Pharmacotherapy of Benzodiazepines in the Aged Patient

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ABSTRACT:
PHARMACOTHERAPY OF BENZODIAZEPINES IN THE AGED PATIENT

Since the introduction of chlordiazepoxide in 1961, benzodiazepines (BZDs) are most commonly prescribed medications in some psychiatric disorders.
Despite the very large utilization of BZDs, there is evidence to suggest that anxious disorders and insomnia.
The aim of this review is to purpose a better utilization of the BZDs in the geriatric population.

Key words: pharmacotherapy, aged patient, benzodiazepines, dependency, geropsychiatry.

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ÖZET:
YAŞLI HASTALARDA BENZODİAZEPİN KULLANIMI

Klordiazepoksidin 1961'de bulunmasından beri, bazı psikiyatrik bozukluklarda benzodiazepinlerin kullanımı oldukça yaygındır. Benzodiozepinlerin bu kadar yaygın kullanımına rağmen gerçek endikasyonları kaygı bozuklukları ve insomnia ile sınırlıdır.
Bu derlemede yaşlı hastalarda benzodiazepinlerin daha iyi kullanımı amaçlanmıştır.

Anahtar sözcükler: farmakoterapi, yaşlı hastalar, benzodiazepinler, bağımlılık, geropsikiyatri.

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INTRODUCTION

Since the introduction of chlordiazepoxide in 1961, benzodiazepines (BZDs) are the most commonly prescribed medications in anxiety and insomnia (as well as their use in a large variety of other pathologies), in spite of a limited number of studies showing their efficiency for these two indications.

It has been shown that the utilisation of these medications in aged patients represents 27% of the whole prescription treatment whereas the aged patients represent only 14% of the population. Otherwise, BZDs represent 38% of hypnotic prescriptions in the United States (1,2).

Despite the very large utilisation of BZDs, there is evidence to suggest that anxious disorders and insomnia are at times under-diagnosed and under-treated in aged patients (3). This poses the problem of their vast and very weak specificity of utilisation, which proves that these medications are relatively misused. Epidemiological studies show that among 25% of over 65 years old patients are in old folks residences and are often treated with BZDs. The anxious disorders are typically chronic disorders with remission periods and may be exacerbated stressful events. Few quality of life studies concerning aged people have been performed, although anxious symptoms have been associated with a mortality increase, all causes disconcerted and notably sudden cardiac deaths. It is also known that anxious people use the medical services more that others (4). BZDs treatment efficiency and its impact on longevity, quality of life and utilisation of services in aged patients suffering with anxious disorders are not well known.

Recently, BZDs have been prescribed to treat behavioural disorders associated with dementia (5). These behavioural disorders can appear in more than 75% of patients suffering with dementia living in retirement homes and more than half of them show two, or more, problematic behaviours. Few short or long term BZDs efficiency studies concerning sleeping problems and/or behavioural associated dementia symptoms in aged patients exist. Most of the studies included non-benzodiazepine molecules like meprobamate, barbiturates and antihistaminergics.

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Over-consummation and dependence definitions varied and studies that included aged patients have been associated with younger populations.

The aim of this article is to propose a better utilisation of the BZDs in the geriatric population.

Benzodiazepine pharmacology in the aged patient.

Utilisation of BZDs poses a problem with aged patients due to their weak therapeutic index when considering the weak interval of doses between their sedative and anxiolytic properties, showing decreased interval in the aged patient (6).

Ever more so in the young patient, it is necessary to avoid the "sedation trap", i.e. overdosage that renders aged subjects more susceptible to tiredness, prevents them from being active and so decreases their socialisation faculties.

Essentially the pharmacokinetics are modified at the time of the administration of medicines to aged patients.

One essentially notes:

- a slowing of the speed of the digestive reabsorption
- a reduction of the fraction bound to plasma proteins
- a modification volume of distribution of the medication
- a reduction of metabolism
- a reduction of the renal elimination.

Slowing of the gastro-intestinal reabsorption of BZDs is only slightly modified in the aged and is not, in any case troublesome in the utilisation of these medicines as anxiolytics. It avoids the apparition of a peak plasma concentration which may as a consequence result in sedation.

