diagnostic criteria (ICHD-II) are as follows:

- A. Headache with at least one of the following characteristics and fulfilling criteria C and D:
 1. Bilateral
 2. Frontotemporal location
 3. Aggravated by physical activity
- B. Ingestion of MSG.
- C. Headache develops within 1 hour after MSG ingestion.
- D. Headache resolves within 72 hours after single intake.

Other Substances

Phenylethylamine, Tyramine, and Aspartame

Phenylethylamine is a substance found in various foods such as chocolate and cacao (48).

Tyramine is an amine derived from tyrosine, first extracted from cheese at the beginning of the century. Tyramine causes arterial hypertension and, perhaps, headaches when ingested (5,76). In 1968, Hannington and Harper found this substance in foods mentioned by patients with dietary migraine (26).

Aspartame is a dipeptide sweetener 180 to 200 times sweeter than sugar, which some have described as causing headache (10). It is worth citing an important study in which it was shown that "capsules... which may include hydrolyzed animal protein [OR], (partially) hydrolyzed vegetable protein (PHVP), known to cause migraine... may give headaches to... migraine patients that are similar to those [that they experience] from foods. This would explain some of the headaches of patients from placebos" (80). The double-blind test and the repeatability of the time measurements demonstrated the validity of the experiments.

However, after extensively reviewing published data, the 2004 IHS classification subcommittee on substance-induced headache concluded that "the headache-inducing potential of phenylethylamine, tyramine, and aspartame" is not sufficiently validated (28).

Cocaine

IHS code and diagnosis: 8.1.6 Cocaine-induced headache
WHO code: G44.83

Headaches can occur as a consequence of the use of several illicit drugs such as central nervous system (CNS) stimulants (amphetamines, cocaine, designer drugs), barbiturates, sedatives, or opiates. The headaches may be associated either with acute use or chronic use and occur during withdrawal from these substances. Here, we will only deal with immediate headaches induced by the acute use of illicit drugs.

Cocaine leads to a rapid block of presynaptic norepinephrine reuptake with potent sympathomimetic effects and acute constriction of vascular smooth muscle and produces a migrainelike headache usually with a benign course (12,18,20,66,85). Acute neurologic complications arising from cocaine include generalized or partial epileptic seizures, ischemic or hemorrhagic strokes, visual loss caused by retinal artery occlusion or optic neuropathy, extrapyramidal symptoms (tics, dystonia), cardiac events (myocardial infarction, dysrhythmias, aortic dissection), pregnancy disturbances (preeclampsia or eclampsia), psychiatric disturbances (agitation, anxiety, depression, psychosis, paranoia, and suicidal ideation) and headaches (18,34,45,46,51,66,84,85). Cocaine may occasionally trigger a syndrome that resembles hemiplegic migraine (47). Cocaine-induced headaches are frequent, begin immediately after drug ingestion, and are usually not associated with nervous system pathology. If prolonged and accompanied by focal neurologic signs, cocaine headaches are often due to hemorrhagic or ischemic stroke or vasculitis (11,46,47). However, there does not seem to be any correlation between the previous use, the amount, the route of administration, and the appearance of neurological complications (11). The growing use of an alkaloid form of cocaine prepared with sodium bicarbonate (crack cocaine), which is cheaper, fast-acting, and highly potent, frequently provokes significant adverse effects (sometimes lethal when it is prepared along with toxic solvents), including ischemic or hemorrhagic events and headaches (9,11,47,66). The mechanism of these headaches is largely unknown but may be related to the sympathomimetic or vasoconstrictive effects of cocaine (12,41).

Cocaine-induced headache diagnostic criteria (ICHD-II) are as follows:

- A. Headache with at least one of the following characteristics and fulfilling criteria C and D:
 - 1. Bilateral
 - 2. Frontotemporal location
 - 3. Pulsating quality
 - 4. Aggravated by physical activity
- B. Use of cocaine.
- C. Headache develops within 1 hour after cocaine use.
- D. Headache resolves within 72 hours after single intake.

Cannabis

IHS code and diagnosis: 8.1.7 Cannabis-induced headache

WHO code: G44.83

Marijuana is a drug prepared by drying the flowering tops of plants of *Cannabis sativa*. Its medicinal use began in India 1000 B.C. and in Western medicine in the 19th century. It was extensively used as an analgesic, a nocturnal sedative, and a hypnotic, and, less frequently, to treat

dysmenorrhea, neuralgia including tic douloureux, muscle spasms, and migraine (19). Marijuana caused mild frontal headache accompanied by other symptoms such as dryness of the mouth, paraesthesia, sensation of warmth, and suffusion of the conjunctivae in 5 of 10 patients observed by Ames (2). Since cannabinoids have been reported to have both a peripheral vasoconstrictor effect and an ability to inhibit platelet serotonin release, they may have a specific migraine prophylactic effect and an abrupt interruption of chronic marijuana intake may also lead to withdrawal headaches (17,18).

