# Rapid reversal of tolerance to benzodiazepine hypnotics by treatment with oral melatonin: a case report

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## Abstract

A 43 year old woman had suffered from insomnia for the past 11 years and was being treated with benzodiazepines. All attempts to stop benzodiazepine treatment resulted in withdrawal symptoms and a renewal of the insomnia. Treatment with 1 mg of controlled release melatonin enabled the patient to completely cease any benzodiazepine use within two days, with an improvement in sleep quality and no side effects. Examination of urinary 6-sulphatoxymelatonin levels before the melatonin treatment indicated that the levels were very low and lacked the typical circadian rhythm of excretion. Reexamination of 6-sulphatoxymelatonin levels during melatonin treatment revealed the existence of a normal circadian rhythm of excretion. This case may suggest that some of the people suffering from insomnia and addicted to benzodiazepines may successfully undergo withdrawal from these drugs and improve their sleep by means of treatment with melatonin. The results of this single case study warrant further investigation of a larger population by means of a double- blind placebo-drug study. © 1997 Elsevier Science B.V.

## 1. Introduction

Benzodiazepine hypnotics are among the most commonly used drugs in the treatment of insomnia. Since insomnia is a very frequent complaint among the adult population of western countries, these drugs are consumed in large amounts (Kryger et al., 1994). The precise mechanism by which benzodiazepines exert their hypnotic effect has not been completely elucidated. It is well documented that benzodiazepines are useful in initiating sleep, but that they reduce the amount of deep sleep [stages 3–4], thus inducing non-restorative sleep (Kryger et al., 1994).

Chronic benzodiazepine administration may induce tolerance, expressed by an ineffective increase in dosage. In order to overcome the reduction in drug effectiveness,

patients tend to add other benzodiazepine preparations. These measures all result in further derangement of sleep architecture. Moreover, withdrawal phenomena may follow abrupt cessation of these drugs (Greenblatt and Shader, 1978). Besides the withdrawal symptoms of tremors, nausea, headaches and malaise, there is a renewal of the insomnia. It is, therefore, recommended, that following chronic administration, benzodiazepines be tapered off gradually over a period of days or weeks (Rall, 1990). No method of rapid withdrawal followed by an effective alternative treatment has yet been reported in patients who developed tolerance to benzodiazepine hypnotics.

Melatonin, an indolamine hormone formed in the pineal gland, plays a major role in mediating the circadian sleep–wake cycle and regulating sleep (Arendt, 1988). There is some evidence that a reciprocal relationship exists between melatonin and benzodiazepines: benzodiazepine binding sites have been identified in the pineal gland (Cardinali et

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al., 1986); benzodiazepines may, in some species including humans, potentiate GABA-induced inhibition of melatonin synthesis and secretion (McIntyre et al., 1988); melatonin mediates changes in GABA and benzodiazepine receptor function (Cardinali et al., 1986); pinealectomy disrupted the diurnal variation of benzodiazepine binding in rat cerebral cortex (Acuna-Castroviejo et al., 1986), whereas chronic melatonin administration restored the binding (Niles et al., 1987).

Therefore, we assumed that the tolerance which develops following chronic benzodiazepine administration may be associated with some derangement in the normal melatonin rhythmic secretion, and that exogenous melatonin may be helpful in alleviating the tolerance phenomenon.



Fig. 1. Actigraphic monitoring before treatment.

## 2. Case report

S.M., a 43 year old female, married with two children, had been suffering from insomnia, accompanied by frequent and severe migraine attacks, for the past 11 years. A thorough neurological assessment was negative. Psychiatric or other organic problems were also ruled out. Throughout these years, she had been treated with benzodiazepines, tricyclic antidepressants and neuroleptic drugs, as well as by biofeedback and relaxation methods, with no apparent relief. For the last year she had been using 4–8 mg lorazepam every night.

An exhaustive psychological evaluation, at the Tel Aviv University Sleep Disorders Laboratory, did not disclose any significant pathology. The quality of sleep was assessed by an actigraph tracing, which automatically monitors the bedtime sleep–wake pattern using a small device attached to the wrist (Sadeh et al., 1989). 24 h of actigraphic recording for five consecutive days showed a derangement in sleep efficiency, sleep latency and waking episodes. The patient's sleep was found to be fragmented and with low efficiency (Fig. 1).

Urine was collected every 3 h (for 24 h) and assayed for the major melatonin metabolite, 6 sulphatoxymelatonin, as an indicator of diurnal secretion of plasma melatonin (Aldhous and Arrendt, 1988). Results showed that 6-sulphatoxymelatonin levels were very low – lower than in the average population – and lacked the typical circadian rhythm of excretion (Fig. 2).