The reduction of plasma protein binding, which increases the liberated fraction and therefore pharmacologically active, doesn't have, in the precise case of benzodiazepines, a therapeutic consequence. Indeed, the increased liberated BZD fraction of little importance when considering the relationship between bound and liberated fraction. For BZD employed as anxiolytics where the percentage binding is 80 to 90%, an increase of activity of some percentage of the liberated fraction implies an increase of activity, apart from the balance of equilibrium phenomenon is attenuated, with correct renal functioning.

However, the BZD half-life is usually lengthened in aged patients, for two essential reasons,:

- because the volume of distribution is increased
- because the clearance rate is decreased.

In fact, the half-life is the relationship between the volume of distribution and the clearance rate:

$t_{1/2} = 0,7 \times V_d/Cl_s$

Some recent studies show that BZDs metabolised by hepatic oxidation had a reduced clearance rate in the aged subject, this phenomenon seemingly more notable in men than women.

The list of BZDs metabolised by oxidation is indicated in the table I. BZDs that are transformed into desmethyl derivatives correspond to this profile (diazepam, clorazepate, prazepam, clobazam, etc.) whereas lorazepam and oxazepam are not oxidised but conjugated before being eliminated. This oxidation capacity can be shown by a test with antipyrine, but it is of course simpler to decrease dosage in a preventive manner. In fact, renal clearance is of equal importance to hepatic clearance.

Creatine which reflects renal function provided that muscular lysis isn't too important must also be considered. An idea of the creatine clearance would be ideal, however this is a parameter not easily obtained in ambulatory medicine.

Otherwise, the volume of distribution (V_d) is increased in aged patients, more so in men than in women. This may explain the sedation decrease associated with a relative increase of fat in contrast to muscular mass that represents aqueous volume, in some patients.

Volume of distribution increase and total clearance ($Cl_t = Cl_{hepatic} + Cl_{renal}$) decrease results in a half-life increase.

Theoratically, half-life increase is due to :

- decrease dosage,
- reduce frequency of dosing

In the case of BZDs with a long half- life, it may be wise to decrease the dosage, taking of medication every 2 or 3 days would be badly discerned by the patient and risk in resulting in inefficient concentrations.

The search of the lowest effective dose lacking sedative effect is achieved initially by dividing the dose administrated to a young adult, while remembering that desmethyldiazepam or desmethylclobazam half-life increases by an hour per year.

The aged patient is often polymedicated, but

Table 1. Metabolic ways of benzodiazepines (7,8)

Initial medication	Metabolic pathway	Active substances in blood
Chlordiazepoxide	oxidation (DM)	Chlordiazepoxide Desmethyldiazepam Oxazepam
Clobazam	oxidation (DM)	Clobazam Desmethylclobazam
Clorazepate	oxidation (DM)	Desmethyldiazepam Oxazepam
Diazepam	oxidation (DM)	Diazepam Desmethyldiazepam Oxazepam
Flunitrazepam	conjugation	Flunitrazepam
Lorazepam	conjugation	Lorazepam
Medazepam	oxidation	Medazepam Diazepam Desmethyldiazepam Oxazepam
Nitrazepam	oxidation	Nitrazepam
Oxazepam	conjugation	Oxazepam
Prazepam	oxidation	Desmethyldiazepam Oxazepam
Halazepam	oxidation (DA)	Halazepam Desmethyldiazepam
Ketazolam	oxidation (OH)	Desmethyldiazepam
Alprazolam	oxidation (OH)	Alprazolam
Temazepam	Conjugation	Temazepam
Lormetazepam	Conjugation	Lormetazepam
Clotiazepam	Oxidation (OH, DM)	Clotiazepam Hydroxyclotiazepam Desmethylclotiazepam
Midazolam	Oxidation (OH)	Midazolam
Triazolam	Oxidation (OH)	Triazolam
Brotizolam	Oxidation	Brotizolam

DM = desmethylation DA = dealkylation OH = hydroxylation

medicinal interactions are rare with BZDs (see paragraph infra) with the exception of the association of two BZDs which compete with each other to bind cerebral sites. Another consequence of ageing, besides pharmacokinetic problems, is an increase sensitivity of the receptor to BZDs.

All these data contribute to decrease BZDs dosage in aged patients. Prudence is necessary for the association of benzodiazepine and alcohol, the latter considerably potentialises the effects of this medicinal class.

Caution is also advised when considering the reputation of good tolerance of BZDs, which may be decreased in the elderly due to the risk of accumulation.

