lateral views "? pneumothorax." An experienced radiographer did the correct examination—namely, views in inspiration and expiration, only to receive patient and form back immediately with the insistence that a lateral view be done. Such a view is certain to be useless if he really *was* looking for a pneumothorax. If there was something else on his mind it was certainly not on the request form.

Our hospital is spread over several acres and the block containing the medical beds is a wet half mile from the main department. It is visited by the radiologist every morning, but most of the work lies in the main department, so that there are many hours when the radiographers in the medical block cannot easily obtain advice from a radiologist. We are thus periodically in the wrong when a request is held up until my visit the next morning. I also apologise abjectly to my consultant colleagues when they complain to me at lunchtime, when presumably in the interest of democracy, their requests for lateral views are also overlooked (or suppressed).

It used to be the promise of every American politician standing for office that, if elected, happy days would be here again and that there would be a chicken in every pot. Many clinicians, senior as well as junior, act as if this happy event has occurred, and the NHS is a veritable widow's cruse, endless in its resources. Unfortunately, as we all know, this is not true. What is more, when it comes to the use of ionising radiation, as in *x*-ray examination, even one unnecessary film may tip the precarious balance for that patient and bring his life to a premature and unnecessary end.

(*Accepted 15 January 1980*)

Contemporary Themes

Systematic review of the benzodiazepines

Guidelines for data sheets on diazepam, chlordiazepoxide, medazepam, clorazepate, lorazepam, oxazepam, temazepam, triazolam, nitrazepam, and flurazepam

COMMITTEE ON THE REVIEW OF MEDICINES

The Committee on the Review of Medicines (CRM) has completed a review of the benzodiazepines and has issued guidelines for use in anxiety, insomnia, and certain other conditions.

Their use in obstetrics, the treatment of epilepsy, and in children other than in anxiety, insomnia, and night terrors will be considered later. Particular consideration was given to the following aspects of benzodiazepine therapy: (1) efficacy in indications other than anxiety and insomnia; (2) long-term efficacy in all indications; (3) residual effects of therapy, particularly daytime sedation; (4) possible dependence potential; (5) withdrawal symptoms; (6) evaluation of the implications differing pharmacological and kinetic properties might have in clinical practice; (7) use in the elderly.

The CRM drew attention in its recommendations to the pharmacological differences between "long"-acting benzodiazepines, whose half life exceeds 10 hours—for example, clorazepate, diazepam, chlordiazepoxide, and medazepam—and the "short"-acting rapidly cleared compounds, such as triazolam, temazepam, oxazepam, and lorazepam. The committee recognised that the pharmacological properties of the latter group, including rapid excretion and lack of accumulation of the whole drug and active metabolites, may offer certain advantages over the longer-acting benzodiazepines, particularly in the elderly. This group may also be preferred in patients with renal or hepatic impairment and in patients where daytime alertness is required. Short-acting benzodiazepines were also considered more suitable for the treatment of insomnia not accompanied by anxiety.

Efficacy

The committee found that all benzodiazepines were efficacious in the short-term treatment of symptoms of anxiety and in insomnia. It found no evidence which could justify the preferential use of any particular benzodiazepine in either anxiety or insomnia. It concluded that the usual division of benzodiazepines into rigid treatment categories of anti-anxiety agents and hypnotics did not appear to be based on the known pharmacological or clinical properties of this group of compounds.

The committee agreed that other acceptable indications for the long-acting benzodiazepines might include the treatment of muscular spasm, symptomatic treatment of acute alcohol withdrawal, and night terrors and somnambulism in children. The committee did not consider the benzodiazepines to have antidepressant or analgesic properties and so considered them unsuitable for such disorders as depression, tension headaches, and dysmenorrhoea occurring in the absence of anxiety. It further found benzodiazepines not efficacious in the treatment of psychotic illness and recommended that they should not be used in the treatment of anxiety or insomnia in children.

The committee took particular note of the lack of firm evidence of efficacy which might support the long-term use of benzodiazepines in insomnia and anxiety. It noted and concurred with the findings of the Institute of Medicine (USA) and the conclusions of a study carried out by the White House Office of Drug Policy and the National Institute on Drug Abuse (USA) that there is little evidence that sedative hypnotics, including benzodiazepines, continue to be effective when used nightly in patients over long periods. This report further observed that sleep laboratory studies show most hypnotics tend to lose their sleep-promoting properties within three to 14 days of continuous use.[1] The committee further noted that there was little convincing evidence that benzodiazepines were efficacious in the treatment of anxiety after four months' continuous treatment. It considered that an appropriate warning regarding long-term efficacy be included in the recommendations, particularly in view of the high proportion of patients receiving repeated prescriptions for extended periods of time.

