insight into its scope and the important part played by the psychologist in many facets of aviation.

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New Drugs

Hypnotics and anxiolytics

N HOCKINGS, BRIAN R BALLINGER

During the past 10 years the benzodiazepine group of drugs has come to dominate the drug treatment of sleep disorders and anxiety. Indeed, they are the most widely used of all prescribed drugs. In this article we shall therefore discuss the benzodiazepines in some detail and contrast them with other drugs.

Benzodiazepines

There is no doubt that the benzodiazepine drugs are effective. In high concentrations they are hypnotic and in low concentrations anxiolytic. Although there are some indications that the structure of a particular benzodiazepine molecule may influence its activity, in practice it is predominantly the duration of action that determines choice between benzodiazepines.

DURATION OF ACTION

Because many benzodiazepines are metabolised in the liver to produce further active forms whose elimination from the body is slower than the parent molecule, care has to be taken when assessing information on the duration of action of these drugs. For example, medazepam has an elimination half life of one to two hours but is metabolised to oxazepam, which has a half life of 6-25 hours. Pharmacodynamic studies where the duration of measurable effects such as sedation are recorded are the best source of this information. These studies need to be done in healthy subjects of all ages and in ill patients, particularly when renal and hepatic function is affected, before one can confidently predict the duration of action in particular patients. Furthermore, to exclude the possibility of accumulation of slowly eliminated metabolites such observations need to be continued over days or even weeks. Because of the difficulty in doing such

Department of Pharmacology and Therapeutics, Ninewells Hospital and Medical School, Dundee DD1 9SY
N HOCKINGS, MB, MRCP, lecturer

Royal Dundee Liff Hospital, Dundee DD2 5NF
BRIAN R BALLINGER, FRCPED, FRCPSYCH, consultant psychiatrist

Correspondence to: Dr N Hockings.

Benzodiazepines currently available in the United Kingdom

Drug (proprietary names)	Approximate elimination half life (hours)
Marketed as hypnotics (in order of duration of action):	
Triazolam (Halcion)	5
Temazepam* (Euhypnos, Euhypnos Forte, Normison)	6
Lormetazepam (Noctamid)	10
Flunitrazepam (Rohypnol)	20
Nitrazepam (Mogadon, Nitrados, Remnos, Somnite, Surem)	24
Flurazepam (Dalmane)	75
Marketed as anxiolytics:	
Diazepam (Valium, Atensine, Evacalm, Sedam, Solis, Tensium)	
Chlordiazepoxide (Librium)	
Clobazam (Frisium)	
Oxazepam* (Serenid-D, Serenid Forte)	
Clorazepate dipotassium (Tranxene)	
Ketazolam (Anxon)	
Lorazepam* (Ativan)	
Medazepam (Nobrium)	
Bromazepam (Lexotan)	
Prazepam (Centrax)	
Alprazolam (Xanax)	

* These drugs do not undergo oxidative metabolism.

studies this type of information is not available for many drugs. Prescribers should be alert to the possibility of hangover effects or accumulation and watch for them, especially in elderly people and in others whose hepatic function may be impaired. Particular caution is needed with the drugs that have long elimination half lives and those that undergo oxidative metabolism in the liver (all except temazepam, oxazepam, and lorazepam).

DEPENDENCE

Dependence on the benzodiazepines does occur. Patients taking these drugs, even at therapeutic doses, for two or more months may develop a physical withdrawal syndrome. The cardinal feature of the syndrome is anxiety, which may be mistakenly interpreted as a recrudescence of the original anxiety for which the drug was prescribed. Anxiety, however, usually subsides to prewithdrawal levels within two to four weeks. In addition, depression, nausea, depersonalisation, and perceptual changes such as intolerance to loud noises, bright lights, and touch may occur. Insomnia may also be expected, especially after withdrawal of shorter acting benzodiazepines when used for sleep disorders. Psychological dependence is more difficult to assess but the fact that the use of benzodiazepines has become so widespread may itself indicate the existence of this problem.

Because of the safety of these drugs to overdosage doctors largely ignore the problems of dependence. Serious physical dependence seems more likely to occur with the long acting drugs used as anxiolytics, where therapeutic concentrations are maintained in the body throughout the day, than with the short acting drugs used as hypnotics, with which psychological dependence is more likely. Withdrawal of treatment from patients after a long period will need close supervision. If the symptoms of withdrawal are explained and support is given over the weeks or months required to gradually reduce and eventually stop medication withdrawal is usually achieved. Nevertheless, the problem of serious dependence seems less than with older drugs such as barbiturates and meprobamate.

