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Nicotine as an Antiepileptic Agent in ADNFLE: An N-of-One Study

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Summary: *Purpose:* To test nicotine patch treatment for a patient with a defined mutation for autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) whose seizures were refractory to standard antiepileptic therapy.

Methods: Open and double-blind trials of nicotine patches in an "n-of-one" study. The double-blind trial comprised periods during which either placebo or nicotine patches were each used for three periods of 2 weeks, randomized in a double-blind manner.

Results: In an open study, nicotine patches reduced seizures from 1.65 ± 2.36 to 0.01 ± 0.0 seizures per day ($p < 0.0001$). In a double-blinded placebo-controlled phase, the average frequency of seizures on nicotine versus placebo was 0 ± 0 versus 0.56 ± 1.14 seizures per day ($p < 0.0001$).

Conclusions: Nicotine patches may be of benefit to some individuals with ADNFLE. **Key Words:** Treatment—Autosomal dominant nocturnal frontal lobe epilepsy.

The rare condition, autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), was described in 1995 (1), and in many families is caused by one of several mutations in the neuronal nicotinic acid acetylcholine receptor $\alpha 4$ subunit (CHRNA4) (2). The effects of mutations on the function of the channel have not been defined, but the prevailing view from oocyte expression studies is that the one functional change common to all mutations may be a gain of function (3). The first mutation causing the disorder was identified in an Australian kindred originally described by Scheffer et al. (1), of which the patient to be described here is a member. We have been unable to find published studies on anticholinesterase or nicotine as possible treatments in this condition by using Medline on Ovid (1966 to 2003) or IDIS (1986 to 2003) CD versions.

METHODS

Open and double-blind n-of-one studies of nicotine patches were conducted in a patient with a known mutation causing ADNFLE (1).

The woman, now age 33 years, has taken dothiepin (Prothiaden), 25 mg per day; oxycodone, 30 mg twice daily; and celecoxib since age 31 years for back pain. She also has polycystic ovary disease, for which she takes an oral contraceptive agent. Her sibling, with severe ADNFLE, has seizures that partially respond to carbamazepine (CBZ), and they do not respond to anticholinesterase or anticholinergic agents. Early morning seizures had occurred since age 12 years. Seizures are characterized by awakening with strong extension of lower limbs, jerking of upper limbs, and inability to talk. Seizures initially persisted for 3 min, but since taking CBZ, they have lasted 4–10 s. She was initially responsive to sodium valproate (VPA), and then CBZ, and had infrequent seizures (approximately two sequentially, 1 day every 6 months) until age 29 years. At this age, the patient ceased smoking, having started at age 13 years and having smoked 16 cigarettes per day for many years. Shortly after, during a distressing personal life experience, her seizures became frequent and disruptive to her life, although they remained brief. They proved refractory to treatment with CBZ, VPA, gabapentin (GBP), and clonazepam (CZP). They were exacerbated by Prothiaden in doses >25 mg/day.

Nicotine patches (Nicoderm CQ, 7 mg, Nicotine Transdermal system; SmithKlineBeecham Consumer Healthcare, Pasippany, NJ, U.S.A.) were first offered in preliminary trials of four 2-week periods, during which she administered one patch per day for 2 weeks, alternating with no treatment. Seizures appeared to be reduced in frequency, and nicotine patches were therefore prescribed for 12 months.

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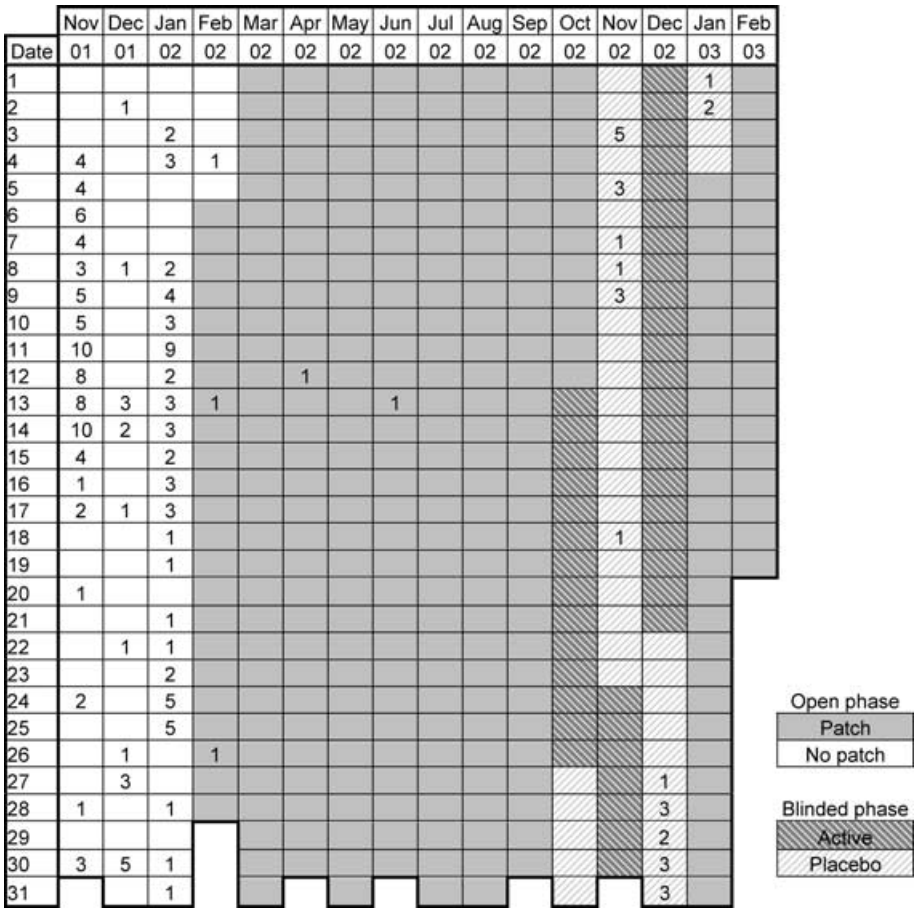