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Safety

The committee gave considerable attention to one of the main areas of current concern—that of the development of possible benzodiazepine dependence. It noted that both the medical and lay press and media had recently drawn attention to the high rate of prescribing of diazepam and similar benzodiazepines, particularly with respect to their extended and habitual long-term use. It further noted that reports had been published on the occurrence of adverse effects following abrupt cessation of benzodiazepine therapy. The committee recognised that a combination of such findings could be interpreted as the development of tolerance and dependence, with abstinence symptoms occurring on withdrawal of treatment.

However, following an extensive review of all available data the committee concluded that, on the present available evidence, the true addiction potential of benzodiazepines was low. The number dependent on the benzodiazepines in the UK from 1960 to 1977 has been estimated to be 28 persons. This is equivalent to a dependence rate of 5-10 cases per million patient months.[2] Such cases of addiction were observed to occur most frequently in drug misusers, particularly in patients with a history of psychological or social inadequacy. Although some reports were available which described dependence occurring during medically supervised treatment, such cases were comparatively rare and occurred usually in susceptible patients only when high doses (often exceeding the therapeutic dose range) were used for extended periods.

The committee was particularly concerned, however, with the question of withdrawal symptoms. It has been reported that symptoms, including anxiety, apprehension, tremor, insomnia, nausea, and vomiting, appear on abrupt withdrawal of benzodiazepine therapy. Such symptoms may occur three to 10 days following discontinuation of treatment with long-acting benzodiazepines and within 24 hours after abrupt withdrawal of benzodiazepines with a short half life. Although symptoms can occur following even short courses—for example, two weeks—and when given in the recommended therapeutic dosage, such effects are usually associated with abrupt discontinuation of high doses taken habitually. Although the committee felt that such symptoms when occurring during the course of medically supervised treatment were not necessarily indicative of true dependence (particularly as most were mild and transitory), they were concerned that the similarity of the withdrawal effects to the symptoms of the original illness might suggest to the doctor that previous treatment had proved inadequate and that a further course of benzodiazepines was indicated. Such a phenomenon might contribute to the high number of repeat prescriptions issued, in spite of the lack of satisfactory clinical studies establishing long-term efficacy.

The committee's guidelines reflect its concern with the problems outlined above. It has recommended that all benzodiazepine therapy—unless given on an occasional basis only—be withdrawn gradually and that doses within the therapeutic range are used wherever possible. It further suggested that patients receiving benzodiazepine therapy be carefully selected and monitored and that prescriptions be limited to short-term use. The committee hoped that the implementation of these recommendations would minimise the incidence of benzodiazepine withdrawal effects, reduce the overall incidence of the side effects, especially daytime sedation (see below), and markedly reduce the demand for their habitual use.

The committee was also particularly concerned with the well-documented findings of unwanted residual daytime sedation. This is seen during administration with the long-acting benzodiazepines, where slow elimination leads to an accumulation of whole drug and active metabolites. Such effects which include drowsiness and impairment of co-ordination and judgment occur irrespective of whether the drug is given as a single nocturnal dose or repeated daytime doses. The implications of impairment occurring in patients driving or operating machinery are obvious. Although the committee recognised that in some cases of anxiety daytime sedation may be advantageous, they were concerned with such effects occurring in patients who were receiving benzodiazepines for simple insomnia unaccompanied by anxiety. In these subjects daytime sedation was undesirable and potentially hazardous. The committee concluded therefore that all patients receiving long-acting benzodiazepines for any indication should be advised not to drive or operate machinery and that the short-acting benzodiazepines might be recommended for use where daytime sedation was not required.

The committee also included a warning regarding the possible potentiation of these and other central nervous system depressant effects by alcohol. Unexpected interactions with alcohol may occur during the day or evening following the use of nocturnal benzodiazepines, which could prove hazardous to car drivers, especially if the patient is not aware of the residual adverse effects of his treatment.

The committee noted the increase in the occurrence of adverse reactions of all kinds in the elderly. Such effects, often accompanied by confusion, occur particularly during drug treatment with the long-acting benzodiazepines, where impaired liver and renal functions delay the elimination of drug and metabolites even further. The committee has suggested that the use of benzodiazepine therapy in the elderly, especially use of the long-acting benzodiazepines for insomnia, be undertaken for short periods of time, and only after careful consideration. Patients should also be closely monitored during the treatment period.