It is notable, however, that "cannabinoid receptors and endogenous cannabinoids... may play a significant role in modulation of nociception" (19). Their presynaptic location may help inhibit excitatory neurotransmitter release, such as glutamate, thus having a potential to prevent or abort migraine. Although no randomized controlled studies have looked at the value of cannabinoids in migraine therapy, uncontrolled studies attest to its effectiveness (67).

Histamine

IHS code and diagnosis: 8.1.8.1 Immediate histamine-induced headache

WHO code: G44.40

Similar to both NO and calcitonin gene-related peptide (CGRP), histamine can cause both an immediate and delayed headache (Tables 117-3 and 117-4) (40,43,48). As noted by the IHS, "the mechanism is primarily mediated via the H₁ receptor as it is almost completely blocked by mepyramine" (40,43).

Immediate histamine-induced headache diagnostic criteria (ICHD-II) are as follows:

- A. Headache with at least one of the following characteristics and fulfilling criteria C and D:
 - 1. Bilateral
 - 2. Frontotemporal location
 - 3. Pulsating quality
 - 4. Aggravated by physical activity
- B. Absorption of histamine.
- C. Headache develops within 10 minutes of absorption of histamine.
- D. Headache resolves within 1 hour after absorption of histamine has ceased.

Calcitonin Generated Peptide

IHS code and diagnosis: 8.1.9 Calcitonin gene-related peptide (CGRP)-induced headache

WHO code: G44.40

IHS code and diagnosis: 8.1.9.1 Immediate CGRP-induced headache

WHO code: G44.40

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CGRP is the most potent vasodilator naturally occurring in the CNS, and has long been implicated in the genesis of migraine. Edvinsson and Goadsby described the rationale for targeting CGRP in preventing or aborting migraine, and showed elevation of CGRP in human external jugular blood during migraine and drop postictally or after treatment with subcutaneous sumatriptan (15,24). Olesen and colleagues have demonstrated that blocking CGRP directly aborts migraine (59,60).

Immediate CGRP-induced headache diagnostic criteria (ICHD-II) are as follows:

- A. Headache with at least one of the following characteristics and fulfilling criteria C and D.
 - 1. Bilateral
 - 2. Frontotemporal location
 - 3. Pulsating quality
 - 4. Aggravated by physical activity
- B. Absorption of CGRP.
- C. Headache develops within 10 minutes of absorption of CGRP.
- D. Headache resolves within 1 hour after absorption of CGRP has ceased.

DELAYED HEADACHE INDUCED BY ACUTE USE OF SUBSTANCES

Nitric Oxide Donor

IHS code and diagnosis: 8.1.1.2 Delayed NO donor headache

WHO code: G44.400

When NTG is given to migraine patients, they develop a delayed headache (mean time from NTG administration is approximately 6 hours) meeting IHS criteria for migraine (33).

Delayed NO donor headache diagnostic criteria (ICHD-II) are as follows:

- A. Headache in a person who suffers from primary headache with the characteristics of that primary headache type and fulfilling criteria C and D.
- B. Absorption of NO donor.
- C. Headache develops after NO is cleared from the blood.
- D. Headache resolves within 72 hours after single exposure.

Most patients describe "bilateral, pulsating, and frontotemporal" headaches. Olesen et al. have described that if nonmigraine patients are given NTG, they develop immediate nonspecific headache. However, when NTG is given to migraine patients, they develop the early-onset nonspecific headache, and then a headache meeting IHS criteria for migraine hours later. The nonspecific headaches may

be due to cGMP activation, while the delayed migraine may be due to the NTG acting as an NO donor (40,60,82). NTG also precipitates delayed cluster attacks in cluster patients during cluster periods (16).

Lassen et al. published a double-blind, placebo-controlled study on L-methylarginine HCL (546C88), a nonspecific NO synthase inhibitor in the treatment of acute migraine. They found that 10 of 15 patients had headache relief at 2 hours compared to 2 of 14 patients who received placebo (42).

Alcohol

IHS code and diagnosis: 8.1.4.2 Delayed alcohol-induced headache

WHO code: G44.83

Previously used terms: Hangover headache

Delayed alcohol-induced headache (alcohol withdrawal headache) is the headache associated with withdrawal of a single abundant ingestion of alcohol. As noted, the headache must be preceded by intake of sufficient alcohol to make the particular individual drunk (21).

The hangover syndrome is characterized by headaches, dry mouth, paleness, nausea, dizziness, and hyperexcitability, which occur several hours after the interruption of the ingestion of alcohol, when the tissue level of the alcohol is low or nil. Headaches are a common but not a constant feature of the syndrome and are generally throbbing and aggravated by body movements, coughing, and rapid head movements. The syndrome usually lasts 5 to 10 hours after the alcohol has been metabolized (49,78). The immediate reduction of symptoms with a fresh ingestion of alcohol indicates that the hangover may be a slight withdrawal syndrome. A delay in the clearance of metabolic products has been suggested as a cause of the hangover syndrome. Ogata et al. (57) found high pyruvate levels in the blood but not acetaldehyde or lactate in hangover syndrome sufferers. The fact that pilots often find that they get relief from the hangover syndrome by inhaling oxygen is consistent with the hypothesis that the hangover syndrome is due to a delay in the metabolic recovery of the redox state modified by ingestion of alcohol (56,57). A close interrelationship and involvement of the hormonal, peptidergic, and opiate system in acute withdrawal syndrome pathogenesis has been suggested (39).