Prevalence and utilisation of BZDs

Rates of prevalence and utilisation of BZDs differ extensively according to the studied populations and according to definitions and usual utilisation in precise indications. Some recent studies reported that utilisation of BZDs in the aged population is on average 15% in an interval from 10 to 42%. Although short half-life BZD utilisation is increased, it was observed that a quarter of the studied aged population used a long half-life BZD. Long half-life BZDs are not generally recommended in the aged patient as an increase of side effects as a result of the accumulation of these medicines may occur.

Because of the heterogeneity of the normal utilisation and abuse definition, there are problems in the interpretation of the long-term risks and advantages of BZD utilisation in aged patients. The categorisation of the utilisation of BZDS has been proposed as acute, intermittent, as well to short, long-term and continuous in an attempt to standardise definitions of utilisation.

Acute utilisation usually of about 7 days or less duration and consist generally of only one dose. Examples include acute treatments in emergency services for a psychotic agitation, pre-operative utilisation or if amnesia is wished, the treatment of the insomniac in the hospital and the treatment of alcoholic withdrawal.

Intermittent utilisation is when the BZD is taken sporadically, generally two or three times per week and for periods not exceeding 60 to 90 days. One can also speak of long term with intermittent utilisation in the measure where the treatment lasts 4 months and more. The treatment of insomnia and anxious disorders with BZDs is very frequent in the aged subject with an intermittent utilisation of these products. When one finely analyses the utilisation in this type of category one perceives that the aged subject is going to use some relatively weak doses and discovers a beneficial effect on morning activity. This is why subjects take doses of 0,5 to 1 mg of lorazepam to facilitate falling to sleep or to decrease their anxiety and are going to indicate to the medicated physician that in fact it permits them to have a better morning. Studies achieved with healthy volunteers demonstrate that small doses of BZDs improved young adult psychometric performance (8,9). A Swedish survey (10) showed that BZDs can have a protective effect against Alzheimer's illness. Authors compared chronic BZD users versus non-users after a period of 3 years. They showed that there was a weaker impact of Alzheimer's illness in the BZD group than in the non-consumers. This negative correlation persists when age, sex, instruction level, utilisation of the anti-inflammatory non-steroids and estrogens are controlled.

Studies in the United States are in progress in the aged subject in the same state of mind to try to understand what underlines the intermittent use of BZDS.

Continuous utilisation is defined by the fact that the subject is going to use the medicine every day, these patients are going to take anxiolytics in a chronic manner and it is especially for anxious disorders, often generalised anxiety and insomnia. The aged subjects and prescribers continue to take these products in a chronic manner in spite of recommendations of a short-term utilisation. Among usual users of BZDs, one finds 21% of users in an action anxiolytic capacity, but 17% in the capacity of a hypnotic action. It corresponds to a rate of prevalence of 3% of continuous utilisation in the general population between 18 and 80 years.

Compared to subjects not using BZDS, continuous users are most often older and most often women, who often take this type of medicine after suffering a bereavement. Indications are often as a result of such a prescription, in fact this prescription causes indirect cardiovascular disorders or rheumatological disorders whatever the nature of these chronic illnesses their treatment is accompanied with a prescription of BZD.

85% of continuous users don't have any support or professional mental health help i.e. these medicines are considered as being in themselves support for the aged patient. Even though no long term efficiency survey of BZDs has been conducted in the aged patient, tolerance to diazepam or other BZDs doesn't develop itself until after 22 weeks of treatment, which is relatively reassuring, i.e., after practically six months most patients have a continuous treatment at a steady dosage that can last effectively for months and years.

Only one survey of efficiency has been conducted in the aged patient to evaluate the continuous utilisation of BZDs in the treatment of chronic insomnia (11). This survey shows that BZDs and behavioural treatments are quite interesting for the treatment of insomnia in the last weeks of life. After

24 months, benefits obtained by the group that did not take the medicine and that therefore had not undertaken behavioural therapy was totally lost, i.e. the basal level was reached. The long-term negative effects of continuous utilisation of these medicines remains unknown other than that of physical dependence. There are some studies that have been carried out concerning the secondary risks such as falls and fractures, cognitive performance reduction and hospitalisation terms i.e., if one either increases or decreases hospitalisations in patients that take this medicine long-term.