FIG. 1. Calendar of seizure occurrences and open and double-blind treatment with nicotine patches.

With approval of the Flinders Clinical Research Ethics Committee and the informed consent of the patient, a study was undertaken to evaluate a possible placebo effect of the treatment. At a time determined by the hospital pharmacy, treatment was interrupted with a study period during which either placebo (TTS Nicotine 7 cm^2 Control/Placebo Patch) or nicotine patches [nicotine, 7-mg patch (7 mg/24 h)] were each used daily for three periods of 2 weeks, randomized in a double-blind manner. The patient recorded seizures daily for a total of 15 months, including an initial 3 months without treatment. She had the perception that she was "more sound asleep" when taking nicotine. The code was broken 6 weeks after the conclusion of the last 2-week period of the trial.

The number of seizures per day proved not to be distributed normally. Although there was a possible tendency for seizures to occur in clusters, seizure occurrences were documented over long periods relative to cluster length. We therefore used the Wilcoxon rank sum test to evaluate the significance of differences in number of seizures per day.

RESULTS

Seizures were frequent without treatment (3 months), exceedingly rare during open nicotine administration (total of 9 months), reappeared during placebo administration (6 weeks), and were absent during the 6 weeks of the active agent (Fig. 1). In the open phase of treatment, the average frequency of seizures with nicotine (294 days) versus no treatment (97 days) was 0.01 ± 0.00 versus 1.65 ± 2.36 seizures per day ($p < 0.0001$). In the double-blinded phase, the average frequency of seizures with active drug (42 days) versus placebo (42 days) was 0 ± 0 versus 0.56 ± 1.14 seizures per day ($p < 0.0001$).

DISCUSSION

Nicotine administered by dermal patches reaches central nervous system (CNS) sites and can safely ameliorate symptoms of nicotine withdrawal after cessation of smoking. This makes nicotine patches potentially suitable for trial in ADNFLE. A beneficial effect of nicotine on ADNFLE seemed likely when the patient reported an increase in seizures on cessation of smoking, a possibility subsequently strengthened by an open trial of nicotine administration by dermal patches as well as a double-blind trial of active versus placebo nicotine patches.

The semiology of the seizures, the stability of the semiology over many years, the presence of seizures on awakening, the temporal distribution of the seizures (clustering

as seen in Fig. 1), and the family history are consistent with refractory ADNFLE. The patient's perception of an improved sleeping pattern is unlikely to have influenced the outcome of the trial, given that this patient's seizures were expected on awakening, rather than after her own consideration of her subjective sleep pattern.

As reviewed by Visi and Lendvai (4), acetylcholine (ACh) nicotinic receptors have incompletely defined CNS actions, but a major one is to modify neurotransmitter release from terminals by altering presynaptic concentration of cations. Nicotine has no presynaptic effects in knockout mice lacking the $\beta 2$ nAChR subunit gene, a knockout that inactivates both the $\alpha 4$ and $\alpha 3$ subunit–containing receptors. Thus nicotine seems relatively selective for nicotinic receptors. If nicotine has its effects largely or entirely through nAChR receptors, seizure control with nicotine implies a beneficial effect through activation of these receptors and also that the net effect of the mutation in ADNFLE could be "loss of function." An alternative possibility, consistent with published evidence for a "gain of function," is that the beneficial effect of nicotine is achieved by desensitization of an overactive mutant receptor. Desensitization is a well-known feature of nicotinic receptors (5). If desensitization is beneficial, this would provide support for a theoretic model of ADNFLE, which occurs during and after sleep (1), as follows: during sleep, while endogenous acetylcholine release is reduced, receptors resensitize; sensitized mutant nicotinic receptors then respond excessively to acetylcholine, which is released during rapid-eye-movement (REM) sleep and at waking (6), to mediate seizures. With continued acetylcholine release after wakening, receptors desensitize, preventing further acetylcholine-mediated seizures.

The indirect effects of nicotinic-receptor activation are legion, involving many other neurotransmitter types (4), so that the beneficial effect of nicotine may be unrelated to the pathophysiology of seizures. Nevertheless, in this individual with refractory ADNFLE, nicotine had a therapeutic effect on seizures, and it may be useful to others with this disorder.

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