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Observations of the “carry-over effect” following successful termination of chronic migraine in the adolescent with short-term dihydroergotamine, dexamethasone and hydroxyzine: a pilot study

Received: 20 September 2004

Accepted in revised form: 14 December 2004

Published online: 25 January 2005

Abstract Chronic migraine management almost always requires daily oral preventative medication with potential adverse effects. Daily oral preventative therapy may also not be effective in terminating chronic migraine.

Chronic central sensitisation caused by repetitive migraine attacks in a young person may lower the threshold for future migraine episodes leading to an intractable and debilitating disease course. The objective was to determine if short-term parenteral dihydroergotamine, dexamethasone and hydroxyzine can terminate chronic migraine and be followed by a continuous respite or conversion to a more benign episodic form without the need for daily oral preventative medication (“carry-over effect”). We treated ten patients, seven adolescents and three adults, with parenteral dihydroergotamine, dexamethasone and hydroxyzine given once a week for a maximum of three weeks. No oral preventative daily medication was administered. The setting was a private practice. Chronic migraine was terminated in all 7 adolescents. Their post-treat-

ment course was converted to a more benign episodic migraine course and no adolescent required daily oral migraine preventative therapy for significantly long carry-over post-treatment observational periods. None of the three adult chronic migraine cases could be terminated satisfactorily as they all required daily oral preventative therapy. In the adolescent group only, this strategy terminated chronic migraine and resulted in a significant carry-over effect that appeared to favourably modify the long-term course without the need for daily pharmacological, potentially toxic, preventative therapy. Although this is a very small study, which requires confirmation by a larger controlled study, our data suggest a significant carry-over effect in the young migraineur by administering short-term parenteral dihydroergotamine, dexamethasone and hydroxyzine.

Key words Transformed migraine • Chronic migraine • Chronic daily headache • Carry-over effect • Adolescent • Central sensitization

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Introduction

Daily oral preventive therapies for frequent and/or disabling migraine attacks are fraught with possible adverse

effects and drug-drug interactions. Curative therapy is non-existent.

Sensitisation of peripheral and central nociceptors are common mechanisms contributing to the development of chronic pain and, along with other morphological changes

of the brainstem, may be operative in chronic headache syndromes [1, 2]. Chronic central sensitisation caused by repetitive uncontrolled severe migraine attacks in a young person might lower the threshold for future attacks ultimately leading to an intractable, treatment-resistant malignant disease course in adult life. Burstein suggested that with repeated migraine attacks over the years, there is an increased likelihood that the patient will exhibit allodynia, thereby experiencing attacks at a higher frequency. Such age-related progression of the disease can become a growing obstacle for migraine treatment [3].

A desirable short-term therapy designed to dampen or extinguish the multiple migraine brain generator sites thought to be present in the brainstem would prevent chronic sensitisation from occurring [4]. This novel approach to migraine would result in a carry-over effect, decrease frequent debilitating headache attacks and decrease the need for daily preventive medications with all their potential adverse events. It would also decrease acute care and rescue medications and emergency room visits. It would probably result in large cost savings.

The “carry-over effect” is cessation of what has been a clinically effective course of therapy followed by a prolonged period of continued relief from pervasive headache without continuance of such therapy. In one study of transformed migraine, only 8 out of 20 patients obtained a sustained carry-over effect only two months following cessation of divalproex sodium prophylactic therapy [5].

Rapoport devised a protocol administering dihydroergotamine 1 mg IM or IV; dexamethasone 4 mg IM or IV; and either promethazine 50 mg IM or metoclopramide 10 mg IM or IV in patients who appeared to be entering into or were in the midst of status migrainosus [6]. Acute care therapy with intramuscular dihydroergotamine has been used safely and successfully in the office setting [7]. It is frequently used intravenously on a repetitive basis for patients with chronic headache who have been hospitalised for treatment [8].

Patients and methods

Our 10 patients initially presented to the office with severe prolonged headache or in status migrainosus. They were given a choice of receiving treatment with the Rapoport protocol or receiving conventional outpatient abortive, rescue and preventative oral medications. Patients who desired or needed rapid parenteral relief and did not want daily preventative medication were treated with outpatient intramuscular dihydroergotamine 0.5–1 mg, dexamethasone 8–12 mg and hydroxyzine 50 mg (DHE/DEX/HYD) given in three separate injection sites. Hydroxyzine was substituted for promethazine or metoclopramide because of its marked sleep inducing properties, which

