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PHARMACOKINETIC AND CLINICAL CONSIDERATIONS IN THE CHOICE OF A HYPNOTIC

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1 Not only has insomnia become much more frequent in the last hundred years but its causes have also changed considerably.

2 In the treatment of insomnia, benzodiazepines—because of their additional anxiolytic effect—offer substantial advantages over other sleep-inducing agents.

3 The residual fraction—the quotient of plasma concentration at 12 h after drug intake to maximum plasma concentration—makes it possible to differentiate between the benzodiazepines according to their suitability as anxiolytics or hypnotics.

4 Midazolam has the lowest residual fraction of all known benzodiazepines and thus, administered in the appropriate dosage, also has the shortest duration of activity.

Introduction

Until the mid-nineteenth century, remarkably little attention had been given by the medical profession to the subject of sleep and sleep disorders. Even where reports of sleeping difficulties are found, they are usually discussed only as symptoms accompanying severe psychic or somatic illness, and not as independent disease entities.

However, 100 years ago, two important developments occurred which were to change this situation entirely. The first of these was that Liebreich initiated the use of chloral hydrate in medical therapy. The second was that with the introduction of electric lighting it became possible, for the first time in history, to convert night into day and thereby change the sleep–wake rhythm at will: a new generation of sleep disorders was born.

Today, it is the by-products of the stress of modern living—anxiety, tension, worry and care—that have become the most important causes of insomnia.

Sleeping problems

Frequency and causes of sleep disorders

Recently, a survey of a representative section of the adult population of the USA was commissioned with the object of assessing sleeping habits and difficulties associated with sleep (Gallup Organization, 1979). This survey revealed that around 80% of the entire US population had at some time experienced problems in sleeping and that, for 40% of the population, these difficulties had not been resolved. It is therefore no exaggeration to state that insomnia is one of the most common complaints of modern living.

Those questioned in the survey cited worrying over problems as by far the most common single cause of sleeping difficulties (Table 1). Analysis of the different causes of insomnia shows that approximately two out of 10 patients blamed environmental influences, four out of 10 named psychological problems as the main reason and three out of 10 attributed their sleeping problem to somatic symptoms.

Measures taken to remedy sleep disorders

Most insomnia sufferers in the US attempt to overcome their sleeping difficulties by non-medical means, usually by reading or watching television. Other common remedies are warm baths, gymnastic exercises or simply a glass of warm milk at bedtime. Sleep-inducing medication is used by about 10% of the affected population, most commonly in sleep disorders of psychological origin and least often in insomnia due to external influences. Where the sleeping difficulty is somatic in origin, the primary symptom will dictate whether and how often hypnotics are used; for example, the presence of muscle or joint pain will often be associated with the use of a hypnotic.

Thus, with some degree or type of insomnia being reported by 40% of the US population, sleeping problems are frequently in the public mind, and

Table 1 Unsolved sleep problems (Gallup study)[a]

Psychical reasons	
Thinking over problems	21%
Inability to relax	15%
Not being sleepy	11%
Dreams	8%
Being over-stimulated	7%
Physical reasons	
Need to go to bathroom	15%
Muscle or joint aches	12%
Headaches	5%
Digestion problems	4%
Breathing problems/head	4%
Breathing problems/lungs	3%
Environmental reasons	
Light/noise	12%
Partner's restlessness/snoring	8%
Sleeping in other than regular bed	7%
Habits causing sleep difficulties	
Eating too close to bedtime	5%
Effect of caffeine	3%
Effect of alcohol	1%

[a] Adult US population = 100%

around 5% of the population of the US use a hypnotic occasionally.

Insomnia as a problem to the medical practitioner

Although in the USA prescription-free hypnotics are used almost as commonly as their prescription counterparts, the physician is still regularly confronted with the problem of managing insomniac patients. One-eighth of the US population has discussed the sleeping difficulties with a doctor. In 3% of the population, the problem is so serious that it is *the* reason for consulting the doctor. Physicians are, however, surprisingly resistant to requests for sleep-inducing medication: only 1.5% of all drugs used worldwide are hypnotics, which is only a small proportion compared with analgesics which account for 8.5% of the entire world drug turnover.

Patterns of hypnotic drug prescription

The manner in which hypnotics are prescribed is extremely interesting. In Switzerland, for example, according to our estimate, a hypnotic alone is administered in around two out of every three cases of sleeping difficulty. In almost 12% of the cases, a hypnotic is prescribed together with an anxiolytic drug, and in slightly more than 12% an antidepressant is co-prescribed. This pattern reflects the fact that some of the most important causes of insomnia today are anxious–apprehension and anxious–neurotic states, depressive moods and depression, as well as difficulty in adapting to changes in external living conditions or surroundings.

