ANALGESIC REBOUND HEADACHE (MEDICATION MISUSE HEADACHE)

Medication misuse headache has been referred to using terms such as analgesic rebound headache, ergotamine rebound headache, and drug-induced headache. Rebound headache is a term that often is used to characterize the headache-perpetuating tendency of immediate relief medications when they are used very frequently.

There appears to be some confusion between the terms recurrence and rebound. Recurrence may be defined as the recurrence of the same headache, which was significantly relieved by an abortive antimigraine agent. Recurrence should occur within the expected natural duration of that migraine attack. Reoccurrence of the same headache may occur when 5-HT$_1$ agonists are used in acute migraine.

Rebound headache, on the other hand, can be defined as perpetuation of head pain in chronic headache sufferers, caused by frequent and excessive use of immediate relief medication. It also can be defined as “a self-sustaining, rhythmic, headache-medications cycle characterized by daily or near daily headache and irresistible and predictable use of immediate relief medications as the only means of relieving headache attacks.”

Evidence for Rebound

The most convincing evidence for analgesic/ergotamine rebound is the fact that mere discontinuation of these medications results in significant improvement. There are sample data in the literature to support the existence of analgesic/ergotamine rebound headache. Silverman et al$^{19}$ reported that moderate or severe headache occurred in 52% of patients on caffeine withdrawal based on a double-blind cessation of caffeine consumption. In a recent survey of physicians engaged in the treatment of headache, more than 40% of the respondents (n=174) indicated that analgesic rebound is present in at least 20% of their patients with headache.$^{13}$ Table 1 lists the commonly used immediate relief medications in a group of 200 patients with CDH.$^{10}$

Clinical Features

Several clinical characteristics are helpful in identifying the occurrence of analgesic rebound headache in patients with primary headache disorders.$^{10}$ The following are the clinical features of analgesic rebound:

The headaches are refractory, daily, or nearly daily.

The headaches occur in a patient with primary headache disorders who uses immediate relief medications very frequently, often in excessive quantities.
The headache itself varies in its severity, type, and location from time to time. The slightest physical or intellectual effort may bring on headache. In other words, the threshold for head pain appears to be low.

Headaches are accompanied by asthenia, nausea and other gastrointestinal symptoms, restlessness, anxiety, irritability, memory problems, and difficulty in intellectual concentration and depression. Those consuming large quantities of ergot derivatives may exhibit cold extremities, tachycardia, paresthesias, diminished pulse, hypertension, light-headedness, muscle pain of the extremities, weakness of the legs, and depression.

There is a drug dependent rhythmicity of headaches. Predictable early morning (2:00 AM to 5:00 AM) headaches are frequent, particularly in patients who use large quantities of analgesic, sedative, caffeine, or ergotamine combinations. Barbiturate-containing analgesics, such as butalbital with caffeine and aspirin (Fiorinal) or with caffeine and acetaminophen (Esgic), suppress rapid eye movement (REM) sleep, which is followed by REM rebound and results in awaking with severe headache.

There is evidence of tolerance to analgesics over time, with patients needing progressively larger doses.

Withdrawal symptoms are observed when patients are taken off pain medications abruptly.

Spontaneous improvement of headache occurs on discontinuing the medications. Concomitant prophylactic medications are relatively ineffective while the patients are consuming excess amounts of immediate relief medications.

Patients of Medication Consumption in Patients with Analgesic Rebound

Many patients consume analgesics in anticipation of headache. Fear of pain drives them to take medication even before the headache develops. There is a predictable and irresistible pattern of use in many patients. Multiple medications are used concomitantly, both prescription and nonprescription. Ferrari and Sternieri analyzed the reasons for daily analgesic consumption in chronic headache disorders. The reasons given by the patient were (1) consumption under medical advice to take the analgesic at the moment of need (57%); (2) inability to cope with pain (67%); (3) apprehension about headache developing if drugs is not taken (62%); (4) recurrence of pain soon after previous consumption (30%); (5) belief that there is no other cure (61%); and (6) ability of analgesic to make headache more bearable, enabling the patient to function at work (62%), to reduce tension and anxiety (41%), and to aid sleep (18%). It should be noted that many patients gave more than one of these reasons for the daily analgesic consumption.

Behavioral aspects of the analgesic consumption are important. Relief of pain gives a negative reinforcement, and changes in the mood produced by some of the agents containing barbiturates or stimulants such as caffeine may give a positive reinforcement for the behavior, resulting in excessive use of immediate relief medications. It is very rare for these patients to use habit-forming doses of barbiturates, which is usually more than 600 to 800 mg/day; therefore, addiction does not appear to be a problem in most patients, although there are exceptions characterized by drug-seeking behavior.

Analgesics use usually does not interfere with the execution of normal social or occupational roles, as may happen when the abuse substance is a narcotic or alcohol. On the contrary, the analgesic represents a kind of necessary crutch for his or her everyday functions.

