

MEGADOSE BROMAZEPAM DEPENDENCE

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SUMMARY

Background: Benzodiazepines (BZDs) are among the most widely prescribed drugs in developed countries. Since BZDs can produce tolerance and dependence even in a short time, their use is recommended for a very limited time. However, these recommendations have been largely disregarded. The chronic use of BZDs causes a number of serious side effects, i.e. cognitive impairment, falls, traffic accidents, dependence and tolerance.

Methods: We present the case of a 37 years old woman taking daily doses of 220 mg of bromazepam. The patient's anxiety, depression and cognitive status were evaluated with a battery of questionnaires. A sleep laboratory test was performed in search of sleep apneas and sleepiness during the day. A Cerebral PET SCAN was executed in search of altered cerebral metabolism.

Results: Blood concentrations of bromazepam reached 7800 µg/L. Questionnaire evaluations showed significant depression and anxiety but only moderate cognitive impairment. Oxygen saturation was normal throughout the Sleep lab test, respiratory events were very few and sleepiness was moderate with an average latency of 9 minutes. Brain cortical glucose consumption was homogeneously slightly reduced.

Conclusions: With doses of bromazepam reaching 15 times the toxic dose, anxiety remained high. Cognition, sleepiness, respiratory sleep events and brain metabolism remained remarkably close to normal.

Key words: dependence – tolerance – megadose – benzodiazepine – BZD - bromazepam

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INTRODUCTION

BZD tolerance and dependency can occur very rapidly, this is why their use is currently recommended only for limited periods (Lader 2011). Tolerance develops following repeated administration, and varies according to the individual. This is an adaptation mechanism by the organism that manifests itself by a lessening of the effectiveness and toxicity of the psychotropic substance. The two principal mechanisms are functional tolerance (loss of neurone sensitivity to the action of the psychotropic substance) and metabolic tolerance (increased rate of metabolism of the substance). There are different types of tolerance: innate, acquired, acute (tachyphylaxis), cross, reverse (Ben Amar 2015). Tolerance to the different effects of BZDs manifests itself at different rates and to different degrees. Thus, it is generally recognised that tolerance to sedation appears first (after a few weeks), tolerance to the anticonvulsive effect occurs more slowly, while the anxiolytic effect subsists for longest (Pelissolo & Bisserbe 1994). Although the literature is divided on the subject, complete tolerance to the cognitive effects does not seem to occur (Lader 2011). Tolerance manifests itself by the need to increase the dose in order to maintain the effect and can thus lead to dependency. There are generally two types of BZD dependency: dependency from pharmacological use induced by the prolonged use of BZDs prescribed in therapeutic doses, and the intentional and recreational abuse of BZDs, often as part of poly-drug use (O'Brien 2005). Chronic use of BZDs is the main risk factor for tolerance and

dependency. In the general population, the prevalence is around 2-7.5%, and it is estimated that 25% à 76% BZD users do so for a prolonged period (Fang et al. 2009). Another problem with BZDs is the consumption of high doses. In a cross-sectional study of the population involving 520,000 patients, Petitjean et al. (2007) estimated that 1.6% of patients were being prescribed doses of BZD more than double the recommended maximum dose. Studies carried out in France, Germany, Italy and the United Kingdom showed that 3.9% of users of hypnotics and 3.3% of users of anxiolytics took a dose higher than the recommended one (Ohayon & Lader 2002).

We will describe here a case of mono-dependency to a megadose of bromazepam. Bromazepam is mainly used as an anxiolytic, although it also has major hypnotic and sedative properties. In order to assess tolerance to the therapeutic and secondary effects of bromazepam, anxiety and depression scales, a polysomnography test, a neuropsychological evaluation and a PET scan were used. To our knowledge, there is no other case in the literature of tolerance to a megadose of BZD documented with objective data.

