CASE REPORT

Transient improvement of poststroke apathy with zolpidem: a single-case, placebo-controlled double-blind study

Katell Autret,¹ Annabelle Arnould,² Sarah Mathieu,³ Philippe Azouvi²

¹Department of PM&R, Pole St Helier, Rennes, France
²Department of PM&R, Hopital Raymond Poincaré and Université de Versailles-Saint Quentin, Garches, France
³Department of PM&R, Hopital Rothschild, Paris, France

Correspondence to
 Professor Philippe Azouvi,
 philippe.azouvi@rpc.aphp.fr

SUMMARY

We report the case of a 44-year-old patient with severe and disabling apathy nearly 2 years after a right hemisphere haemorrhagic stroke. The effect of a single dose of zolpidem was tested over a 2-week period, in alternation with either no treatment or a placebo in a double-blind randomised trial. Zolpidem was associated with a dramatic improvement in apathy, as assessed with the Apathy Inventory and the Behavioral Dysexecutive Syndrome Inventory. No adverse effect occurred during the trial.

BACKGROUND

Apathy is a frequent consequence of brain damage, which has been found to be associated with poor recovery and rehabilitation outcome after stroke.¹ However, there is, to date, no known treatment for apathy.

Recent findings suggested that zolpidem, an ω -1 γ -aminobutyric acid agonist, commonly prescribed for treatment of insomnia, may have paradoxical awakening effects in a few brain-injured individuals with disorders of consciousness (vegetative or minimally conscious states).^{2–3} In addition, other case reports showed positive responses to zolpidem of other neurological impairments, such as aphasia,⁴ cerebellar ataxia,⁵ akinetic mutism⁶ or behavioural inhibition in a case of schizophrenia.⁷ As per our knowledge, a beneficial effect of zolpidem on post-stroke apathy has not been reported previously.

CASE PRESENTATION

The patient was a 44-year-old man, director of a department store, without any previous neurological or psychiatric condition, who suffered from a right retro-rolandic arteriovenous malformation, responsible for headache. Four days following endovascular treatment of the malformation, he presented with sudden onset of a very severe left sensorimotor hemiplegia, related to a large retro-rolandic right hemisphere haematoma. He underwent emergency neurosurgical intervention to remove the haematoma. He was referred to our department for rehabilitation 6 weeks later. Upon admission, he showed a dense left hemiplegia, with no residual upper limb motor function, but with partially preserved lower limb motricity. He also suffered from severe cognitive impairments including disorientation for time and place, left hemineglect, attentional deficits and cognitive slowing. After a few months of multidisciplinary rehabilitation, there was a moderate improvement of

motor function (he was able to walk under supervision but did not recover arm and hand function), and a marked improvement of cognitive abilities. Neuropsychological assessment, 18 months post-stroke onset, showed that he was fully oriented for time and place; speed of information processing was within normal limits and there was no longer any detectable sign of unilateral neglect on cancellation and line bisection tests. He nevertheless suffered from impairments in higher order cognitive functions, related to a mild dysexecutive syndrome (with deficits of flexibility, planning and inhibition) and to disorders of divided attention and working memory. At this time, his functional independence was predominantly limited by a major apathy. He was unable to initiate by himself any elementary activity of daily living (including dressing, grooming, bathing and transferring from wheelchair), although he was able to carry out such activities when strongly prompted to by his therapists. He tended to attribute this lack of initiative to fatigue. Different pharmacological treatments were successively tested, including ropinirole, modafinil and antidepressants (fluoxetine, then paroxetine, then an association of venlafaxine and mirtazapine), but these were totally ineffective, and the patient's apathy remained stable over time. It was then decided to introduce zolpidem, 23 months poststroke onset.

TREATMENT

A double-blind placebo-controlled design was used, during which the effect of a single-dose of 10 mg of zolpidem was compared with placebo and with baseline (no additional medication). The rationale for using such a design with three arms (baseline, placebo and treatment) was to control for two potential confounding factors: the first one was possible spontaneous fluctuations of apathy (independent of treatment), and the second one was a placebo effect (which could be potentially high on a complex symptom such as apathy). All other medications, including antiepileptics and antidepressants, were continued without any modification. This treatment was tested over a 9-day period during which the patient randomly received zolpidem, placebo or no treatment. Zolpidem was given on days 2, 4 and 5, placebo was given on days 6, 7 and 9 and no treatment was given on days 1, 3 and 8 (baseline). The patient and his family were informed of the experimental nature of the treatment and gave their consent to participate.

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Treatment efficacy was assessed on each of the 9 days of the trial by an examiner blind to the treatment.

The primary outcome measure was the Apathy Inventory.⁸ This scale has been designed for global assessment of apathy, with separate assessments for emotional blunting, lack of initiative and lack of interest. Two versions of the scale were used: one for the caregiver and the other for the patient (self-assessment). Both frequency and severity of changes that have occurred since the onset of the disease were scored by the examiner on a Likert-style scale. The maximal score (indicating more severe apathy) was 4 for each of the 3 subscores and 12 for the total score.

The secondary outcome measure was the Behavioral Dysexecutive Syndrome Inventory.⁹ This is a behavioural questionnaire encompassing different cognitive and behavioural problems related to deficits of executive functions. For each item of the scale, both severity and frequency of occurrence of the disorder were rated, and the score used in the present study was frequency $\times$ severity (maximal score indicating more severe disorder=12). Two subscores were computed from this latter questionnaire: an apathy subscore, which was the mean of the three following items: activity reduction, poor initiation and lack of interest; a disinhibition subscore (to control for any adverse effect due to lack of control), based on the average of the following items: euphoria, irritability/aggressiveness, impulsivity, perseveration and social behaviour impairment.

