Drug-Induced Headache —
Does a Critical Dosage Exist?

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Introduction

Although the clinical problem of chronic daily headache induced by chronic intake of ergotamine tartrate and/or analgesics is known to clinicians (Lippman 1955; Horton et al. 1963; Rowse1 et al. 1973; Wainscott et al. 1974; Andersson 1975; Ala-Hurula et al. 1982; Kudrow 1982; Saper 1983; Dichgans et al. 1984), no information is as yet available about the dosages of different drugs necessary to provoke this response. The patients' histories show a gradual increase in frequency and dose of drug intake, eventually ending in daily administration of high dosages. It is unknown whether the daily intake itself or the drug dosage plays the crucial role.

With ergotamine tartrate, it took a long time to learn about the conditions leading to headache since early studies were not even able to detect ergotamine in blood samples, although clinical effects were observable (see Tfelt-Hansen 1982 and this volume). Surprisingly, different analgesics and secale alkaloids, including ergotamine tartrate and dihydroergotamine derivatives, with quite different pharmacological properties induce headaches which are clinically similar or even identical (Isler 1982; Kudrow 1982; Saper 1983; Dichgans et al. 1984). Whereas ergotamine tartrate is known to exert long-lasting effects on blood vessels, probably resulting in a prolonged vasoconstriction (Tfelt-Hansen 1986) and thus inducing "vascular" headache, the pathophysiology of drug-induced headache is still completely unknown. It is tempting to speculate on the role of prostaglandin, vasopressin, and kinins, substances known to alter the sensitivity of vascular smooth muscles (Saxena 1982). Another possible mechanism is muscle tension. We have as yet no explanation why a great number of patients complain about intensive pain in the neck musculature during and shortly after withdrawal.

We have tried to investigate possible causes and risks of analgesic drug consumption by analyzing what dosages of particular drugs or drug combinations were able to induce chronic headache and then comparing these dosages with the usual intake in migraine patients without chronic headache.
Patients and Methods

Migraine Patients

Data on the drug intake in 61 migraine patients were collected prospectively. We used the diary data of patients who were to join a study for prophylactic migraine treatment. In an 8-week baseline period before the start of prophylactic treatment, patients were instructed to take their abortive medication as usual and to register drugs, migraine duration, migraine days, and concomitant headaches, but to avoid prophylactic drugs like beta-blockers and calcium channel blockers. None of them had daily or near daily headache.

The dose of each different substance taken was calculated from these data and the intake per month estimated. The overall dosage during the 4-week period was calculated as intake per month. The intake per month was divided by the headache days, which were similar to the days with drug intake, in order to estimate the mean daily intake per headache day for each single substance.

This group was subdivided into subgroups (group 1) with 1–9 headache days per month (mean 5.2 days, SD 2.3 days) and an “at risk” group (group 2) with 10 and more headache days (mean 12.2 days, SD 2.1 days). Our hypothesis was that group 2 patients would show the development or a tendency to a higher drug intake compared to group 1 and thus be at an intermediate stage on the way to chronic daily headache. As shown in Table 1, patients with migraine (groups 1 and 2) showed approximately the same male:female ratio and the same mean age as patients with chronic daily headache (3:1).

Chronic Daily Headache Patients

A total of 39 patients with daily drug-induced headache were treated on an inpatient basis by strict withdrawal of all analgesic drugs. Their drug intake was evaluated retrospectively. Our operational definition of this group (group 3) was that patients should report headache every day over a time period of at least 1 year. On their 1st day in the clinic, they underwent a standardized interview about their previous drug intake behavior. They were questioned about the drugs, the mean and maximum daily intake, their overall intake during the last 14 days, the duration of their chronic headache and drug abuse, and the different drugs they had been taking in their medical history. Furthermore, they were questioned about the specific headache symptoms and whether or not changes in symptomatology had taken place in order to clarify when chronic daily headache had started. From their overall mean daily intake, we calculated the monthly and daily intake of chemically defined substances. Since most patients took tablets as well as suppositories in varying amounts, we calculated the overall dosage without specifying the route of administration. We are well aware of the fact that the route of administration is important as the uptake is greater rectally than orally. Demographic data of the patients are given in Table 1.

The final diagnosis of the primary headache in patients with chronic daily headache was made using the biographic data and the outcome of drug with-