METHODS

A 37 year-old patient attended the toxicology consultation for an anxiolytic use disorder. These were initially prescribed to treat a generalised anxiety disorder; when we met her, the patient has been taking a daily dose of 220 mg of bromazepam for several years. She has no major medical or psychiatric antecedents,

notably none of other substance use disorder. She is 173 cm tall and weighs 71 kg. The patient is complaining of anxiety and affective depression. She drives, carries out her activities and looks after her children. Although the clinical examination was unremarkable, given the size of the dose taken, we wanted, on the one hand, to preclude an intoxication that could lead to respiratory depression. We asked for a sleep laboratory test to look out for apneas and sleepiness. On the other hand, we fear confusion or impairment of cognitive functions which we know patients are not necessarily aware of (Ashton 2002, Golombok et al. 1988). We ask for a neuropsychological assessment. As some authors (Kitabayashi et al. 2001, Schmauss & Krieg 1987) have reported the possibility of cerebral lesions induced by prolonged use of high doses of BZDs, we have a PET scan carried out. Finally, we carry out toxicology analyses to rule out the use of other substances.

RESULTS

The blood concentration of bromazepam is 7800 µg/L. Various questionnaires are used (Symptom Check List -90R, BATE Questionnaire, Caroll depression scale, CES-D, abridged Bech questionnaire, Penn State Worry Questionnaire, Intolerance of uncertainty Questionnaire) and indicate scores for depression and anxiety that are moderate to high. The polysomnography shows generally good oxygen saturation, an apnea 0.4 per hour of sleep, and the presence of some episodes of anxiety type respiratory episodes. Daytime sleepiness is slight, with an average sleep latency of 9 minutes in the multiple sleep latency test. This result is considered as non-pathological according to the recently-modified American Academy of Sleep Medicine manual (2014). The neuropsychological assessment shows capacities in long term verbal memory (California Verbal Learning Test, Buschke 16, Rey 15 item test), working memory (Digit span, Brown Peterson, Alpha Span), visuoconstruction abilities (Drawing a cube, Ruche test) and verbal fluency that is within the norms. In terms of attention functions (Zazoo), the quality is normal, but the speed of information processing is slightly deficient (D2, parts 1 of the Stroop and Trail Making Test (TMT)). At the executive level (Tower of London, REY complex figure), the spontaneous (fluency) and reactive (TMT) flexibility processes are within the norms; the inhibition processes are pathological (Stroop). Finally, the PET scan shows only a slight and non-significant tendency to an overall cerebral hypometabolism.

DISCUSSION

In the literature, relatively few cases concerning the prolonged use of BZD megadose have been reported. Prabhat et al. (2003) reported the case of a patient, who had alcohol dependency antecedents, who, for more

than a year, took 300 mg of lorazepam daily. Mowla et al. (2007) wrote about a patient with a borderline personality disorder who took 180 mg of clonazepam a day in a context of multiple drug use. Quaglio et al. (2012) presented a case of dependency to a megadose of bromazepam (400 mg per day), also in a context of abuse of other substances and of major psychiatric comorbidities. The fact that patients with an alcohol or other substance abuse disorder tend to use higher doses of BZDs through a phenomenon of cross tolerance has been widely documented (Lader 2011). The case we are discussing is particularly interesting, since there is no history of addiction other than to bromazepam. Furthermore, the authors either only mention a clinical impression of tolerance (Mowla et al. 2007, Quaglio et al. 2012), or highlight major sleepiness (Prabhat et al. 2003). In none of the reported cases of dependency to a megadose of BZD has a tolerance to the therapeutic and secondary effects been demonstrated. Therapeutic plasma concentration levels of bromazepam are of 80 to 170 µg/L. Concentrations higher than 250 µg/L are generally considered as potentially toxic. Our patient has developed a highly significant level of tolerance that enables her to support a plasma concentration level of 7,800 µg/L without, as we shall see, any major clinical problem. Given the value of the plasma concentration level, unlike Mowla et al. (2007), we may believe that the principal mechanism of tolerance to BZD is not an increase in the rate of metabolism. This hypothesis is also supported Gravielle (2015), who concludes that tolerance to BZDs would be the result of multiple mechanisms involving different modifications to the GABA_A receptors.