Thus for many insomniac patients, the ideal drug therapy would be one that would facilitate falling asleep, delay premature awakening and provide freedom from anxiety, fears and guilt feelings during the day. In others, however, the main difficulty may lie in relaxing long enough to fall asleep and, for such patients, it would suffice simply to ease the induction of sleep.

Benzodiazepines as hypnotics and anxiolytics

While benzodiazepines possess both hypnotic and anxiolytic properties, their anxiolytic action is present at plasma concentrations below those at which a sedative or hypnotic effect is detectable. Reports in the literature (Garattini *et al.*, 1973) indicate that the clinical profile of benzodiazepines—that is, for example, the quantitative relationship between sleep-inducing and anxiolytic effect—is dose-related; relief from anxiety can therefore be obtained with doses lower than those required for sleep induction. Thus, benzodiazepines are particularly suited to the treatment of sleep disorders in which anxiety, tension and stress are important causative factors. Since anxious–apprehension, anxious–neurotic states and anxiety neuroses are among the most common causes of insomnia, this fact at least partly explains why benzodiazepines have achieved such success as hypnotics in recent years.

Although the various benzodiazepines scarcely differ pharmacologically, many are exclusively used only in certain indications, such as for anxiolysis, sleep induction or as hypno-anxiolytics. While anxiolytics are expected to exert as constant an effect as possible over the day, in contrast the effect of a hypnotic is expected to be limited to the hours of sleep. However, in patients in whom the major causes of insomnia are anxiety and tension, it would be useful to have a hypnogenic effect at night while maintaining anxiety relief during the day.

Effect is, under certain conditions, closely related to plasma concentration. Figure 1, using the example of intravenously administered midazolam, illustrates the correlation between plasma concentration and reaction time in one subject and shows the classic dose-effect curve: in the lower concentration range, while plasma levels of midazolam are readily measurable, no clinical effect can be detected. In the central section of the curve, clinical effect increases rapidly as plasma levels rise, but once a certain effect has been achieved, it cannot be intensified by a further rise in plasma concentration.

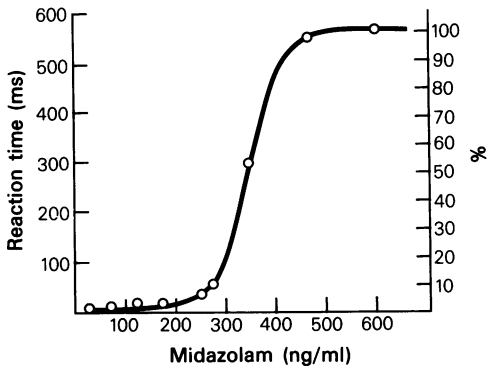

Figure 1 Midazolam: correlation between plasma concentration and reaction time. During the first 6 h, this is a classic dose-effect curve: it can be seen that clinical effect is negligible at plasma levels of up to approximately 50 ng/ml. The central section of the curve, however, reveals a rapid and marked increase in effect. When a certain plasma level is attained (around 600 ng/ml) no further intensification of effect is observed.

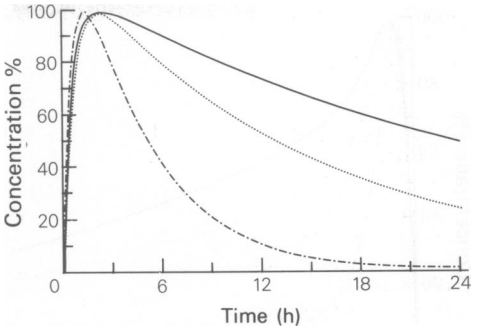

Figure 2 The figure represents a theoretical model of three different compounds in which only the elimination phase differs. Rate of absorption and volume of distribution are the same in all cases. Thus, it can be seen that this difference has a marked influence on effect. —— $t_{1/2} = 20$ h, ····· $t_{1/2} = 10$ h, – · – $t_{1/2} = 6$ h.

Benzodiazepine classification according to pharmacokinetic behaviour

In pharmacokinetic terms, benzodiazepines can be differentiated by the rate and extent of their appearance in the systemic circulation and their distribution in the body, and by the rate and manner of their metabolism in the liver.

