A PROBLEM WITH LORAZEPAM?

Last October's BBC2 *Brass Tacks* programme spotlighted addiction to lorazepam. Is the drug so bad, or is it just one tranquilliser problem among many? A leading medical authority assesses the evidence.

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AMONG THE benzodiazepine tranquillisers, lorazepam — marketed in the UK under the trade names Ativan and Almazine — has acquired a particularly bad public reputation for causing drug dependence and withdrawal symptoms.[1, 2] Clear scientific evidence is lacking, but clinical impressions in general support lorazepam's 'bad press',[3, 4] and in a recent study, 20 out of 50 patients consecutively referred for help with benzodiazepine withdrawal were receiving lorazepam.[5]

WHY DOES lorazepam seem to cause greater problems than other benzodiazepines? There are several reasons:

► Lorazepam is extremely potent: its anxiety-relieving activity per milligram is estimated to be up to 10 times that of diazepam (Valium).[6] A patient taking what appears to be a small to moderate dose of lorazepam (typically 1mg three or four times a day) may actually be taking the equivalent of 30-40mg diazepam, a very considerable dose. The high potency of lorazepam has not been fully appreciated by medical practitioners. It is thought to result from the especially high affinity of this drug for benzodiazepine receptors in the brain, coupled with a slow rate of dissociation after binding to these receptors.[7] Other potent benzodiazepines, such as triazolam and alprazolam, give rise to similar withdrawal problems.

► The problem of potency is compounded by the tablet strengths in which the drug is supplied. Since its introduction, lorazepam has only been available in 1mg or 2.5mg tablets. It is not uncommon for patients to be prescribed three 2.5mg tablets daily, roughly equivalent to 75mg diazepam, a dose greatly in excess of that required for most anxiety states. At such high dosage, relative to other benzodiazepines, it is not surprising that problems of dependency and difficulty in withdrawal are pronounced with lorazepam.

► The tablet strengths in which lorazepam is supplied also make slow withdrawal difficult. If someone decides to reduce dosage, the smallest decrement of lorazepam that can practically be achieved is 0.5mg, obtained by halving a 1mg tablet. This cut (approximately equivalent to 5mg diazepam) may represent a sizeable proportion of the daily dose — enough to precipitate a withdrawal reaction.

► Withdrawal symptoms are most severe when blood concentrations of benzodiazepines are falling.[8] Lorazepam is eliminated from the body moderately quickly (within 10-20 hours blood concentrations fall to half the peak level obtained from a single dose[9]). Even with chronic dosing, blood concentrations are likely to fall appreciably between each tablet. Such falls can be enough to precipitate withdrawal symptoms, and concomitantly patients may develop a craving for the next tablet which they know will alleviate the discomfort. Other rapidly eliminated benzodiazepines, such as triazolam, produce similar acute withdrawal effects.

► Lorazepam is traditionally prescribed for daytime anxiety-reduction (ie, as an anxiolytic), in contrast to many other benzodiazepines which are given as nighttime hypnotics (eg, nitrazepam, Mogadon). Possibly patients deemed by their doctors to require daytime treatment have more severe anxiety and are more susceptible to dependence on tranquillisers than those judged to need only a hypnotic.

ALL BENZODIAZEPINES produce, to a greater or lesser extent, the same problems as lorazepam. However, benzodiazepine withdrawal is generally smoother and more convenient with diazepam,[10] which is less potent, has a very much slower rate of elimination,[11] and is available in smaller tablet strengths (diazepam 2mg tablets are roughly equivalent to 0.2mg of lorazepam). There is thus a trend for long-term lorazepam users to be transferred to diazepam, which is then slowly withdrawn.[12] Recent observations of 35 patients on lorazepam for up to 16 years show that diazepam substitution can usually be accomplished without difficulty.[13] Over three-quarters of these patients felt better or reported no change in symptoms after changing to diazepam. Eight experienced temporary drowsiness or increased anxiety, but these symptoms could usually be overcome by individual adjustments to dosage.

HELPING PATIENTS to withdraw from lorazepam, diazepam, or other benzodiazepines, does not of course solve the tranquilliser problem. Although total prescriptions for benzodiazepines are now declining, their use as hypnotics continues to rise,[14] and new anxiolytics are being introduced. Despite present optimism, it is hard to conceive of any drug which effectively relieves anxiety and insomnia yet does not carry a risk of dependence and withdrawal effects. The challenge for medicine, and indeed for society in general, is to find alternative, non-pharmacological, long-term methods for managing stress and anxiety. □

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"When somebody comes into my office and says that they've been trying to stop their lorazepam, my heart sinks because I know I shall have twice as much of a problem as getting them off, say, Valium: the symptoms are more severe, they're more persistent, more bizarre, and people are much more distressed by them . . . I feel that this compound should not now be prescribed because of the problems which may arise in some patients."
— Professor Malcolm Lader, member of the Committee on the Review of Medicines.

"We have much more difficulty getting people off Ativan than we do heroin, mainly because with heroin . . . within a couple of weeks they're off and then the problem is staying off. But with Ativan it's much more prolonged and they take up a lot more time in terms of treatment than do heroin users."
— Jim Corcoran, Torbay Drug Addiction Team.

"There's no scientific evidence to indicate that one particular tranquilliser is worse than another . . . To act just against one would be wrong because there is a problem with the whole group."
— Professor Michael Rawlins, member of the Committee on the Safety of Medicines and chair of its Subcommittee on Safety, Efficacy and Adverse Reactions.

From BBC 2's *Brass Tacks* programme, 20 October 1987.

In 1986 in Great Britain, pharmacists dispensed 3,149,000 prescriptions for lorazepam. More statistics on page 6.