1 mg of oral controlled release melatonin formulation (Neurim Pharmaceuticals, Israel) was prescribed, to correct for the deficiency and distortion of the melatonin rhythm. The tablets were administered daily at 8:30 p.m. The patient was asked to gradually reduce the number of benzodiazepine tablets taken each night. Surprisingly, within two days, the patient stopped using the benzodiazepine hypnotics altogether, and claimed that her insomnia had improved remarkably. In addition, her headaches also subsided gradually. She continued this
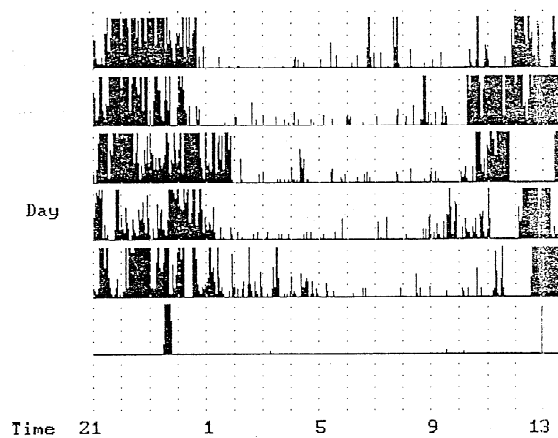
treatment for 4 weeks, during which she claimed to have no sleep problems. During the fourth week we repeated the actigraphic monitoring, as prior to treatment. The objective actigraphic results confirmed the patient's subjective report of sleep quality improvement. A comparison of the actigraphic data before and after the melatonin treatment [$t$-test] shows that following treatment there was a tendency to fall asleep earlier, to spend a shorter period of time in sleep, to have longer periods of uninterrupted sleep, as well as a significant reduction in the number of awakenings ($t=5.32$, $p<0.0002$) (Fig. 3).

We then asked the patient to stop taking the melatonin, and after a 1-week wash-out period, urine samples were again collected, for a period of 24 h. Although the results (Fig. 4) indicated only a slight increase in the amount of 6-sulphatoxymelatonin, a very clear nocturnal peak at 3 a.m. (within the normal range) of urinary 6- sulphatoxymelatonin was apparent.

Since the patient again complained of a decline in her sleep quality following melatonin withdrawal, melatonin administration was resumed and her complaints subsided. A 5-month follow-up, under continuous melatonin treatment of 1 mg daily, confirmed that the patient has maintained her quality of sleep and hardly suffers from headaches.

## 3. Discussion

The mechanism of tolerance to benzodiazepines is uncertain. However, it has been shown, with several benzodiazepine derivatives, that tolerance is associated with benzodiazepine receptor down regulation and decreased GABA-A receptor function (Miller et al., 1988).

We have recently demonstrated that in rats treated daily with intraperitoneal diazepam for 3 weeks, melatonin binding sites were suppressed in the medulla-pons. Even more interesting was the observation that exogenous melatonin was able to augment benzodiazepine binding
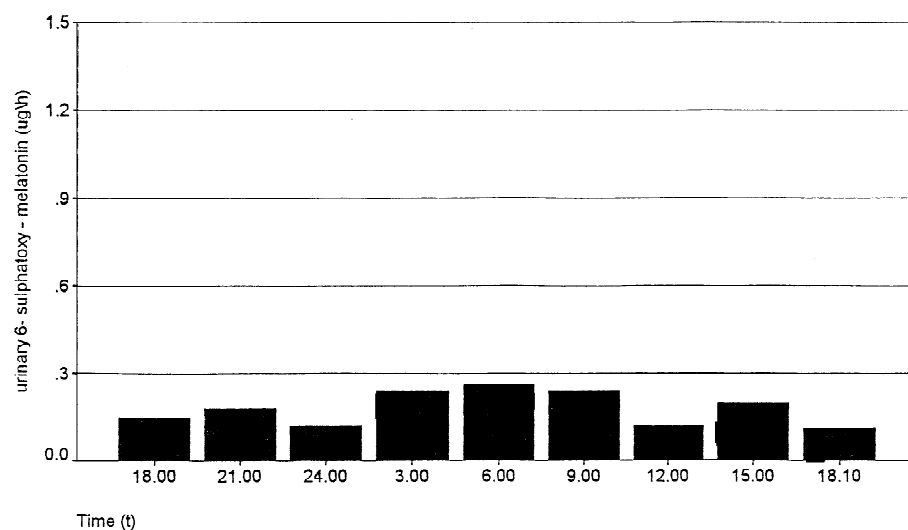
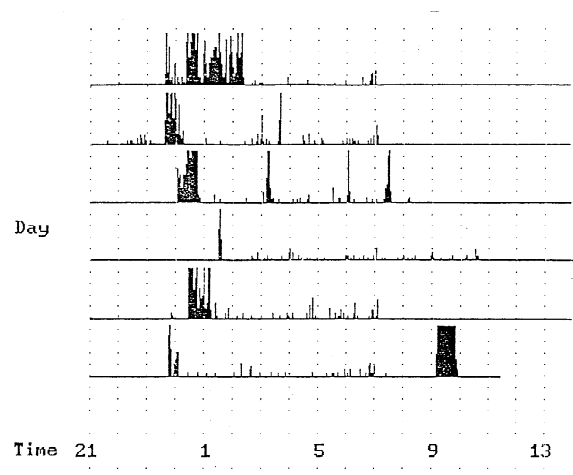Fig. 2. Urinary 6-sulphatoxy-melatonin before treatment.