There has been no dearth of attempts in recent years to classify and describe benzodiazepines on the basis of isolated pharmacokinetic values and, of these, many have sought to describe the duration of action of benzodiazepines in terms of the elimination half-life (β). The β half-life, however, is an inadequate means of characterization as the decline in plasma concentration is tied to two different processes, namely, the distribution of the active substance to other tissues (concentration reduction by dilution) and the elimination by metabolism. For some benzodiazepines, the distribution phase plays a relatively minor role but for others, distribution processes are the major reason for the rapid initial decline in plasma concentration (Amrein & Leishman, 1980).

Figure 2 describes three theoretical benzodiazepine models with fast absorption and no distribution phase. It can be seen that the plasma concentration changes according to the elimination phase, from which it might be assumed that the duration of action can be estimated from the half-life of elimination. However, this simple one-compartment model is valid only for a few benzodiazepines. In reality, many benzodiazepines feature a pronounced distribution phase which has to be taken into account. For such compounds, even where the elimination half-life (β) remains the same, the plasma concentration profile can vary markedly, depending on the prominence of the distribution phase (α). Extremely different concentration profiles can also result when the relation between the volumes of distribution changes, as shown in Figure 3, or when the rate of absorption alters.

Figure 4 shows the plasma concentration profile of four benzodiazepines used for sleep induction (Knowles & Ruelius, 1972; Cano *et al.*, 1977; Klotz *et al.*, 1977; Boxenbaum *et al.*, 1978; Heizmann *et al.*, 1983). It can be seen that the half-life of elimination alone is insufficient to describe the course of plasma concentration during the period most relevant to the clinical effect (Amrein & Leishman, 1980).

Necessity for a comprehensive approach to classification: the residual fraction

The ideal sleep induction agent is expected to help the insomniac fall asleep soon after administration, to maintain as undisturbed a sleep as possible and to allow the patient to awaken refreshed and without hangover. Thus, two essentially contradictory requirements must be fulfilled: firstly, rapid sleep induction must be obtained, meaning that, shortly after drug ingestion a markedly hypnogenic plasma concentration must be attained. Secondly, this effect must have disappeared by the following morning, so that plasma concentrations must again have fallen to below the critical level for a hypnogenic effect.

Since there is for all real hypnotics and sleep

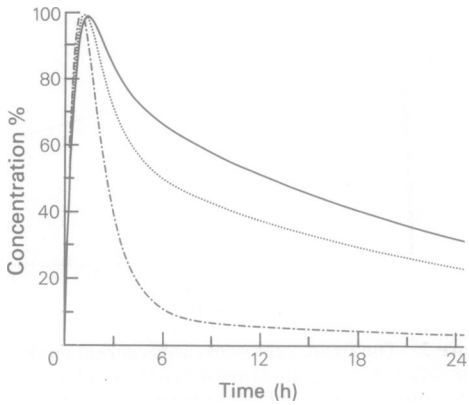

Figure 3 For all three curves, the following are the same: 1) absorption rate Ka = 2.0 (= invasion $t_{½}$ of 20 min); 2) diffusion rate α = 0.693 (= $t_{½}\alpha$ = 1 h); 3) elimination rate β = 0.035 (= $t_{½}\beta$ = 20 h). The differences amongst the three curves are due solely to the differences in the ratio between volumes of distribution in each individual curve. —— A:B = 2:3. ····· A:B = 3:2, – · – A:B = 19:1.

inducers a close relationship in the therapeutic range between dose and plasma concentration and between dose and effect, well-considered dosage selection for any drug capable of exerting a hypnotic effect will permit fulfilment of at least one of the two requirements. To be realistic, however, assessment of a hypnotic must be based on close study of how a particular dose influences sleep during the night and the patient's behaviour the following morning.

From the point of view of pharmacokinetics, two time points are of particular significance in this connection: the time at which maximum concentration is reached and the mid-point between two administrations, i.e. 12 h after intake in the case of hypnotics. The time at which maximum concentration is attained can be assumed to coincide with the maximum effect. Twelve hours after drug intake, at the very latest, the patient should no longer be able to feel a sedative effect, even in cases where a certain anxiolytic effect would be desirable.

Benzodiazepines that attain maximum concentration very quickly with subsequent rapid decline within the next few hours are more likely to be good hypnotics than benzodiazepines that reach maximum concentrations only relatively slowly and decline gradually. Benzodiazepines of this latter type would be more suitable as pure anxiolytics. Thus, if we calculate the relationship between the concentration 12 h following drug intake and the maximum concentration, the resultant quotient—the residual fraction ($r_{12,1}$)—will provide a guide to the therapeutic applications of the different benzodiazepines.

Benzodiazepines with a low quotient are particularly suited as hypnotics; those with a high quotient are particularly suitable for use as anxiolytics; those with a medium quotient lend themselves best to use as so-called 'hypno-anxiolytics' (Amrein & Eckert, 1980; Dettli, in press).

