Introduction

Myotonic dystrophy (MD) is a multi-system disorder, the most well known symptoms being muscle weakness and myotonia. Distressing daytime sleepiness and diminished spontaneous activity, often referred to as inertia, reduced initiative, inactivity or apathy, are frequently reported. These latter symptoms often seem to cause more hindrance in daily life, both to patients and their spouses, than muscle weakness itself. Hypersomnia can even be present when there is virtually no weakness [1]. Recent reports [2, 3, 4] have demonstrated that modafinil has a beneficial effect on daytime sleepiness in MD. Although the relationship between excessive sleepiness and the lack of spontaneous activity is not clear, it seemed reasonable to suppose that increasing vigilance might result in an increase in spontaneous activity. The present study intended to answer the following questions: firstly, do patients with MD undertake more activities when using modafinil; secondly, does any such improvement relate to a change in somnolence or to another disease characteristic?

Patients and methods

Thirteen outpatients (5 males) participated in a randomized double-blind crossover placebo controlled study. Their mean age was 43.5 years (SD: 13.9 years). Age of onset of symptoms was before 12 years of age in 3 patients; all three lived independently at the time of study, although they needed professional social support with respect to their household or daily...
activities. Three patients were employed in highly responsible jobs. The remaining patients had been considered unfit for normal paid employment for reasons related to their disorder. They were mainly involved in housekeeping. With the exception of two elderly men with considerable weakness of the legs, weakness had little impact on activities of daily living (ADL) functions. Even these two men were ambulant, although they used a wheelchair regularly. Twelve patients had a partner or housemate.

Medication was given during two periods of 14 days, separated by a one-week washout period. The study was preceded by a two-week period free of all drugs with an exception being made for contraception. Patients were randomized for either placebo first or modafinil first. The modafinil dose was 200 mg per day for the first week. The patients were instructed to double the dose during the second week of each period if they perceived an insufficient effect.

The main outcome measure was an increase in spontaneous activity, assessed using a novel structured interview of both the patient and the partner or housemate, if present. These interviews took place at home after the first period, and by telephone after the second one. After the first medication period the patient and the partner/housemate were asked to compare the level of activity with that of the preceding two (-baseline-) weeks. After the second medication period they were asked to compare that period with the baseline weeks.

The following issues were addressed, and scores attributed:

- have you, during the past two weeks, been more active than during the baseline period? (0–5 points)
- no (0 points)
- to some degree (1 point)
- definitely (2 points)
- can you give one (1 point), two (2 points) or three (3 points) substantial and observable examples of activities/specific actions you undertook that you would otherwise not have done?

The range of the score was therefore zero to five points. The partner was asked the same questions with respect to the patient. During the interview patients and partners were asked whether they had guessed which medication, modafinil or placebo, the patient had used in the past period. If so, they were asked what made them believe so. The answers were not used in the assessment of medication effects, but served to estimate possible unblinding. The RAND-36 questionnaire was used to measure possible changes in subjective general health [3]. This was filled in before the start and after the end of each medication period. The questionnaire was restricted to issues considered relevant to the study: General Health, Role Limitations by emotional and physical problem, Social Functioning, Vitality, and Mental Health. The Epworth Sleepiness Scale (ESS, [6]) was used to assess possible changes in hypersomnolence.

After completion of the trial the remaining capsules in the medication boxes were counted to assess compliance. The institutional Committee of Medical Ethics had approved the study. Patients gave written informed consent after study information was provided orally and in writing at the patients’ home.

Results

All patients completed the trial. Medication compliance was good: only three patients had omitted one dose each. The only reported side effect was slight headache in one patient using modafinil. Ten patients doubled the dose of both modafinil and placebo after the first week, meaning that results largely concern a daily dose of 400 mg modafinil. More often than not both patients (67%) and their partners/housemates (77%) correctly guessed when they had been taking either modafinil or Placebo, usually on the basis of a ‘decreased sleepiness’ and/or ‘increased activity’.