OTHER EFFECTS

Certain other side effects may be troublesome, including ataxia, which may occasionally be gross. Drowsiness may be a hazard when driving or operating machinery and mental confusion may be precipitated or made worse, particularly in elderly people. Loss of control leading to aggressive behaviour is a problem in a few patients.

Age—The production of active metabolites is dependent on oxidative metabolic pathways in the liver, and the elimination of conjugated metabolites is dependent on renal function. Both these processes are known to deteriorate with age and thus the elderly will eliminate benzodiazepines more slowly. This may result in higher peaks of drug concentration in the body after dosing and prolongation of the duration of action. The aging brain also appears to be more sensitive to the effects of these drugs. For these reasons the dose of benzodiazepines usually needs to be smaller in elderly people and the shorter acting drugs are generally indicated to avoid hangover effects when used as hypnotics.

Interactions—Alcohol and benzodiazepines taken concomitantly may result in greater impairment of psychomotor function than either agent alone. There are many possible explanations for this observation but acute alcohol intake may inhibit the metabolism of most benzodiazepines, probable exceptions being those that do not undergo oxidation (see below). The usual effect of the combination of alcohol and benzodiazepines is an increase in the sedative effects of the benzodiazepine, but cases of aggressive behaviour have been reported.

Another commonly used drug that may theoretically cause considerable interaction is cimetidine, which inhibits oxidative metabolism in the liver. Only three available benzodiazepines are not metabolised by this pathway and would be free of this effect—namely, temazepam, oxazepam, and lorazepam. If an adverse effect does occur, expressing itself as increasing sedation or morning hangover, one of these drugs should be selected. Alternatively, ranitidine, which does not inhibit oxidative metabolism, should be substituted for cimetidine.

Hypnotics

The patient's condition should be evaluated carefully before a hypnotic is prescribed. Not all people complaining of difficulties in sleeping really have insomnia, and the variation in sleep patterns and requirements with age and among individuals should be remembered. Particular causes of insomnia should be sought, including the use of stimulant drinks such as tea or coffee at bedtime, discomfort, and noise. Painful physical illness and depression may be associated with sleep problems and these will resolve with appropriate treatment. The aim should always be to give hypnotics for as short a period as possible, and intermittent use, perhaps for three nights a week rather than every night, should help to prevent dependence developing.

Benzodiazepines that are promoted for use as hypnotics may be divided into those with short durations of action and those with longer durations of action. The short acting ones tend to be the newer drugs and are thus more expensive. Short acting benzodiazepines (triazolam, temazepam, and lormetazepam) are indicated for patients in whom residual effects are particularly undesirable and are generally preferred when insomnia is not accompanied by daytime anxiety. They are also the most suitable benzodiazepine hypnotics in elderly people, although caution is still required.

Longer acting benzodiazepines are indicated when early morning waking is a problem and possibly when daytime anxiolytic activity is needed but some impairment of psychomotor function is acceptable. In very old people drowsiness, confusion and unsteadiness can be very serious problems, and longer acting benzodiazepines should be avoided.

OTHER DRUGS

The barbiturates can no longer be recommended as hypnotics because they are dangerous in overdose, readily cause psychological and physical dependence, and are potent inducers of liver enzymes. Chloral hydrate is effective and cheap but may cause side effects, including gastric irritation and rashes. Gastric irritation may be reduced by using one of the derivatives, such as dichloralphenazone or trichlofos, but these preparations are more expensive and therefore the main advantage

is lost. Although not often the hypnotic of choice in younger patients, chloral hydrate or one of its derivatives may still be very useful in elderly patients. Chlormethiazole has been recommended for use in the elderly because of its short half life. It often causes nasal and conjunctival irritation when first used, but this effect is said to disappear on repeated dosing. Chlormethiazole is as expensive as the short acting benzodiazepines and is less safe in overdose. Reports of dependence are many, and we would rarely recommend its use. It may be helpful in a few elderly patients when other drugs have failed.