Table 2 lists the residual fraction and the elimination half-life of five benzodiazepines. Although midazolam and triazolam have almost the same $t_{½}\beta$, 12 h after intake, the plasma level of midazolam has declined to less than 1% of C_{max} whereas triazolam has only dropped to 16% of C_{max}. On the other hand, flunitrazepam, with a $t_{½}\beta$ 10 times as long as that of triazolam, has almost the same $r_{12,1}$ as the latter owing to intensive distribution processes.

According to a classic dose-effect curve, for which it is assumed that the point of maximum concentration coincides with the maximum effect, an attempt to predict the sedative effect of flunitrazepam on the basis of the plasma concentration curve would produce the theoretical activity profile shown in Figure 5. As this figure shows, this theoretical curve is confirmed in practice.

If the dose is selected so that, at the maximum concentration, the maximum effect is attained, then as shown in Figure 5, the following sedative residual effects can be expected 12 h after intake: with an $r_{12,1}$ of 0.25 or less, a residual sedative effect of, at most, 5% can be expected; with an $r_{12,1}$ of 0.5, the sedative residual effect could easily be 20–40%. Our own experimental findings with different benzodiazepines as well as an exhaustive search of the literature on

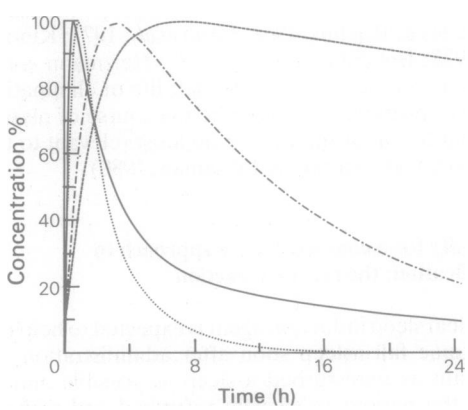

Figure 4 Plasma concentration profile of four benzodiazepines used for sleep induction. Desmethyldiazepam1(-----) and oxazepam (- · -) can be described in terms of a single-compartment model and have $t_{½}$ of 50.9 and 8 h, respectively. Flunitrazepam (——) and midazolam (·····) are described in terms of a two-compartment model and have a $t_{½}$ of 18 h and 2.3 h, respectively. After flunitrazepam, the plasma concentration declines far more rapidly than after oxazepam, despite the former's longer $t_{½}$.

Table 2 Residual fraction ($r_{12,1}$) and half-life ($t_{½}\beta$) of five benzodiazepines

	$r_{12,1}$[a]	$t_{½}\beta$ (h)
Midazolam	≤ 0.01	2
Triazolam	0.16	2
Flunitrazepam	0.25	22
Oxazepam	0.40	8
Desmethyldiazepam	0.71	84

[a] $r_{12,1}$ = quotient of plasma concentration at 12 h after drug intake to plasma C_{max}.

residual effects of benzodiazepines—to be published elsewhere—essentially confirm this hypothesis. Residual effects of 10% or less can be regarded as irrelevant since, even in healthy subjects in excellent health, who are not receiving any medication, there may be as much as a 10% fluctuation in subjective condition.

The residual fraction, as the ratio between plasma concentrations at two selected points, does not seek to describe the nature of the plasma concentration curve in the intervening period. Although it is possible for two benzodiazepines to have an identical residual fraction but widely differing concentration curves between C_{max} and the second measuring point, this in no way detracts from the usefulness of the residual fraction as a predictor of residual effect. It is influenced not only by the elimination half-life but also by the other most important pharmacokinetic parameters. The residual fraction as a predictor of residual effect is of particular usefulness in the case of hypnotics which, by their very nature, are designed to exercise a pronounced but time-limited effect.

It should be borne in mind, however, that for the patient with sleeping difficulties in whom anxiety and tension represent an important contributory factor, a slight degree of sedation during the day may be therapeutically acceptable or even desirable when associated with a marked anxiolytic effect. Benzodiazepines with an $r_{12,1}$ of 0.29 or less are, therefore, from the pharmacokinetic point of view, particularly suitable for use as hypnotics. A residual fraction of between 0.3 and 0.66 is characteristic for hypno-anxiolytics and an $r_{12,1}$ of 0.66 or more identifies the 'pure' anxiolytics.