Table 1 Pre-treatment frequency and intensity of headache

Case	Monthly frequency	NPS*
1. 14 y/oF	15	9/10
2. 15 y/oF	Daily	10/10
3. 15 y/oF	22	8/10
	8	10/10
4. 15 y/oF	16	10/10
5. 15 y/oF	10	5/10
	12	10/10
6. 16 y/oF	12	5/10
7. 17 y/oF	26	6/10
	4	10/10
8. 21 y/oF	20	8/10
9. 23 y/oM	26	5/10
	4	10/10
10. 31 y/oF	Daily	10/10

*1/10 mildest headache.....10/10 worst headache ever

was felt to be beneficial in breaking the chronic migraine cycle, and to minimise the chances of acute dystonic reactions. All patients met the new IHS criteria for chronic migraine (without analgesic overuse). Pretreatment parameters that were recorded were the number of headache episodes per month, and the average intensity of each headache using a numeric pain scale (NPS) of 1–10; a 1 level was rated as the mildest headache and a 10 level was the worst headache of one’s life (Table 1). All had normal neurological examinations, brain MRI scans, laboratory investigations and had no other health problems. Except for mild to moderate pain from the hydroxyzine injection, no other adverse effects were reported. Within 30 min of treatment, virtually all patients fell asleep for several hours. Treatments were administered 1–3 times, separated by 1 week intervals depending upon clinical response and/or patient preference. No patient was placed on daily pharmacological preventative treatment. Abortive treatment with either a triptan or analgesic was permitted.

Results

All 7 of the adolescents experienced satisfactory abortive relief with significant sustained decrease in frequency and pain intensity for periods of post-treatment observation that ranged from 6 months to 4 years. The 3 adults did not convert to a less debilitating headache course (Table 2). Case 2 was satisfied taking a prn triptan 8 times a month without any loss of school or social activity, triptan adverse effects or triptan rebound. Two of the adults (cases 9 and 10) whose chronic migraine could not be terminated with the DHE/DEX/HYD treatments, required daily pharmacological preventative therapy. Adult patient, case no. 8, required inpatient IV DHE followed by daily

Table 2 Post-treatment patient characteristics

Case	No. of treatments*	Monthly frequency	NPS	Post-treatment observation**
1. 14 y/oF	1	1	3/10	2 years
2. 15 y/oF	3	8	7/10	6 months
3. 15 y/oF	1	1	2/10	4 years
4. 15 y/oF	3	2	2/10	6 months
5. 15 y/oF	3	4	3/10	6 months
6. 16 y/oF	2	1	2/10	4 years
7. 17 y/oF	2	2	6/10	1 year
8. 21 y/oF	1	20	9/10	5 days
9. 23 y/oM	2	26	5/10	1 month
		4	10/10	
10. 31 y/oF	3	Daily	10/10	2 weeks

*Treatment consisted of DHE 0.5–1 mg IM, DEX 8–12 mg IM and HYD 25–50 mg IM given at weekly intervals

**Patients 1–7 period of clinical follow-up during which no patient relapsed back to pretreatment status. Patients 8–10 did not respond or were severely disabled requiring alternative/urgent treatment

pharmacological preventative treatment. The adolescent group demonstrated a significant carry-over effect. The 3 adults did not obtain a carry-over effect.

Conclusions

All of the 7 adolescents with chronic migraine that were treated with 1–3 treatments of IM DHE/DEX/HYD clearly were converted to a benign or improved post-treatment headache course without requiring daily oral preventative therapy. A carry-over effect occurred only in these young migraineurs. A carry-over effect did not occur in the 3 adult cases and they required daily pharmacological therapy for headache management.

Loder, in a recent review of disease modification of migraine, raised the question, “Who will benefit?” [9]. Although our study cannot infer disease modification, our favourable clinical results suggest it is the adolescent with chronic migraine who might benefit. The combination of IM DHE/DEX/HYD in producing an excellent carry-over effect and the failure to do so in the adult may be due to

the fact that in the adult, central sensitisation has already become well established so that a successful carry-over effect is physiologically impossible.

HYD probably induces sleep by blocking cholinergic neurons in the pontine tegmentum modifying serotonergic sleep raphe nuclei and also by blocking histamine release. DHE is a known 5HT₁ receptor agonist. Dexamethasone inhibits neurogenic inflammation.

Magnoux was able to induce a remission of the chronic form of refractory cluster headache and transform it to the episodic form [10]. We accomplished analogous results with our adolescent chronic migraine series, but our study is obviously limited by the small number of patients. In the young migraineur, IM DHE/DEX/HYD attenuated prolonged or frequent headache probably by preventing the establishment of central sensitisation through suppression of multiple migraine brain generator sites. The small number of adolescents treated with IM DHE/DEX/HYD had a significant carry-over effect without exposure to the potential drug toxicity from daily prophylactic migraine therapy. A larger randomised trial, possibly with outpatient intravenous DHE and steroids, needs to be conducted before more definitive conclusions can be drawn.

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