Section B

Clinical experience with lorazepam in hospital patients

N. W. Imlah,* M.B., Ch.B., Dipl. Psych.

All Saint's Hospital
Birmingham, England

Curr. med. Res. Opin., (1973), **1**, 276. Paper read: 26th November 1972

Summary

Clinical experience of lorazepam (2.5 mg.) as a hypnotic, compared with amylobarbitone sodium (200 mg.) is described in 12 elderly demented patients. The results suggest that 2.5 mg. lorazepam is a very effective hypnotic in the elderly but that a lower dosage is advisable because of the high incidence of post-hypnotic sedation.

In order to determine the dependence liability, a small study on 16 in-patients receiving single doses of 2.5 mg. lorazepam at night revealed no side-effects attributable to abrupt withdrawal of the drug after 2 to 3-week periods of continuous use in this dosage.

Clinical impressions gained over a period of time in treating patients with neurotic disorders suggest that 1 mg. lorazepam t.d.s. is most closely comparable to diazepam in 5 mg. dosage, but somewhat less likely to cause over-sedation in anxious patients. It is considered, however, that this 1 to 5 ratio is not necessarily reproduceable in terms of simple sedative effects at higher dose levels, e.g. 2.5 mg. lorazepam appears to be a more effective hypnotic than 12.5 mg. diazepam. It is concluded that lorazepam must be regarded as an important addition to the range of drugs used in the treatment of neurotic disorders.

Key words: Lorazepam – insomnia – drug addiction – neuroses, anxiety – aged

Introduction

In Britain, the benzodiazepine group of drugs is well established in psychiatry as anxiolytics and as hypnotics. In conditions where the primary problem is anxiety and associated tension, these drugs are widely accepted as the drugs of choice both for the psychiatrist in hospital and for the family doctor. The drugs currently in use for this purpose are chlordiazepoxide, diazepam, medazepam and oxazepam. It is generally agreed that medazepam is a very similar drug to chlordiazepoxide and that chlordiazepoxide and oxazepam are less sedative in their effects than diazepam. There are really no other drugs or group of drugs that rival the use of this group as first choice in the treatment of anxiety.

In the hypnotic field, only one of the benzodiazepines is widely used, *viz* nitrazepam, although diazepam can be and is used as a hypnotic on occasions. In con-

*Medical Director and Consultant in Psychiatry

trast to the anxiolytic field, there are many other hypnotics which may be favoured in the first instance, but some are falling into considerable disfavour and it is considered likely that in the future there will be an increased use of benzodiazepines as hypnotics.

The steadily-growing problem of drug abuse and drug dependency in the U.K., as in other countries throughout the world, is focusing ever increasingly on the barbiturates and already there is considerable propaganda building up to curtail the use of barbiturates, both as daytime sedatives in neurosis, and especially as hypnotics. Already in many areas of the country a voluntary ban exists on the prescribing of amphetamines: it may well be that this will set a precedent which will affect some barbiturates and possibly some other drugs as well. Such a trend is also likely to affect other non-barbiturate hypnotics which give rise to considerable problems such as dependency and misuse in association with alcohol.

It appears, looking at the general preference for benzodiazepines in these areas, that they have attained this situation on three counts. Firstly, is their relative superiority over any other pharmacological substances, particularly in the field of anxiety; secondly, is their very high level of safety; and, thirdly, the fact that, although they do in some instances cause dependency and give rise to an abstinence syndrome, they have not as yet shown any tendency to form a part of the current drug abuse scene to any serious extent. Their future potential would appear to be considerable, therefore, both as anxiolytics and hypnotics, provided they do not become incriminated among the drugs creating a serious problem in abuse.

In the face of ever-increasing stress symptoms the benzodiazepines are liable to be even more increasingly used for the next decade at least. At the same time, however much of an improvement the benzodiazepines may be upon other drugs, there is still room for improvement on those currently in use. Nitrazepam is the only one in the group used as a hypnotic, and while diazepam is currently the most popular anxiolytic drug used in Britain, it can cause problems of over-sedation, and, in many cases, the benefits experienced by the patients are minimal. Patients with particularly low stress tolerance do not do as well comparative to barbiturates as do patients with a relatively good stress tolerance, but who are under excessive environmental pressures. On the evidence of the many reports, there is every reason to believe that lorazepam will be an effective improvement upon existing drugs.

The author's experiences with lorazepam, apart from providing some early material for biochemical and haematological studies, have been in three different areas, namely, (1) an assessment of its potential as a hypnotic in elderly demented females, (2) an investigation of the possibility of the drug producing dependence on a short-term basis, and (3) a general clinical use of the drug among a variety of out-patients suffering from anxiety, for the purpose of forming a general clinical impression.

