8.1 Headache induced by acute substance use or exposure

Coded elsewhere:

10.3.6 *Headache attributed to acute pressor response to an exogenous agent.*

Introduction

This group of headache disorders can be caused 1) by an unwanted effect of a toxic substance, 2) by an unwanted effect of a substance in normal therapeutic use and 3) in experimental studies.

Substances that cause headache through their toxic effects, such as carbon monoxide, cannot be studied experimentally and the causal relationship between exposure and headache has therefore to be demonstrated in clinical cases where the substance has been used accidentally or for suicide attempt.

Headache as a side effect has been recorded with many drugs, often as just a reflection of the very high prevalence of headache. Only when it occurs more often after active drug than after placebo in double-blind controlled trials can headache be regarded as a true side effect. The double-blind design can also be used experimentally to study the relationship between drug effects and headache. In some cases, for example NO donors, such studies have led to a deeper understanding of the involvement of neuro-transmitter mechanisms in primary headaches. A number of substances such as NO donors and hista-mine induce an immediate headache in normal vol-unteers and in migraineurs. However, it is now clear that sufferers of primary headache also develop a delayed headache one to several hours after the inducing substance has been cleared from the blood.

Knowing the potential headache-inducing effects of substances in clinical use is important in order to label these substances appropriately. In general, migraine sufferers are much more susceptible to such headaches than other individuals and the same may be true for sufferers of chronic tension-type headache, episodic tension-type headache and cluster headache during cluster periods.

Paradoxically, the headache encountered by most people after heavy alcohol use may be a positive feature because it helps avoid excessive drinking.

Combinations such as alcohol and disulfiram may cause headache when individual agents might not.

8.1.1 Nitric oxide (NO) donor-induced headache

8.1.1.1 Immediate NO donor-induced headache

Previously used terms:

Nitroglycerine headache, dynamite headache, hot dog headache

Diagnostic criteria:

A. Headache with at least one of the following char-acteristics and fulfilling criteria C and D:
   1. bilateral
   2. frontotemporal location
   3. pulsating quality
   4. aggravated by physical activity
B. Absorption of a NO donor
C. Headache develops within 10 minutes afterabsorption of NO donor
D. Headache resolves within 1 hour after release of NO has ended

8.1.1.2 Delayed NO donor-induced headache

Diagnostic criteria:

A. Headache, in a person who suffers from primary headache, with the characteristics of that primary headache type[1] and fulfilling criteria C and D
B. Absorption of a NO donor
C. Headache develops after NO is cleared from the blood[2]
D. Headache resolves within 72 hours after single exposure

Notes:

1. Normal subjects rarely develop delayed NO donor-induced headache whilst migraineurs develop an attack of migraine without aura, tension-type headache sufferers develop a tension-type headache and cluster headache suf-ferers develop a cluster headache attack.

2. Migraine and tension-type headache develop after a mean of 5-6 hours, cluster headache typically after 1-2 hours.

Comments:

The headache is typically bilateral, pulsating and frontotemporal in location.

All NO donors (*eg*, amyl nitrate, erythrityl tetranitrate, glyceryl trinitrate [GTN], isosorbide mono- or dinitrate, sodium nitroprusside, mannitol hexanitrate, pentaerythrityl tetranitrate) can cause headache of this subtype particularly in persons with migraine. GTN is the best studied substance. It reliably induces headache in most normal individuals and migraine sufferers develop a more severe immediate headache than non-migraine sufferers. GTN can also cause a delayed head- ache in migraine sufferers which fulfils the diagnostic criteria for 1.1 *Migraine without aura*, even in patients whose spon-taneous migraine attacks are with aura. In people with chronic tension-type headache, GTN has been shown to induce a delayed headache which has the characteristics of tension-type headache. It is not known if it has the same effect in sufferers of episodic tension-type headache. Cluster headache sufferers do not develop delayed headache outside cluster periods but, during a cluster period, GTN fairly reliably induces a cluster headache attack usually occurring 1-2 hours after intake. The delayed headache in those with migraine or tension-type headache occurs at variable times but on average 5-6 hours after exposure.