Fig. 3. Actigraphic monitoring after treatment.

sites in this area, and abrogate the diazepam-mediated suppression of melatonin binding sites (Atsmon et al., 1995).

It may be possible that the initial problem of this patient was low levels of endogenous melatonin secretion of unknown cause, which resulted in insomnia. If so, all the drugs used by the patient would have failed to improve her sleep. The long period of benzodiazepine administration may have further reduced the overall amount of melatonin and, even more notably, have abolished the circadian secretion of her melatonin. The successful treatment in this case is due, first of all, to the reorganization of the circadian melatonin secretion and secondly, to the elevation of the amount of melatonin.

Melatonin replacement therapy has recently been shown to effectively improve sleep quality in melatonin-deficient
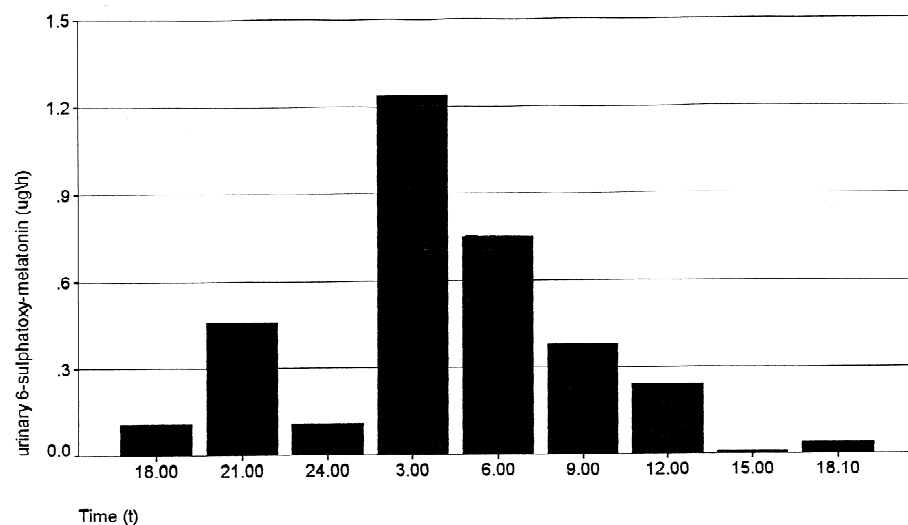


Fig. 4. Urinary 6-sulphatoxy-melatonin after treatment.

elderly patients (Haimov et al., 1994; Garfinkel et al., 1995). While the effect of prolonged benzodiazepine treatment on melatonin receptors in the human brain is still unknown, it is pertinent to suggest that melatonin might act to augment benzodiazepine and melatonin receptors, thereby reinforcing sleep-promoting mechanisms.

Although this case was not treated as a double-blind placebo-drug study, the fact that there was a change in the levels and circadian pattern of excretion of the urinary melatonin metabolite, minimises the possibility that the change was due to a placebo effect.

Although this case report is preliminary and further investigation is warranted, it may indicate a breakthrough in relieving the many patients who do not respond to conservative treatment with benzodiazepine hypnotics and whose quality of life has been impaired by insomnia. Moreover, exogenous melatonin may serve as the treatment of choice in a sub-group of low melatonin insomniacs and a method for rapid and symptomless withdrawal from benzodiazepines in tolerant patients.

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