1. Lorazepam as a hypnotic in geriatrics

A small investigation was designed to assess the potential of lorazepam in a group of very demented elderly, wandering, restless, agitated females. This is a group in which

night sedation presents many problems and a group in which it is widely believed barbiturates are unhelpful or undesirable.

Method

Twelve patients were selected in this investigation, with a trial period covering 14 days. On the first four nights, 6 patients received no sedation, the other 6 patients received amylobarbitone sodium 200 mg. on each of 4 successive nights. From Night 5 until Night 14 all 12 patients received lorazepam 2.5 mg. All drugs were administered at 9.30 p.m. and subsequently observations were made and recorded hourly from 10.00 p.m. until 6.00 a.m. marking the patient either asleep or awake. A record was kept of any pre-sleep excitement or post-hypnotic suggestion; any other side-effects were observed. We had used this method of recording previously in other comparisons of hypnotics. The day-time medication of these patients was not standardised, and they continued upon the day-time medication to which they had become established, with instructions that this was not to be changed throughout the 14-day period of the investigation.

Results

The results of this investigation were as follows: 9 of the patients slept better on lorazepam than they did on the 4 nights prior to receiving the drug. Three patients slept better on the 4 nights prior to receiving lorazepam, 2 while on placebo and one while on amylobarbitone sodium. While it may appear at first sight surprising that patients should appear to sleep better on placebo, it must be remembered that all of these patients were brain damaged and that some elderly brain damaged patients do, in fact, sleep better without any medication at all.

The percentage times that the patients were actually asleep were also compared. On lorazepam the patients were asleep 77.2% of the total time; on amylobarbitone sodium they were asleep 69.2% of the total time, and on placebo 67.6% of the total time.

Discussion

Although no attempt has been made to apply statistics to these results, it would appear from them that in the dosage used lorazepam was a more effective hypnotic than amylobarbitone sodium. However, it was also recorded that 10 of the 12 patients on lorazepam suffered from post-hypnotic sedation.

It is suggested by this pilot study that 2.5 mg. lorazepam is a very effective hypnotic in elderly patients, but that the dose was probably excessive for patients in this category because of the high incidence of post-hypnotic sedation which occurred. It is considered that, although 2.5 mg. lorazepam may well be a tolerable hypnotic dose in younger patients, it would be advisable to use a lower dosage as a hypnotic in the elderly, possibly 1.5 to 2 mg. being sufficient.

2. A dependency study on lorazepam

The dependency study was undertaken because of the views of the Committee on

the Safety of Drugs based on volunteer studies carried out in Oklahoma State Penitentiary. It is the author's view that the withdrawal syndrome which was experienced by these volunteers has been observed with benzodiazepine-derived drugs in current use where the stoppage of the drug has been sudden after regular intake over a period. This observation has been made in neurotic patients under treatment who have taken it upon themselves to dispose of their medication with the impulsive intention of managing in the future without the assistance of their drugs. Within 24 hours they have complained of excessive nervousness and agitation, feelings of nausea, abdominal upsets and crawling sensations on the skin, nasal congestion and insomnia. These symptoms are soon relieved by re-starting the benzodiazepine. This withdrawal syndrome has been observed with both chlordiazepoxide and diazepam, where the doses have been within the normal therapeutic range, but where the drug has been taken for periods in excess of 30 days of regular use. It is the author's opinion that after a time these drugs do, in many subjects, produce an abstinence syndrome if withdrawal is abrupt and it is the practice never to advise patients to stop these drugs suddenly, but reduce gradually the dose over a period of time as the patient's general condition improves. Provided this practice is followed, it is considered that in their normal therapeutic range these drugs give extremely little withdrawal problems. There have, of course, been reports in the literature of dependence to these drugs, but it does in my experience appear to be mainly physical dependence. There is little tendency to increase progressively the dose among psychiatric patients, possibly because the effects of excessive dosage tend to be unpleasant and there certainly appears to be little tendency to take these drugs purely for 'kicks' or psychological uplift, as is the case with the drugs which are so widely abused at the moment. It is the lack of this psychological element in the dependence which is the most hopeful picture for the future of these drugs and, provided one recognises that a degree of physical dependence can arise, appropriate management of the case can control this feature. In view of the possible dependency problems, it was necessary to establish whether or not lorazepam showed any evidence of dependence in the short-term in normal dosage.

Method

The methodology of such an investigation gave rise to some problems and the first attempt was discarded because it was clear that anticipated ratings were being made, rather than observed ratings, although on the balance of probabilities there did not seem to be any problems of dependence. However, on the basis of this first attempt, another trial was designed with the intention of eliminating the problems of methodology. In this investigation 16 patients were included. They were all in-patients, admitted to the hospital with an expected duration of stay of at least 4 weeks. The diagnoses were mixed, but all patients had insomnia which, in normal circumstances, would require a hypnotic at night.