The structured interview regarding activity and actions did not show significant differences between modafinil and placebo (p = 0.2 for patients and p = 0.5 for partners/housemates).

The RAND-36 questionnaires revealed a poor perception of general health for the whole group with a mean value of 29 points out of 100 (range 0–50) on the General Health rating.

The ratings were virtually identical for each patient over the four assessments (p = 1, Wilcoxon test). The perception of Role Limitations varied widely: mean 66 out of 100 (range 0–100). A medication related change was not observed (p = 0.7, Wilcoxon test). This also held for the perception of Social Functioning (p = 0.6), Vitality (p = 0.2) and Mental Health (p = 0.5). The ESS revealed a significant improvement with modafinil, in that the mean score decreased from 10.5 (range: 3–18) to 6.8 points (range: 1–15); for placebo the corresponding values were 10.5 (range: 3–18) and 10.7 (range: 2–17) points (p = 0.015, Wilcoxon test). There was no suggestion of a difference in outcome between patients with high and those with low scores. There was no significant relationship between the increase in activity/actions as perceived by the patient/partner and indicated by the structured interview, and changes in perceived hypersomnolence as measured by the ESS (p = 0.38, Spearman’s test).
Discussion

The present study confirmed the beneficial effect of modafinil on excessive sleepiness in MD, but did not detect a concomitant effect on spontaneous activity as measured by a structured interview of the patients and their partners. This interview, not formally validated, was designed to reflect a clinically relevant and observable increase in daily activity by asking for specific actions. Examples might be that patients went to the theatre after a busy day, when they would otherwise have postponed such a visit, or cleaning up the shed. By asking for specific actions we hoped to distinguish actions from the mere feeling of being active or the intention to become so.

The study was small, leaving open the possibility that minor changes have been missed. The study was also focused on short-term effects and thus it is not able to detect changes of behaviour that take more time to become manifest, but we believe that a fortnight is long enough to detect relevant improvements in activity as defined above. A further consideration is the unblinding we have observed, which was most probably due to a correct perception of an effect on somnolence. This might have confounding effects on the interpretation of intended double-blind studies of modafinil on symptoms other than hypersomnolence. In the present study this does not seem to have happened, as the effect on hypersomnolence was neither related to perceived improved activity, nor to perceived aspects of general health. That many patients and partners reported more activity in addition to less sleepiness when asked why they thought that modafinil or placebo had been used, might be the result of the expectations implied in the aim of the study as discussed with the participants. The structured interview did not detect this increased activity, which we feel speaks in favour of its validity.

In a previous study of 11 patients modafinil improved excessive daytime sleepiness in MD, measured with the Multiple Sleep Latency Test and the Epworth Sleepiness Scale [2]. Possible effects on spontaneous activity were not considered. MacDonald et al. [3], in a double-blind cross-over placebo-controlled study of 40 patients with a time-scale identical to ours confirmed the reduction of somnolence as measured by Epworth and Stanford Sleepiness Scales. They also found modafinil-induced decreased fatigue-inertia, and increased vigor-activity, as measured by the Profile of Mood States. The latter findings might predict improved observed activity, but the study did not include this issue and our study did not demonstrate such effect. Using the RAND-36 they also observed enhanced measures of energy and perception of health, but no changes in the other items of the test; the former effects were not confirmed in our study. Talbot et al. [4] performed a similar double-blind cross-over study of 19 patients selected for hypersomnolence (ESS 10 or more points), using the ESS, a Modified Maintenance of Wakefulness test (MWT), a steering simulator, the Short Form 36 and an “activity diary” as measures. They found a reduction of sleepiness, especially in the MWT, less convincingly in the ESS. The other tests did not show significant changes. Data from the activity diaries are not given.

It is apparent that the symptoms referred to as inertia, reduced initiative, inactivity or apathy are hard to define and even harder to measure. Recently, van der Werf et al. inferred that the lack of correlation between fatigue scores and sleepiness in MD suggests that different pathophysiological mechanisms underlie these clinical manifestations [7]). We believe that our findings point in the same direction.

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