Guidelines for data sheets (February 1980 revision)

It should be noted that pharmaceutical companies holding licences to which these guidelines are applicable will be invited to apply for a revised product licence and to draw up data sheets in accordance with the committee's recommendations. Modifications may be made to the guidelines (and so appear in the data sheet) at the request of pharmaceutical manufacturers with respect to their own individual products. Such requests for change, however, will be accepted only if, in the view of the committee, sufficient evidence has been submitted in support of their claim.

The DHSS has asked us to make it clear that in the case of individual products doctors must be guided in the interim by the terms of the current data sheets.

Diazepam, chlordiazepoxide, medazepam, and clorazepate

Indications—ADULTS: treatment of the symptoms of anxiety, short-term treatment of insomnia where daytime sedation is acceptable, muscle spasm, symptomatic treatment of acute alcohol withdrawal. CHILDREN: night terrors and somnambulism.

Dosage—ADULTS: current data sheets are generally acceptable. May be given in single or divided doses. ELDERLY: half the normal adult dose may be sufficient for a therapeutic response in the elderly (see Warnings and Adverse Effects). CHILDREN (for night terrors and somnambulism): current data sheets are generally acceptable.

Dosage of intramuscular preparations—Current data sheets are generally acceptable. To be given only when oral dosing is not possible or advisable.

Contraindications—Known sensitivity to benzodiazepines, acute pulmonary insufficiency.

Use in pregnancy—There is no evidence as to drug safety in human pregnancy nor is there evidence from animal work that it is free from hazard. Do not use during pregnancy, especially during the first and last trimesters, unless there are compelling reasons.

Precautions—Chronic pulmonary insufficiency, in chronic renal or hepatic disease. In labour: high single doses or repeated low doses have been reported to produce hypotonia, poor sucking, and hypothermia in the neonate and irregularities in the fetal heart. Avoid if possible in lactation. The concurrent use of other central nervous system depressant drugs should be avoided.

Warnings and adverse effects—Common adverse effects include

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drowsiness, sedation, blurring of vision, unsteadiness, and ataxia. These effects occur following single as well as repeated dosage and may persist well into the following day. Performance at skilled tasks and alertness may be impaired. Patients should be warned of this hazard and advised not to drive or operate machinery during treatment. These effects are potentiated by alcohol. The elderly are particularly liable to experience these symptoms together with confusion especially if organic brain symptoms are present. See also Dependence Potential and Withdrawal Symptoms below. Abnormal psychological reactions to benzodiazepines have been reported. Rare behavioural adverse effects include paradoxical aggressive outbursts, excitement, confusion, and the uncovering of depression with suicidal tendencies. Other rare adverse effects, including hypotension, gastrointestinal and visual disturbances, skin rashes, urinary retention, headache, vertigo, changes in libido, blood dyscrasias, and jaundice, have also been reported.

Dependence potential and withdrawal symptoms—In general the dependence potential of benzodiazepines is low but this increases when high dosages are attained, especially when given over long periods. This is particularly so in patients with a history of alcoholism or drug abuse or in patients with marked personality disorders. Regular monitoring of treatment in such patients is essential and routine repeat prescriptions should be avoided. Treatment in all patients should be withdrawn gradually as symptoms such as depression, nervousness, rebound insomnia, irritability, sweating, and diarrhoea have been reported following abrupt cessation of treatment in patients receiving even normal therapeutic doses for short periods of time. Abrupt withdrawal following excessive dosage may produce confusion, toxic psychosis, convulsions, or a condition resembling delirium tremens.

Further information—This is a long-acting benzodiazepine. Repeated dosage will lead to accumulation of whole drug and metabolites. The elderly and patients with impaired renal and/or hepatic function will be particularly susceptible to the adverse effects listed above. Treatment should be kept to a minimum and given only under close medical supervision. Little is known regarding efficacy or safety of benzodiazepines in long-term use. It is advisable to review treatment regularly and to discontinue use as soon as possible.

Remarks—(1) Psychosomatic illnesses, tension headache, nocturnal enuresis, organic brain disease, dysmenorrhoea, behaviour disorders, cerebral palsy, and psychotic diseases should not be included as indications except in the context of treating anxiety associated with those conditions. (2) Benzodiazepines are not suitable for the treatment of depression. (3) Benzodiazepines are not suitable for use in combination products. (4) The use of benzodiazepines in epilepsy will be considered separately at a later time. (5) With respect to the indicated uses of the benzodiazepines under discussion, no claims should be made which might suggest specificity of either pharmacological or clinical action. (6) The only indication recommended at the present time for use in children is night terrors and somnambulism. Benzodiazepines are not considered suitable for use in insomnia in children. Evaluation of their place in the management of children with mental handicap, cerebral palsy, and certain behavioural disorders will be carried out at a later date.