Additional considerations

One factor which has a particularly important influence on the duration of action has not yet been mentioned: the dose. As has already been stated, the relation between the plasma concentration and the effect can be described in terms of a classic dose-effect curve. A particular dose will attain a maximum possible effect and a dosage increase does not lead to an intensification of effect, although it will prolong it markedly. Thus, within certain limits, the intensity of effect of benzodiazepines can be enhanced by dosage increase, but the main effect is to prolong the duration of action. For this reason, hypnotics require especially careful individual dosage titration, the basic rule being to start with as low a dose as possible, since an initial dose that is too high will only negligibly speed the onset of action, scarcely enhance the effect and considerably prolong the duration of residual effects the following morning.

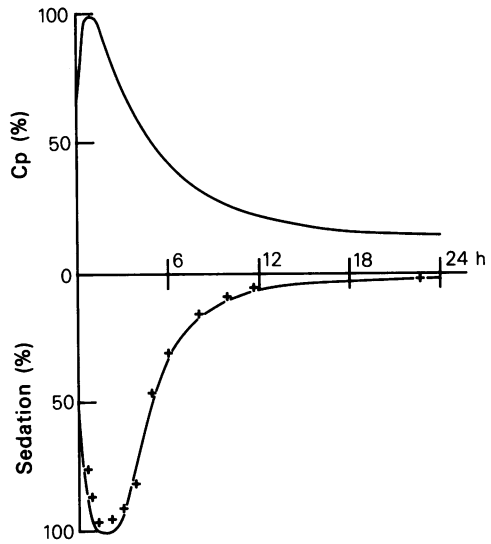

Figure 5 Flunitrazepam: correlation between plasma concentration and sedation. The upper half of the graph shows the course of plasma concentration after oral intake of 2 mg flunitrazepam. The lower half is a theoretical dose-effect curve, calculated on the assumption that, at C_{max}, E_{max} is also reached and that the effect can be described in terms of a log dose-response curve. The experimental findings (+) correspond closely to the theoretical curve.

A second important consideration concerns the active metabolites produced by many of the benzodiazepines. To be of real use in clinical practice, any assessment must take these into account, determining their concentration in relation to the parent drug and their relative potencies, and applying these values in the calculation of the residual fraction. These data are still not available for many benzodiazepines.

The residual fraction in clinical practice

Midazolam is unusually quickly absorbed; after attainment of the maximum concentration, the level

declines again—partly as the result of distribution processes, partly as a consequence of metabolism—faster than in any other presently known benzodiazepine. The active metabolites produced are so short-lived that they, at most, only briefly intensify but do not prolong the effect. Appropriately, midazolam possesses a residual fraction of less than 0.01. No other benzodiazepine known has even remotely similar pharmacokinetic properties.

Midazolam is therefore in theory well-suited for:

1) sleep disorders in which the main component is difficulty in falling asleep;
2) sleep disorders for which only relatively short sleep or short additional sleep is required, for example, in premature awakening, changing time zones, necessity to sleep at unaccustomed times (change of work shifts, frequent variation in working hours);
3) in situational sleep disturbances: insomnia due to noise, snoring bedmate, unfamiliar bed or change in surroundings;
4) in sleep disorders in which pathological anxiety states play little or no role;
5) in cases where the effect must be short-acting.

On the other hand, midazolam will in theory be less appropriate in circumstances in which chronic anxiety or tension states are the primary reason for the sleep disorder. Thus, it appears that for insomnias associated with severe anxiety, in neuroses, manifest depression, or schizophrenic states of agitation, midazolam or other ultra-shortacting benzodiazepines are not the drugs of first choice except when such patients are receiving other basic sedative or anxiolytic medication. In such a situation, midazolam would be used only as what might be termed a 'sleep-starter'. As midazolam ($r_{12,1}$ = 0.01) has a pronounced distribution phase and an extremely short elimination half-life, the duration of action will vary only slightly with increasing doses, so that doubling the dose (within the therapeutic range) will prolong the sedative effect by, at most, 2 h.

In contrast, benzodiazepines such as flunitrazepam ($r_{12,1}$ = 0.25) are ideally suited for induction and maintenance of sleep over a period of time which can be determined by dosage adjustment (0.5–2 mg) over a broad range.

Flurazepam has a relatively high residual fraction (~ 0.60) due to the combined effect of its two active metabolites: hydroxyethylflurazepam and desalkylflurazepam. The parent drug and its derivative, hydroxyethylflurazepam, are both extremely short-lived and account for the actual sleep-inducing effect (Amrein *et al.*, 1983). The desalkyl metabolite has a long active life but represents only 5% of the total flurazepam dose.

These three examples should serve to demonstrate that the residual fraction is an easily calculable parameter that permits a prediction of the relative duration of action of hypnotic agents, and is thus a useful practice-related consideration in the selection of a hypnotic.

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