Headache is well known as a side effect of therapeutic use of nitroglycerine and other NO donors. With chronic use tolerance develops within a week, and GTN-induced headache disappears in most patients within that time. With intermittent use headache continues, and may be severe enough to compromize the use of NO donors for angina. Most heart patients are, however, male and beyond middle age, which probably explains why the problem is not of greater magnitude.

Other NO donors have been much less studied but available evidence suggests that they too may produce headache. Isosorbide mononitrate has been the subject of one formal doubleblind placebo-controlled study and causes a much longer-lasting headache than GTN owing to its slow release of NO.

8.1.2 Phosphodiesterase (PDE) inhibitor-induced headache

Diagnostic criteria:

A. Headache with at least one of the following char-acteristics 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 phosphodiesterase inhibitor has been given

C. Headache develops within 5 hours of PDE inhibitor intake

D. Headache resolves within 72 hours

Comment:

PDEs are a large family of enzymes that break down cyclic nucleotides cGMP and cAMP. When PDEs are inhibited, the levels of cGMP and/or cAMP there-fore increase. PDE-5 inhibitors sildenafil and dipyridamole are the only formally studied compounds in this group. The headache, unlike GTN-induced headache, is mono-phasic. In normal volunteers it has the characteristics of tension-type headache but in migraine sufferers it has the characteristics of migraine without aura. Headache has been noted as a side effect of sildenafil in clinical trials but only recent experimental studies have shown that, in young persons-especially females-the side effect occurs in a majority of subjects and in migraine patients sildenafil usually induces a migraine attack. Migraine sufferers should be warned of this side effect.

8.1.3 Carbon monoxide-induced headache

Previously used terms:

Warehouse workers' headache

Diagnostic criteria:

A. Bilateral and/or continuous headache, with quality and intensity that may be related to the severity of carbon monoxide intoxication[1], fulfill-ing criteria C and D

B. Exposure to carbon monoxide (CO)

C. Headache develops within 12 hours of exposure

D. Headache resolves within 72 hours after elimination of carbon monoxide

Note:

1. Typically: mild headache without gastrointestinal or neurological symptoms with carboxy-haemo-globin levels in the range 10-20%; moderate pulsating headache and irritability with levels of 20-30%; severe headache with nausea, vomiting and blurred vision with levels of 30-40%.

Comments:

With higher carboxyhaemoglobin levels (>40%) headache is not usually a complaint because of changes in consciousness. There are no good studies of the long-term effects of CO intoxication on headache. Casuistic evidence suggests the possibility of chronic post-intoxication headache.

8.1.4 Alcohol-induced headache

8.1.4.1 Immediate alcohol-induced headache

Previously used terms:

Cocktail headache

Diagnostic criteria:

A. Headache with at least one of the following char-acteristics and fulfilling criteria C and D:

1. bilateral

2. frontotemporal location
3. pulsating quality
4. aggravated by physical activity

B. Ingestion of beverage containing alcohol[1]
C. Headache develops within 3 hours after inges-tion of alcoholic beverage
D. Headache resolves within 72 hours

Note:
1. The effective dose has not been determined.

Comment:
A few subjects develop headache due to a direct effect of alcohol or alcoholic beverages. This is much rarer than delayed alcohol-induced headache.

8.1.4.2 Delayed alcohol-induced headache

Previously used terms:
Hangover headache
Diagnostic criteria:
A. Headache with at least one of the following char-acteristics and fulfilling criteria C and D:
1. bilateral
2. frontotemporal location
3. pulsating quality
4. aggravated by physical activity

B. Ingestion of a modest amount of alcoholic bever-age by a migraine sufferer or an intoxicating amount by a non-migraine sufferer C. Headache develops after blood alcohol level declines or reduces to zero
D. Headache resolves within 72 hours

Comment:
This is one of the commonest types of headache. It remains unclear whether, in addition to alcohol, other components of alcoholic beverages play a role. It also remains uncertain whether the mechanism is a delayed response to toxic effects or whether mechanisms similar to those responsible for delayed NO donor-induced headache may be involved.