Development of tolerance is evidenced by escalating consumption with no appropriate adverse consequences. Withdrawal symptoms on discontinuation can be very prominent. Such symptoms include restlessness, sleeplessness, increased headache, diarrhea, and occasional seizures, especially in those who consume large amounts of butalbital containing analgesics. An increase in headache pain with a decrease in analgesic efficacy occurs over time.
<table>
<thead>
<tr>
<th>Medications</th>
<th>Average No. of Tablets per Week</th>
<th>Range No of Tablets (or Dose) per Week</th>
<th>No. of Patients</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butalbital/ aspirin/acetaminophen/ caffeine with or without codeine</td>
<td>30</td>
<td>14-86</td>
<td>84</td>
<td>42</td>
</tr>
<tr>
<td>Natural or synthetic codeine-containing preparations</td>
<td>28</td>
<td>10-84</td>
<td>80</td>
<td>40</td>
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<tr>
<td>Aspirin or acetaminophen with caffeine</td>
<td>42</td>
<td>14-108</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>Ergotamine with or without Phenobarbital</td>
<td>15mg</td>
<td>6-42mg</td>
<td>44</td>
<td>22</td>
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<tr>
<td>Acetaminophen</td>
<td>52</td>
<td>15-105</td>
<td>34</td>
<td>17</td>
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<tr>
<td>Propoxyphene</td>
<td>26</td>
<td>14-56</td>
<td>32</td>
<td>16</td>
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<tr>
<td>Nasal decongestants and antihistamines</td>
<td>14</td>
<td>6-30</td>
<td>24</td>
<td>12</td>
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<tr>
<td>Aspirin</td>
<td>28</td>
<td>10-64</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>

Consequence of Rebound

Clinical evidence from various centers around the world points to the fact that the rebound phenomenon alters the natural history of migraine.

Phenomena Analogous to Rebound Headache

There are few medical phenomena analogous to rebound headache. These include worsening of nasal congestion by frequent use of decongestants, insomnia aggravated by sleeping pills, chronic constipation due to frequent laxative use, and idiopathic edema caused by diuretics.

Mechanisms of Analgesic Rebound

Analgesic rebound phenomenon is actually a paradoxical response. Those taking the most medications experience the most pain. The question then arises: Is a high level of pain experience the cause of high analgesic consumption, or is the overuse of analgesics due to certain psychological predispositions? This leads to the question: Is analgesic rebound headache a result of addictive behavior?

There is no evidence of addictive personality in these patients. Sensation-seeking behaviors are not high in these patients with chronic headache.

Relapses of migraine occur in migraineurs who have been placed on analgesics for other ailments. The association between analgesics overuse and headache has been studied in conditions other than primary headache disorders. Chronic overuse of analgesics does not cause increased headache in nonmigraineurs. For example, a group of arthritis patients who were consuming fairly large amounts of analgesics regularly for arthritis did not show increased incidence of headache. There are no major differences in the abilities of the various types of analgesics used in the treatment of chronic headache to produce analgesic rebound headache. The conclusion drawn from various clinical observations and studies is that analgesic rebound headache may be restricted to those who are already headache sufferers.

The pathogenesis of analgesic-induced headache is not clearly understood, although there is evidence to suggest involvement of 5-HT in the process. Hering et al reported reduction in whole-blood 5-HT in patients with analgesic rebound headache, which was normalized on discontinuing the analgesics. This rise in 5-HT level in the whole blood paralleled the improvement in headache frequency. Patients with analgesic-induced headaches have lower basal content of platelet 5-HT, reduced 5-HT uptake ability when incubated with excess of the amine, and a greater density of 5-HT receptors on platelet membrane than in migraineous patients without analgesic reduced headache. These observations suggest that chronic analgesic overuse interferes with the intrinsic pain modulatory system by depletion of 5-HT and, consequently, the upregulation of its postsynaptic receptors. It is likely, therefore, that analgesic-induced headache is at least partly due to defective mechanisms of 5-HT uptake caused by analgesic use. Alteration in the central pain modulation mechanism may account for perpetuation of headache.

Sicuteri postulated central opioid receptor impairment as an underlying mechanism for migraine. Natural opioids play a vital role in regulating pain. There appears to be an opioid deficiency in the mechanism of migraine headache as well as in morphine abstinence syndrome. Sicuteri pointed out the neuro-chemical and other similarities of these two conditions. Both involved central serotonin and dopamine sensitivity. Their prominent symptoms included headache, anhedonia, autonomic symptoms, and hypernociception. Opioids appear to act on the CNS to limit pain. Impairment of the opioid system would lower the pain threshold in patients with chronic headache. Prolonged use of analgesics may lead to suppression of antinoceptive opioids, thus resulting in heightened pain sensitivity if the drug use were to be discontinued.
The possible neurophysiologic mechanisms of CDH are:

Long-term plasticity/central sensitization/central functional reorganization
Kindling
Activation of nociceptive facilitatory systems, such as “on cells” in the ventral medial medulla
Lack of inhibitory modulation.

Lance et al\textsuperscript{8} postulated that further suppression or downregulation of an already partly suppressed or abnormal antinociceptive system due to excessive symptomatic medications is a possible explanation for analgesic rebound headache in the migraine population. Alterations in the density and function of postsynaptic neuronal receptors as a result of chronic medication use may be another explanation for the refractory headache these patients develop (central sensitization and long-term plasticity). A phenomenon akin to kindling seen in epilepsy may be occurring in chronic headaches, also.

Activation of facilitatory nociceptive “on cells” in the ventral medulla as a result of excessive analgesic/narcotic use may be another explanation. “On cells” in the ventromedial medulla facilitate nociceptive reflex responses such as the tail flick response. “On cells” show increased firing during naloxone-induced morphine withdrawal.\textsuperscript{4} Mechanisms, such as this, although not adequately understood, may provide a physiologic explanation for analgesic-induced headache.

References