Outcome measures were scored by a therapist blind to the treatment, during a physiotherapy session that took place in the morning, about 1 h after ingestion of treatment (or around 10:00, on days without treatment).

OUTCOME AND FOLLOW-UP

The mean scores (out of three measures under each condition) on the main outcome measures are shown in table 1. It appears that zolpidem was associated with a dramatic improvement of each of the 3 subscores and of the total score of the Apathy Inventory (therapist's ratings), and also of the apathy subscore of the Behavioral Dysexecutive Syndrome Inventory.

Table 1 The mean (SD) outcome measures across 3 days under baseline, placebo or zolpidem

	Baseline	Placebo	Zolpidem
Apathy inventory			
Emotional blunting	4 (0.0)	3.6 (0.6)	0.3 (0.6)
Lack of initiative	3.3 (1.5)	4.0 (0.0)	0.0 (0.0)
Lack of interest	4.0 (0.0)	4.0 (0.0)	0.3 (0.6)
Global Score	11.3 (1.1)	11.7 (0.6)	0.7 (0.3)
Behavioral Dysexecutive Syndrome Inventory			
Activity reduction	11.0 (1.7)	12.0 (0.0)	0.0 (0.0)
Poor initiation	9.0 (3.0)	12.0 (0.0)	0.0 (0.0)
Lack of interest	8.3 (4.0)	12.0 (0.0)	0.0 (0.0)
Mean Apathy Score	9.4 (0.5)	12.0 (0.0)	0.0 (0.0)
Euphoria	0.0 (0.0)	0.0 (0.0)	8.0 (0.0)
Irritability/aggressiveness	5.0 (4.5)	4.0 (6.9)	1.3 (2.3)
Impulsivity	0.0 (0.0)	0.0 (0.0)	2.7 (2.3)
Perseveration	2.0 (3.5)	2.0 (3.5)	0.0 (0.0)
Social behaviour impairment	2.0 (5.2)	2.0 (3.5)	2.7 (2.3)
Mean disinhibition score	2.0 (1.7)	1.6 (2.7)	2.9 (0.4)

Higher scores indicate more severe disorder.

Kruskal-Wallis tests were computed and showed that the effect of condition (zolpidem vs placebo vs baseline) was significant for the three subscores of the Apathy Inventory (H corrected for ties=6.8, 7.0 and 7.7 for emotional blunting, lack of initiative and lack of interest, respectively, all $p < 0.05$) and for the total score as well (corrected $H = 5.9$, $p = 0.05$). The effect of condition was significant also for the three apathy-related items and for the apathy subscore from the Behavioral Dysexecutive Syndrome Inventory (corrected $H = 7.0$, 7.1, 7.1 and 7.7 for activity reduction, poor initiation, lack of interest and mean apathy subscore respectively, all $p < 0.05$). Clinical observation indicated that the effect occurred about 30 min after ingestion, and lasted about 3–4 h.

This improvement in apathy was not accompanied by an increase of disinhibited behaviour, as indicated by the lack of any significant change of the disinhibition subscore of the Behavioral Dysexecutive Syndrome Inventory, although the score of one of the items, euphoria, tended to increase (mean disinhibition score, Kruskal-Wallis corrected $H = 1.12$, $p > 0.1$).

The self-assessment ratings of the Apathy Inventory could unfortunately not be analysed statistically, due to insufficient patient participation, particularly on days without zolpidem. He completed the questionnaire on only two occasions without treatment (on days 3 and 8), and on two occasions with zolpidem (days 2 and 5). Total scores tended to decrease from 10 and 25 without treatment to 7 and 6 under zolpidem.

No other change was observed regarding motoricity and cognitive functions (as assessed with the Mini Mental State Examination).¹⁰ However, therapists noted that, during the days with zolpidem, the patient tended to be more active and participating in rehabilitation. For example, 30 min after ingestion of zolpidem, he was able to dress and groom himself alone, without any stimulation, though this was impossible on the other days. No adverse effects occurred, and the patient and his family agreed to continue taking zolpidem (twice a day, in the morning) after the end of the experimental trial.

DISCUSSION

Administration of a single dose of zolpidem produced a transient but dramatic improvement in apathy, as compared both with baseline (no additional treatment) and with placebo, without any adverse effect, and particularly, without any increase of behavioural disinhibition. This patient was in a chronic stage (nearly 2 years) after a right hemispheric stroke and all other medications had been previously ineffective. As per our knowledge, this is the first report of a beneficial effect of zolpidem on poststroke apathy, a severe condition without any known treatment. The mechanism of action of zolpidem remains unclear. Previous studies using functional neuroimaging with zolpidem in patients with disorders of consciousness or aphasia found that the therapeutic effect was related to the transient release of a dynamic diaschisis, permitting the temporary increase of activity in structurally intact but functionally underactivated brain regions.^{4 6 7 11}

This study suggests that zolpidem can be beneficial to some individuals with brain injury, and that its potential action is not limited to disorders of consciousness, but may also concern other behavioural or cognitive impairments, such as apathy. However, previous studies suggested that, for some unknown reason, not all patients benefit from this treatment. Further research is needed to find out how many patients may be zolpidem-responders and which criteria may predict individual's response to treatment.

Learning points

- ▶ Apathy is a disabling consequence of stroke.
- ▶ There is, to date, no known treatment for post-stroke apathy.
- ▶ Zolpidem may be useful in a few patients with severe post-stroke apathy.
- ▶ However, response to treatment is unpredictable.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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