Drugs of the antihistamine type such as promethazine and trimeprazine are used, particularly in children. They have long durations of action, and we can see no advantage in their use. When insomnia occurs in the presence of other psychiatric illness drugs that are not primarily hypnotics may be indicated. For example, sleep disturbance with depressive illness may respond to the use of a sedative antidepressant such as amitriptyline or dothiepin, often given as a single dose at night thus avoiding the use of a hypnotic. In patients with dementia with nocturnal restlessness a sedative neuroleptic such as thioridazine may be useful, again given as a single evening dose. These drugs, however, should not be used as hypnotics unless there are other indications because of potential side effects.

Anxiolytics

Anxiety is a normal reaction but when severe and disabling it becomes pathological. It is important to assess patients carefully to detect associated problems in their lives and seek evidence of underlying illness such as depression or organic brain disease that may present as anxiety. Conversely, it should be remembered that up to a quarter of patients presenting with anxiety have some underlying physical illness. Drugs are often not necessary in treating neurotic anxiety and psychotherapeutic measures, or sometimes behaviour therapy, may be successful.

In the treatment of anxiety the benzodiazepines with longer durations of action are commonly prescribed. Diazepam and chlordiazepoxide have been used for many years and are the cheapest. Medazepam and chlorazepate are newer and more expensive. All four drugs have a suitably long duration of action and, apart from cost, they differ little in practice. Oxazepam and lorazepam are shorter acting and may be useful in acute attacks of anxiety. They are also indicated if liver disease is reducing elimination of other members of the group as they do not undergo oxidative metabolism. Clobazam is claimed to produce less impairment of psychomotor function than other benzodiazepines when given in doses achieving equal anxiolytic effect.

The decision to start giving anxiolytic treatment to a patient should not be taken lightly, and treatment should be limited to those whose anxiety is clearly influencing their lives. The risk of dependence increases if the duration of treatment exceeds about two months, and therefore at the onset patients should be told that treatment is for a limited duration only. Some patients with chronic anxiety will need more prolonged treatment, although this is controversial. Many doctors responsible for supporting neurotic patients over long periods find that a few are better on longer term drug treatment, but regular review is essential. To justify continued prescription there should be a critical clinical assessment of response. Tolerance may develop to the anxiolytic effects of the benzodiazepines, and treatment for more than two months is usually best avoided.

OTHER DRUGS

Again barbiturates can no longer be recommended for the reasons stated above. The two non-benzodiazepine drugs, benzoctamine and meprobamate, are less effective than the benzodiazepines and meprobamate is less safe. Beta-receptor blockers—for example, propranolol—have a role in the management of some patients, controlling the somatic symptoms of anxiety such as tremor and palpitations. Many people find them useful for treating the anxiety associated with public speaking and similar activities. Before recommending any drug for this purpose one must be sure that the patient is not going to develop an idiosyncratic reaction to the drug and that the drug will not adversely affect performance. A test dose will help to avoid these problems.

Small doses of neuroleptics such as trifluoperazine have sometimes been used for anxiety and they have the advantage of not causing dependence. Nevertheless, given the potential hazards of these agents, such as tardive dyskinesia, they are not usually advisable in the long term treatment of neuroses. The sedative antidepressants have an anxiolytic effect but should be used only in managing anxiety when coexisting depressive illness justifies antidepressant treatment. The monoamine oxidase inhibitors such as phenelzine may be useful in managing some cases of phobic anxiety, including agoraphobia, although usually only after a trial of behaviour therapy or benzodiazepines, or both. Interestingly, whereas much work has been done on the adverse effects of drugs acting on the central nervous system there is little information on whether anxiolytics may actually improve the performance of subjects whose level of anxiety is high.

Conclusions

Although they are not perfect drugs, the benzodiazepines are effective hypnotics and anxiolytics and dominate the field. Their greatest attribute is their safety. We are unaware of any case report of an otherwise healthy subject dying after an overdose of oral benzodiazepines. Although dependence does occur, it is relatively low grade and, unlike those addicted to barbiturates, benzodiazepine addicts rarely commit crimes to obtain supplies. Nevertheless, dependence does occur and with care its occurrence can be limited. If hypnotics are required they should be recommended for use intermittently rather than to be taken every night, and anxiolytics should usually be prescribed for periods of under two months if possible. Finally, care should be taken when assessing patients for withdrawal of benzodiazepine treatment as there is evidence that some dependent subjects will substitute alcohol.

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