The susceptibility to hangover headache of well-diagnosed headache patients compared with non-head- ache sufferers has not been determined. In migraine sufferers a migraine attack can be indu- ced the next day after modest intake of alcoholic bever-ages, while non-migraineurs usually need a high intake of alcoholic beverages in order to develop 8.1.4.2 *Delayed alcohol-induced headache*.

8.1.5 Headache induced by food components and additives

Previously used terms:
Dietary headache

Diagnostic criteria:
A. Headache with at least one of the following char-acteristics and fulfilling criteria C and D:
1. bilateral
2. frontotemporal location

3. pulsating quality
4. aggravated by physical activity

B. Ingestion of a minimum dose of food component or additive[1]
C. Headache develops within 12 hours after sub-stance intake
D. Headache resolves within 72 hours after single intake

Note:

1. Phenylethylamine, tyramine and aspartame have been incriminated but their headache-inducing potential is not sufficiently validated.

8.1.5.1 Monosodium glutamate-induced headache

Previously used terms:

Chinese restaurant syndrome

Diagnostic criteria:

A. Headache with at least one of the following char-acteristics and fulfilling criteria C and D:
1. bilateral
2. frontotemporal location
3. aggravated by physical activity

B. Ingestion of monosodium glutamate (MSG)
C. Headache develops within 1 hour after MSG ingestion
D. Headache resolves within 72 hours after single intake

Comment:

MSG-induced headache is typically dull or burning and non-pulsating, but may be pulsating in migraine sufferers. It is commonly associated with other symptoms of this syndrome including pressure in the chest, pressure and/or tightness in the face, burning sensations in the chest, neck or shoulders, flushing of face, dizziness and abdominal discomfort.

8.1.6 Cocaineinduced headache

Diagnostic criteria:

A. Headache with at least one of the following char-acteristics 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 use

Comment:

Headache is a reported side effect of cocaine use. It is frequent, develops immediately or within one hour after use and is not associated with other symptoms unless there is concomitant stroke or TIA.

8.1.7 Cannabis-induced headache

Diagnostic criteria:

A. Headache with at least one of the following char-acteristics and fulfilling criteria C and D:
   1. bilateral
   2. stabbing or pulsating quality
   3. feeling of pressure in the head

B. Use of cannabis

C. Headache develops within 12 hours after cannabis use

D. Headache resolves within 72 hours after single use

Comment:

Cannabis use is reported to cause headache associ-ated with dryness of the mouth, paresthesias, feel-ings of warmth and suffusion of the conjunctivae.

8.1.8 Histamine-induced headache

Comment:

Histamine has been shown to cause an immediate headache in non-headache sufferers and an imme-diate as well as a delayed headache in migraine sufferers. The latter fulfils criteria for 1.1 *Migraine without aura*. The headache-inducing property of histamine has been studied after intravenous adminis-tration, after cutaneous administration and after inhalation: All routes of administration have the same effect. The mechanism is primarily mediated via the H1 receptor because it is almost completely blocked by mepyramine.

8.1.8.1 Immediate histamine-induced headache

Diagnostic criteria:

A. Headache with at least one of the following char-acteristics 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 after absorption of histamine

D. Headache resolves within 1 hour after absorption of histamine has ceased

8.1.8.2 Delayed histamine-induced headache

Diagnostic criteria:

A. Headache, in a person who suffers from primary headache, with the characteristics of that primary headache type[1] and fulfilling criteria C and D

B. Absorption of histamine

C. Headache develops after histamine is cleared from the blood[2]

D. Headache resolves within 72 hours after single exposure

Notes:

1. Normal subjects rarely develop delayed hista-mine-induced headache whilst migraineurs develop an attack of migraine without aura, tension-type headache sufferers develop a tension-type headache and cluster

headache suf-ferers develop a cluster headache attack.