Unresolved questions about delayed alcohol-induced headache are:

- 1. Is the headache due to the alcohol or to excipients in the alcoholic drink? This is the red wine/white wine/spirits argument.
- 2. Is the delayed headache due to delivery of NO? (1,87)

Histamine

IHS code and diagnosis: 8.1.8.2 Delayed histamine-induced headache

WHO code: G44.40

The character of the delayed headache induced by histamine varies with the primary headache disorder, with migraineurs developing migraine, tension-type headache patients developing tension-type headache (both around 5 to 6 hours after exposure), and cluster patients developing cluster headache (around 1 to 2 hours after exposure) during cluster periods (40,43).

Calcitonin Generated Peptide

IHS code and diagnosis: 8.1.9.2 Delayed CGRP-induced headache

WHO code: G44.40

The character and time of the delayed headaches for histamine are similar to those for CGRP (28). In one study, 12 patients with migraine without aura were given human α -CGRP (2 μ g/min) intravenous or placebo for 20 minutes (44). Between 1 and 12 hours postinfusion, all patients experienced headaches after α -CGRP vs. one patient after placebo ($p = 0.0004$), with three patients developing delayed headache fulfilling the IHS criteria for migraine without aura. Thus, some, but not all, migraineurs administered CGRP develop migraine, but all do develop headache (44).

Medications Used for Other Indications

IHS code and diagnosis: 8.1.10 Headache as an acute adverse event attributed to medication used for other indications

WHO code: G44.41

The diagnostic criteria for headache attributed to medication used for other indications (ICHD-II) are as follows:

- A. Headache fulfilling criteria C and D.
- B. Use of a medication for a therapeutic indication other than headache.
- C. Headache develops within minutes to hours after use.
- D. Headache resolves within 72 hours after cessation of use.

An exhaustive list of these medications is in the appendix of the ICHD-II, page 144. A causal relationship cannot be established with many of the listed drugs in the absence of adequately controlled studies.

Other Acute Substance Use or Exposure

IHS code and diagnosis: 8.1.11 Headache attributed to other acute substance use or exposure

WHO code: G44.4 or G44.83

Multiple substances have been implicated in headache genesis.

Intoxication with a number of organic and inorganic substances that are listed below is associated with headaches (56). Headache is not generally dealt with in great detail in the literature on intoxication, but is mostly of the diffuse toxic-metabolic type mentioned above. The following list of substances is not exhaustive but contains those most commonly encountered, and is listed by the IHS: inorganic compounds are arsenic, borate, bromate, chlorate, copper, iodine, lead, lithium, mercury, and toluene hydrochloride; organic compounds include alcohols (long-chain), aniline, balsam, camphor, carbon tetrachloride, chloroform, digitalis, disulfiram, EDTA, heptachlor, hydrogen sulphide, kerosene, methyl alcohol, methyl bromide, methyl chloride, methyl iodine, naphthalene, nicotine, and organophosphorus compounds (parathion, pyrethrum) (28).

PROGNOSIS

The prognosis of headaches associated with acute use of substances in general is good, because the symptoms fade spontaneously after exposure ceases. The development of chronic headache is rare, but headache can appear upon renewed contact with substance. Excessive exposure to CO can be lethal as can excessive use of illicit drugs, particularly those containing contaminants or combinations with other substances such as crack or amphetamine analogs (e.g. "Ecstasy").

MANAGEMENT

It is important to identify the clinical syndrome and to stop further exposure to the substance immediately. Specific measures may be necessary (e.g., pure or hyperbaric oxygen in case of CO intoxication) (88).

Patients need to be advised that contact with the substance or substances should be avoided in the future. If this is not possible, symptomatic medication may be indicated. Ergotamine can abort 40% of headaches induced by NTG (72), but the pretreatment with a daily dose (80 to 160 mg) of propranolol does not stop headaches from occurring (58). Injectable sumatriptan also terminates the delayed headache induced by an NO donor (33).

968 The Secondary Headaches

NSAIDs may be used to prevent alcohol withdrawal headaches (58,87). Transdermal clonidine is an effective treatment for the relief of the main symptoms and signs of the acute alcohol withdrawal syndrome, namely headache, dizziness, fatigue, cognitive disturbances, arterial hypertension, accelerated heart rate, and diarrhea (6). Buspirone may be useful in the management of acute severe alcohol and opiates withdrawal syndromes (8,35).

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