Tolerance to anxiolysis

While the effects of prolonged use of high doses of BZDs are very little documented, the secondary effects linked to their chronic use – such as sedation, impairment of psychomotor and cognitive performance, the risk of cognitive decline and falls (particularly among older people), as well as the risk of accidents in the home or on the road – are now well known and some of those effects appear to be dose-dependent (Lader 2011, Ashton 2002). The studies dealing with the effects of prolonged use of BZDs at high doses are rare, as we have said, but it would appear that an increase in anxiety and the underlying depression can appear (Galanter & Kleber 2008). This aggravation of the symptoms could be due to tolerance of the anxiolytic effects, and thus to the appearance of “withdrawal” symptoms despite the continued presence of the drug (Ashton 2002). However, while tolerance to the anxiolytic effect following chronic exposure has been demonstrated in pre-clinical trials, it has been more difficult to prove it in humans. Thus, tolerance does not seem to be a reality for all. Several authors (Worthington et al. 1998, Lucki et al. 1986, Hollister et al. 1981) have shown that BZDs retained their

anxiolytic properties even after being administered for several years. In our patient, the anxiolytic effect has not lasted. On the contrary, it would appear that there has been an increase in anxiety and depression. Nonetheless, a limiting factor is that we do not have an objective assessment made prior to the administration of bromazepam.

Tolerance to the cognitive effects

The most problematic secondary effects of chronic use of BZDs are impairment of the cognitive functions that can affect numerous areas: attention/concentration, visuospatial (Barker et al. 2004, Golombok et al. 1988), the rate of information processing, working memory, implicit and explicit memories (Barker et al. 2004, Buffett-Jerrott & Stewart 2002), psychomotor speed, motor control/performance, overall intelligence, verbal reasoning, problem solving, sensory processing (Barker et al. 2004). Against all expectations, the results of the cognitive tests carried out on our patient brought to light only a specific disorder in inhibition and processing speed. It must be noted, however, that certain areas were not tested (psychomotor speed, motor control/performance, sensory processing). Overall intelligence was not assessed either, but, since the patient is an accredited teacher of secondary school mathematics, we may reasonably infer that her IQ was normal. The results of the study by Lucki et al. (1986) go in the direction of the case we present. They compared the performance of 43 chronic takers of BZD (average period of five years) with those of 26 control anxious patients. They did not find any statistically significant differences in motor speed, psychomotor functions, explicit memory, sustained attention and subjective sedation; however, processing speed was slightly reduced in BZD users. It therefore appears that a tolerance to most of the cognitive effects of BZDs can develop in certain subjects following chronic, or even, as in our case, massive use. Furthermore, the affective depression present in our patient may also be at the origin of the reduction in processing speed and the inhibition disorder (Fossati et al. 2002).

Tolerance to sleepiness

By binding to the GABA_A receptors, BZDs facilitate the action of GABA, the main CNS inhibiting neurotransmitter. Intoxication from BZDs alone are thus at the origins of a depression of the CNS that is manifested itself by sleepiness and can lead as far as a calm hypotonic coma, which is rarely very deep. The severity of the CNS depression is notably influenced by the dose (Gaudreault et al. 1991). Surprisingly in our patient, despite the daily megadose of bromazepam taken, we did not bring to light any sleepiness. To our knowledge, this is the first time that a tolerance to sleepiness has been shown by a MSLT in a case of chronic use of high level of BZD.