By a random allocation method, 12 patients received 2.5 mg. lorazepam at night for 21 nights, followed by an identical placebo for 7 nights. Four patients were allocated 2.5 mg. of lorazepam for 14 nights and an identical placebo for 7 nights and

2.5 mg. lorazepam for the final 7 nights. The latter 4 patients served as a control group as a check against rater bias due to possible anticipation of results.

It was also decided that all patients would be re-rated for withdrawal symptoms throughout the whole period of the trial. This was to counteract the effects of suggestion which might arise through rating only during the withdrawal periods. The ratings were on a four-point severity scale covering the following symptoms: nausea, vomiting, abdominal cramps, bowel dysfunction, muscular twitchings, agitation and restlessness, convulsions, paraesthesia. In addition to this, the quality of the sleep reported by the patient was recorded on a three-point scale: poor, indifferent and good.

Results

The results showed that post-drug effects were recorded in 4 patients; 2 of them showed agitation and restlessness, 1 patient had paraesthesia of the left hand, and 1 patient complained of nausea. The latter patient had a previous bout of nausea on the fifth day of the trial. Against this, effects noted during the first week of the trial while the patients were on active drugs were; 2 patients with agitation and restlessness, 1 patient with bowel dysfunction, 2 patients with nausea and 1 patient with abdominal cramps. One patient had been excluded from the trial, leaving hospital against advice. Out of the 15 patients remaining, 6 patients did not exhibit any of the rated features throughout the 4-week period of the trial. There was no incidence of vomiting or muscle twitching and the only convulsion was recorded on the third day of the trial in a patient who had a previous history of convulsions.

Of the 2 patients recorded with agitation, it was considered that in one case the agitation was not clinically different from similar periods of agitation recorded in the same patient and was consistent with the patient's psychiatric disorder. In the other case, the agitation lasted for one day and did not occur until 5 days after cessation of lorazepam. The patient who experienced nausea had also suffered from nausea a fortnight earlier and the post-drug effect did not occur until 7 days after the cessation of the trial drug. The patient who experienced paraesthesia felt the effect in one hand only. Since the onset was 7 days after cessation of lorazepam, this effect was not regarded as attributable to the drug.

Conclusion

Although assessment of the quality of sleep did not form the main part of this investigation, it was found that 8 of the 15 patients had a reduced impression of sleep during the placebo period. It was concluded that lorazepam (2.5 mg.) appeared to be successful as a sleep-inducing agent in the dosage used in these patients and that there were no side-effects attributable to abrupt withdrawal of lorazepam after 2 and 3-week periods of continuous use in this dosage.

3. Clinical impressions of the anxiolytic properties of lorazepam

Lorazepam has now been used for some time in hospital practice in a considerable number of appropriate cases. No specific records have been kept of these because

no attempt has been made to carry out any form of statistical or controlled evaluation. It is, however, useful to employ drugs such as this as part of one's normal practice so that a personal opinion can be formed of the efficacy of the drug. This is what the doctor in his practice normally does with any drug, and whether he continues to use it or not ultimately depends upon his own personal impressions.

Lorazepam has been used in 0.5 to 1 mg. doses, mainly three times a day. It would appear that 1 mg. doses are more efficient, and most closely comparable to diazepam in 5 mg. dosage, but somewhat less likely to cause over-sedating effects in anxious patients. Paradoxically, 2.5 mg. lorazepam appears to be a more effective hypnotic than 12.5 mg. diazepam. The ratio of 1 mg. lorazepam to 5 mg. diazepam, which has been reported in a number of studies and which appears from my own observations to hold good, is not necessarily reproduceable in terms of simple sedative effects at higher dose levels; but, if this is so, it has some bearing on recommended dosages of lorazepam for use as an anxiolytic or as a hypnotic.

Discussion

On the basis of experience to date, it is considered that lorazepam is the most interesting benzodiazepine to become available for clinical use, for it has an immense potential both as an anxiolytic and as a hypnotic. Because lorazepam is indicated in the treatment area in which many doctors are well satisfied with existing drugs, such as diazepam and oxazepam, it may take some time, however, for its potential as an anxiolytic to be fully appreciated. In the U.K. it is possible that lorazepam may become more rapidly accepted as a hypnotic because current pressures are upon doctors to change their prescribing habits. Because nitrazepam has so far remained free of any serious criticism, doctors may well turn to a potent drug with the same kind of chemical background to nitrazepam.

There is little doubt, however, that provided lorazepam fulfils its current promise it must be regarded as an important addition to the range of drugs used in the treatment of patients with neurotic disorders.