NO CLINICALLY RELEVANT EFFECT OF INTRAVENOUS IMMUNOGLOBULINS ON CATAPLEXY IN A DOUBLE-BLIND N=1 TRIAL

Rolf Fronczek, Jan Verschuuren and Gert Jan Lammers.

Leiden University Medical Centre, Department of Neurology, PO Box 9600, NL-2300 RC Leiden, The Netherlands

INTRODUCTION

Narcolepsy with cataplexy is caused by a loss of hypocretin producing neurons in the lateral hypothalamus\(^1,2\). The strong Human Leukocyte Antigen (HLA DQB1*0602) association supports an autoimmune aetiology\(^3\). Still, there is no direct evidence for anti-neuronal antibodies or T-cell mediated autoimmunity to support this hypothesis\(^4,5\). Treatment with high-dose prednisone after acute onset of hypocretin-deficiency in an 8-year-old boy without cataplexy was not effective\(^6\). However, two studies suggested that treating narcoleptics with intravenous immunoglobulins (IVIg) shortly after disease onset may dramatically reduce the frequency and severity of cataplexy\(^7,8\). We present a n=1 study in a patient suffering from narcolepsy with cataplexy for 7 years, who was almost unresponsive to any regular treatment, but had a dramatic response on open label treatment with IVIg.

The 55 year old female patient had typical complaints of narcolepsy (EDS and cataplexy) with typical findings on a Multiple Sleep Latency Test (MSLT: mean stage 1 latency was 2 minutes, sleep onset REM at 3 testing times). She was HLADQB1*0602 positive, and had no detectable hypocretin-1 in her CSF. She suffered from very frequent complete cataplectic attacks, according to her diary (3.30±0.15 attacks per day; range 3-4). Together with her severe excessive daytime sleepiness, she was invalidated with a profound impact on her quality of life. The patient was almost homebound and evaded social activities to avoid a provocation of her complaints. After informed consent, we treated her with open label IVIg (1gm/kg/day over 2 days). After treatment she reported a profound reduction of cataplectic attacks and several days without any attacks. This effect lasted for three weeks and disappeared gradually. Repeated treatment six months later showed a similar response. We started a double-blind placebo-controlled n=1 trial to analyse this remarkable response.

METHODS

The study consisted of four successive treatment periods in which IVIg or placebo was randomly administered. If the patient did not experience significant clinical improvement within 10 days after treatment, she could request for ‘rescue’ medication. This rescue medication was IVIg when the treatment period was started with placebo and placebo when the treatment period was started with IVIg. The next treatment period was started after the patient indicated that the treatment effect had disappeared, and at least 4 weeks after the previous treatment. During the entire study period, the patient was asked to keep a diary in which she noted the number of complete cataplectic attacks (since complete attacks are
scored more reliable than partial attacks), and the severity of sleepiness (Visual Analogue Scale, 1 = very awake, 10 = very sleepy). Every 14 days a Maintenance of Wakefulness Test (MWT)\(^9\) and a vigilance test (Sustained Attention to Response Task, SART)\(^10\) were performed. Since the effect of IVIg on cataplexy was dramatic when administered in an open fashion, the primary outcome measure was defined as the patient’s ability to distinguish active drug from placebo. Secondary outcome measures were the total number of complete cataplectic attacks, subjective sleepiness according to the VAS, the MWT latency and the performance score on the SART. Differences between placebo and IVIg periods were analysed using t-tests after correction for the number of days within each period.

Figure 1. Total number of cataplectic attacks (grey line) and severity of subjective sleepiness (visual analogue scale, 1 = very awake, 10 = very sleepy, black line) for each day. Each treatment period is marked by a roman number. White areas represent placebo, while shaded areas represent IVIg. During the third and fourth treatment period rescue medication was requested, indicated by the arrows. An asterisk indicates days on which the patient visited the hospital for the maintenance of wakefulness test (MWT).

RESULTS AND DISCUSSION

The study lasted for 188 days. Regarding the primary outcome measure, the patient correctly identified placebo and/or IVIg treatment in half (50%) of the treatment periods: the second (IVIg, 63 days) and third (placebo, 65 days). She mistook placebo for IVIg in the first treatment period (26 days) and IVIg for placebo in the fourth treatment period (34 days). During the preceding two month long baseline situation 1.45±2.72 cataplectic attacks per day (mean ± standard error of mean) were scored. During the study period both treatments
resulted in a decrease of cataplectic attacks. IVIg treatment decreased the attack rate to 0.27±0.73 per day, and placebo to 0.48±1.28 attacks per day. The reduction of attacks of both treatments was significantly lower compared to the pre-study period (p<0.001 for IVIg and p<0.001 for placebo.). There was, however, no significant difference between the two treatment modalities (p=0.17).

Comparing secondary outcome measures between IVIG and placebo there was a significant difference in the severity of subjective sleepiness between the two treatment modalities in favour of IVIg. The subjective sleepiness during placebo treatment was 6.7±0.4, and during IVIg 5.4±0.1 (p<0.01). In contrast, the MWT and the SART did not show any differences between the placebo and IVIg periods. Days when the MWT was administered were very demanding for the patient. This was clearly reflected in her subjective sleepiness according to the VAS, as can be seen on the asterisk-marked MWT days in Figure 1. After exclusion of these demanding days the difference in subjective sleepiness during placebo treatment (6.6±0.1) and IVIg treatment (5.2±0.1) was still significant (p<0.01).

CONCLUSIONS

Open treatment with IVIg led to a striking improvement in the frequency of cataplectic attacks in this patient. However, during a double-blind placebo-controlled n=1 trial the patient was not able to convincingly distinguish placebo from IVIg. Thus, according to our primary outcome measure, administration of IVIg had no clinically useful effect in this patient. In contrast, there was an impressive placebo effect. The patient reported less cataplectic attacks after the first drug administration of the study, which was a placebo gift. The amount of cataplectic attacks decreased dramatically during treatments with both IVIg and placebo. Earlier studies found a decrease of cataplectic attacks around disease onset during IVIg treatment7,8. Although our patient reported less attacks during IVIg this was not significantly lower. There was a small, but significant difference in subjective sleepiness between the placebo and IVIg periods. This is a remarkable finding because an effect on EDS has not been observed before.

Altogether, it is questionable whether the observed effects are clinically relevant.

At this stage we conclude that treatment with IVIg in a chronic stage of disease is not a promising treatment for narcolepsy. Our study demonstrated that the placebo effect can be unexpectedly strong. A larger, double blind study in patients shortly after disease onset is mandatory before use in narcolepsy patients can be recommended.

REFERENCES