Medicinal interactions

BZDs metabolised by oxidation are suggested to effect medicines managed in a concomitant manner at the level of the cytochrome P 450 hepatic system, particularly isoenzymes CYP 3A and CYP 2C19. Medicines inhibiting actions of metabolites of these isoenzymes can decrease the rate of clearance of these BZDs and so increase their half-life and therefore their plasma concentration and can in fact increase their clinical effects in the aged patient. The powerful inhibitors of the CYP 3A are essentially inhibitors of serotonin reuptake, anti-fungal such as the ketoconazole and itraconazole as well as antibiotics of the macrolides group such as azithromycin, erythromycin and clarithromycin. All BZDs are not affected in the same way by serotonin reuptake inhibitors. Indeed, a survey in healthy volunteers receiving alprazolam or clonazepam with a co-administration of fluoxetine or placebo, it was shown that fluoxetine prolonged the half-life of alprazolam and reduced its clearance rate but didn't have an effect the half-life of clonazepam or its clearance. In a similar manner cimetidine inhibits the clearance of BZDs metabolised such as diazepam, chlordiazepoxide or clorazepate but not conjugated derivatives such as lorazepam and oxazepam. The most important interaction to consider in the aged patient is the interaction between the BZDs and alcohol which has been mentioned previously. No problem of association in the aged patient receiving BZDs and neuroleptics exists (12).

Withdrawal

When BZDs are stopped after a physiological dependence has developed, a syndrome can appear.

The prevalence of these withdrawal syndromes has been estimated between 0 and 100% according to studies; it is interesting to note that roughly 40% of patients treated for at least 6 months with a BZD can present some withdrawal syndromes after abrupt cessation. Withdrawal symptoms are essentially tremors, confusion, anxiety and insomnia. Severe symptoms such as convulsions and psychotic reactions can occur as well as an appreciable increase of arterial pressure and a myocardial ischemia, which can occur at the time of abrupt cessation. Few withdrawal studies in the aged have been carried out, the aged patients when compared with young adults present less severe withdrawal symptoms, however it was observed that post withdrawal psychotic reactions seem more notable in the aged than the young patient. It is suggested that withdrawal is linked to a hyperactivity of the noradrenergic, serotoninergic and cholinergic systems that have been inhibited by the chronic administration of BZD. The fact that BZD plasma concentrations decrease more slowly can perhaps explain the fact that symptoms of withdrawal in the aged patient seem less severe.

It seems that risks of withdrawal are increased particularly with the abrupt cessation of BZDs having a short half-life and presenting a rapid reduction of plasma concentrations, as well as elevated doses, elevated daily dosage and the long-term utilisation. BZDs having a short or intermediate half-life, at the time of their cessation, can generate symptoms of withdrawal that appear between 24 and 36 hrs after the cessation, whereas BZDS with a long half-life can induce withdrawal symptoms after practically one week and in this case BZD cessation is not always incriminated. It seems that other factors can contribute to the severity of the withdrawal syndrome, such as a premorbid personality, and notably passive-dependent personalities.

Obviously important physiological differences exist, but the previous consumption of alcohol and a low level of education can facilitate a notable withdrawal syndrome.

Conclusion

Problems posed by BZDs in the aged patient are of a pharmacodynamic and pharmacokinetic order. In comparison to young adult users, BZDs users in the aged are essentially women; the latter take these medicines during important periods in their lives and

often have a strong comorbidity, such as cardiovascular or rhumatological problems or even psychiatric problems such as depression or panic disorders.

Aged patients who take BZDs at high doses can also consume other drugs such as alcohol and who have a psychiatric history. Some important secondary effects are associated with the utilisation of BZDs; essentially concerning falls and it has been noticed for some years that problems posed by aged car drivers can be effectively raised by BZDs. It is difficult to know if continual users of BZDs really have an advantage to other users. It is certain that it is necessary in every possible measure to have a recourse strategy for cessation, to use as much as possible BZDs with a short half-life that are not oxidised, i.e. essentially BZDs that are not metabolised in the strictest sense of the term such as lorazepam or temazepam. Daily doses must be extremely limited and duration of use mustn't surpass 2 or 3 months in young patients. Other types of anxiolytics are advised for prescription to the aged patient and a good experience with anti-depressants such as clomipramine, which doesn't have the AMM, but can sometimes be very useful for the aged patient. A new medicine, venlafaxine can be prescribed at doses that induce too many secondary effects.

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