2. Migraine and tension-type headache develop typically after 5-6 hours, cluster headache typically after 1-2 hours.

8.1.9 Calcitonin gene-related peptide (CGRP)-induced headache

Comment:

The headache-inducing property of CGRP has been studied only in one double-blind controlled trial. There is, however, no doubt that CGRP causes an immediate headache. Delayed migraine attacks were induced in 3 out of 10 subjects. Recently, it has been shown that a CGRP antagonist is effective in the acute treatment of migraine.

8.1.9.1 Immediate CGRP-induced headache

Diagnostic criteria:

A. Headache with at least one of the following char-acteristics 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 after absorption of CGRP
D. Headache resolves within 1 hour after absorption of CGRP has ceased

8.1.9.2 Delayed CGRP-induced headache

Diagnostic criteria:

A. Headache, in a person who suffers from primary headache, with the characteristics of that primary headache type[1] and fulfilling criteria C and D
B. Absorption of CGRP
C. Headache develops after CGRP is cleared from the blood[2]
D. Headache resolves within 72 hours after infusion of CGRP

Notes:

1. Normal subjects rarely develop delayed CGRP-induced headache whilst migraineurs develop an attack of migraine without aura, tension-type headache sufferers develop a tension-type headache and cluster headache sufferers develop a cluster headache attack.

2. Migraine and tension-type headache develop typically after 5-6 hours, cluster headache typically after 1-2 hours.

8.1.10 Headache as an acute adverse event attributed to medication used for other indications

Diagnostic criteria:

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

Comments:

Headache has been reported after use of a number of drugs. The following are the most commonly incriminated: atropine, digitalis, disulfiram, hydralazine, imipramine, nicotine, nifedipine, nimodipine. Alonger list can be found in the appendix(Table 1). The headache characteristics are not very well defined in the literature but most are dull, continuous, diffuse and moderate to severe.

Table 1. Drugs that may induce headache or worsen pre-existing headache

Acetazolamide	Codeine	Interferons	Ondansetron
Ajmaline	Didanosine	Isoniazid	Paroxetine
Amantadine	Dihydralazme	Meprobamate	Pentoxifylline
Antihistainirncs	Dihydroergotamine	Methaqualone	Perhexiline
Barbiturates	Dipyridamole	Metronidazole	Primidone
Beta-interferon	Disopyramide	Morphine and derivatives	Prostacyclines
Bromocriptine	Disulfiram	Nalidixic acid	Ranitidine
Caffeine	Ergotarnine	Nifedipine	Rifampicin
Calcium antagonists	Etofibrate	Nitrofurantoin	Sildenafil
Carbimazol	Gestagens	Nitrates	Theophylline and derivatives
Chinidine	Glycosides	Non-steroidal anti-	Thiamazole
Chloroquine	Griseofulvin	inflarnrnatory drugs	Triinethopriln +
Cimetidine	Guanethidme	Octreotide	sulfamethoxazole
Clofibrate	Immunoglobulins	Oestrogens	Triptans
		Omeprazole	Vitamin A

8.1.11 Headache induced by other acute substance use or exposure

Diagnostic criteria:

A. Headache fulfilling criteria C and D

B. Acute use of or other acute exposure to a substance other than those described above

C. Headache develops within 12 hours of use or exposure

D. Headache resolves within 72 hours after single use or exposure

Comments:

Headache has been reported after exposure to a number of organic and inorganic substances. The following are the most commonly incriminated substances: *Inorganic compounds*: Arsenic, borate, bromate, chlorate, copper, iodine, lead, lithium, mercury, tolazoline hydrochloride. *Organic compounds*: alcohols (long-chain), aniline, balsam, camphor, carbon disulfide, carbon tetra-chloride, clordecone, EDTA, heptachlor, hydrogen sulfide, kerosene, methyl alcohol, methyl bromide, methyl chloride, methyl iodine, naphthalene, organophosphorous compounds (parathion, pyrethrum).

The headache characteristics are not very well defined in the literature but most are dull, diffuse, continuous and moderate to severe.