Lorazepam, oxazepam, temazepam, and triazolam

The guidelines for the four substances are the same as those for diazepam, etc, with the exception of the following amendments.

Indications—Treatment of the symptoms of anxiety, short-term treatment of insomnia (this indication is not applicable to oxazepam).

Dosage—ADULTS: current data sheets are generally acceptable. ELDERLY: half the normal adult dose may be sufficient for a therapeutic response in the elderly (see Warnings and Adverse Effects). CHILDREN: not recommended.

Dosage of intramuscular preparations—Current data sheet recommendations are generally acceptable (applicable to lorazepam only).

Warnings and adverse effects—Common adverse effects include drowsiness, sedation, blurring of vision, unsteadiness, and ataxia. Patients should be warned of the possible hazard when driving or operating machinery. These symptoms are liable to be potentiated by alcohol. The elderly are more liable to experience such effects (see also Dependence Potential and Withdrawal Symptoms). Abnormal psychological reactions to benzodiazepines have been reported. Rare behavioural adverse effects include paradoxical aggressive outbursts, excitement, confusion, and the uncovering of depression with suicidal tendencies. Other rare adverse effects, including hypotension, gastrointestinal and visual disturbances, skin rashes, urinary retention, headache, vertigo, changes in libido, blood dyscrasias, and jaundice, have been reported.

Further information—This is a short-acting benzodiazepine. As accumulation tends not to occur patients are less likely to experience excessive drowsiness or impairment in the performance of skilled tasks. The short half life of this group of benzodiazepines may offer advantages in the treatment of the elderly, in patients with impaired renal and liver (except triazolam) function, and in situations where daytime alertness is desirable.

Remark—The absence of post-hypnotic effects or daytime sedation is dose dependent. High doses of short-acting benzodiazepines may require the same warnings as those given for diazepam and other long-acting benzodiazepines.

Nitrazepam and flurazepam

The guidelines for nitrazepam and flurazepam are the same as those for diazepam, etc, with the exception of the following amendments.

Indications—Short-term treatment of insomnia where daytime sedation is acceptable. CHILDREN: not recommended.

Dosage—ADULTS: current data sheets are generally acceptable.

Dosage of intramuscular preparations—Not applicable.

References

1 White House Office of Drug Policy and National Institute on Drug Abuse. *FDA Drug Bulletin* August 1979;16.

2 Marks J. *The benzodiazepines: use, overuse, misuse, abuse.* Lancaster: MTP, 1978.

A ship's engineer was exposed to fluorocarbon gas from a ruptured pipe for three days, after which he became ill. What likely after effects might occur?

The question is not specific enough to answer precisely. One needs to know which fluorocarbon, the likely concentration, and the nature of the signs and symptoms of the illness from which the engineer suffered. Several fluorochlorohydrocarbons are in widespread use. Useful reviews of their biological and toxic effects will be found in *Food and Cosmetics Toxicology*.[1 2] The most serious toxic effect that has been observed in some species of animals is cardiac sensitisation but this has been seen only at very high levels of exposure. Jenkins *et al*[3] exposed rats, guinea-pigs, monkeys, and dogs continuously to trichlorofluoromethane 1000 ppm for 90 days without ill effect. Others have found that exposure to levels of 50 000 ppm and higher caused tremors, narcosis, and convulsions in guinea-pigs. A move in parts of the USA to restrict the use of chemicals of this kind stems from a fear, possibly with little foundation, that they find their way into the upper atmosphere where they interact with ozone to cause the depletion of a barrier which reduces the amount of ultraviolet radiations that reach the earth's surface. If this fear were justified then an increased risk of skin cancer might eventually result. Apart from this there are no grounds for believing that any of the fluorocarbons are carcinogenic.

1 Charlesworth FA. The fate of fluorocarbons, inhaled or ingested. *Food Cosmet Toxicol* 1975;**13**:572-4.

2 Charlesworth FA. Fluorocarbons near and far. *Food Cosmet Toxicol* 1977;**15**: 72-4.

3 Jenkins LA, Jones RA, Coon RA, Siegel J. Repeated and continuous exposures of laboratory animals to trichlorofluoromethane. *Toxicol Appl Pharmacol* 1970;**16**: 133-42.

Is there an association between spastic colon and perennial rhinitis? If here is are such patients more liable to peptic ulcer?

There is no known association between spastic colon and perennial rhinitis. It has been suggested that some patients with a spastic colon may have the condition caused by a food allergy but in reality this rarely turns out to be the case. Food allergy may cause some cases of perennial rhinitis, but these patients do not usually have bowel symptoms.

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