Tolerance to respiratory effects

While, as we have said, a deep coma with cardio-respiratory arrest is rare (Gaudreault et al. 1991), pulmonary aspiration and a certain level of pulmonary depression can sometimes lead to death in some cases of BZD intoxication (Drummer & Ranson 1996). The mechanism for respiratory depression is not yet clearly understood but, as well as a central component, a peripheral component such as obstruction of the airways, notably through myorelaxation, is probable (Megarbane & Baud 2002). The same processes would be at the root of an increase in the risk of respiratory disorders during sleep, notably in cases of occlusive sleep apneas (Brion & Pallanca 2015). We should note that the risk of respiratory depression is increased in the case of use of other substances, such as opiates. Treating our patient involved, initially at least, prescribing very high doses of bromazepam. It was therefore essential to exclude, on the one hand, the use of other substances and, on the other hand, the presence of apneas, and therefore carry out a polysomnography. Surprisingly, the latter did not bring to light any significant apnea or oxygen desaturation. Our patient has therefore developed a respiratory tolerance to BZDs.

Effects on the cerebral metabolism

Since prolonged use of BZDs can be linked to impairment of cognitive functions, research has been carried out to determine whether they were, or not, associated with physiological and anatomical alterations in the brain. Studies using PET scans are, to our knowledge, rare and do not deal with chronic users of BZDs. Studies using CT scanners are more numerous. Schmauss & Krieg (1987) studied 8 patients who had a dependency on high doses of BZD and 9 patients who had a dependency on therapeutic doses; they found a significant positive correlation between the ventricular-brain ratio and the dose or duration of BZD use. Inversely, the study by Busto et al. (2000) on 20 chronic BZD users did not reveal any cerebral atrophy. Kitabayashi et al. (2001), for their part, reported the case of a patient with a dependency on a high dose of nitrazepam (50-100 mg per day over several years) for which a SPECT scan and cognitive tests were carried out. The SPECT scan showed a persistent frontal hypometabolism, while the post-withdrawal cognitive tests showed residual inhibition and divided attention disorder. The authors conclude that prolonged use of BZDs could be linked to a localised lesion of the frontal lobe. We do not confirm this lesion, as our patient's PET scan was normal.

As early as 1961, Hollister and his colleagues were concerned about the risk that patients, given the appearance of tolerance, would increase their doses of BZD. However, in the 1960s and 1970s, this phenomenon was obscured by the enthusiasm raised by the use of these new molecules, and by the fact that their

study dealt with doses much higher than the usual therapeutic doses. The case we present and the few others described in the literature oblige us to once more examine this issue and open our knowledge to question. Indeed, if, as we have said, until now two forms of BZD dependency have been identified, some authors (Lugoboni et al. 2014) draw our attention to a new form of dependency: patients who are perfectly socially and occupationally integrated, with no other history of addiction and no major psychiatric co-morbidity, for whom BZDs were originally prescribed for a problem with insomnia or anxiety, start to progressively increase their doses in a spectacular manner. The authors highlight the negative impact of this mono-dependence on high doses of BZDs on the quality of life and social functioning due to the high level of psychological distress.

CONCLUSIONS

Our case brings to light the possibility of a high degree of tolerance to bromazepam. With doses reaching 15 times the toxic dose, cognition, sleepiness, respiratory events and cerebral metabolism remained remarkably close to normal, while anxiety remained high. For the first time in a case of dependence on a megadose of BZD, tolerance to respiratory effects was demonstrated by a polysomnography, tolerance to sleepiness by a MSLT, as well as tolerance to cognitive effects through neuropsychological tests. Furthermore, within the controversy surrounding the possibility of cerebral lesions linked to prolonged use of BZDs, our case, with a PET scan within the norms, suggests the absence of such lesions. Finally, our case brings to light a seemingly underestimated form of single dependency on high doses of BZD initially prescribed for therapeutic reasons. Other studies are needed, on the one hand to understand why some patients and not others will develop a tolerance to BZDs, on the other hand to better document this phenomenon of mono-dependency on high doses of BZDs.

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