



## drug information quarterly

Psychiatric Bulletin (2002), 26, 460–462

**CAROL PATON**

### Benzodiazepines and disinhibition: a review

#### AIMS AND METHODS

To describe and attempt to quantify the incidence of disinhibitory reactions to benzodiazepines and to identify those at risk. Medline search, 1966–January 2002.

#### RESULTS

The overall incidence of disinhibitory reactions is small, but those

with impulse control problems, neurological disorders, learning disabilities, the under 18s and the over 65s are at significant risk.

#### CLINICAL IMPLICATIONS

It is important to be aware of the ability of benzodiazepines to cause behavioural disinhibition and to maintain a high degree of vigilance

when these drugs are administered to patients known to be at risk. In patients who have experienced behavioural disinhibition with benzodiazepines, antipsychotic drugs should be used to modify behaviour in any future emergencies.

Some psychiatric disorders are associated with pathological anger and aggression. These include psychotic disorders, depression, bipolar disorder and various personality disorders (Fava, 1997). Benzodiazepines have been widely used in the management of this behavioural disturbance (Pilowsky *et al*, 1992). However, no single drug produces totally predictable sedation in all patients (Van der Bijl & Roelofse, 1991) and a paradoxical increase in hostility and aggression can occur after the administration of benzodiazepines. This is obviously problematic when the benzodiazepine is administered to control behavioural disturbance. So, how common is this adverse effect, who is at risk and why?

#### Mechanism of action of benzodiazepines

Gamma-aminobutyric acid (GABA) is the most abundant neurotransmitter in the central nervous system (CNS) and GABA receptors are widely distributed throughout the brain, with high concentrations in the cortex and limbic system. Benzodiazepines bind to the GABA<sub>A</sub> receptor, reducing the quantity of GABA required to open the chloride channel, hyperpolarise the neuron and inhibit neurotransmission. In contrast with drugs, such as barbiturates, that bind at other sites on the GABA<sub>A</sub> receptor, benzodiazepines cannot directly open the chloride channel, rendering them safer in overdose (Nutt & Malizia, 2001).

#### Paradoxical reactions

A drug can have the potential to both decrease and increase aggressive behaviour depending on the

underlying characteristics of the person who consumes it. Amphetamines, methylphenidate, benzodiazepines and alcohol are examples. In the majority of recipients, benzodiazepines have a calming effect but in a minority they can cause paradoxical reactions (also called disinhibitory reactions) characterised by acute excitement and an altered mental state: increased anxiety, vivid dreams, hyperactivity, sexual disinhibition, hostility and rage. Other sedatives that bind at the GABA<sub>A</sub> receptor, such as alcohol, are robustly linked with aggressive behaviour. Acute alcohol consumption is known to increase feelings of hostility and competitive and retaliatory behaviour, and epidemiological data show that alcohol is involved in over 50% of acts of violence (Miczek *et al*, 1997).

#### Prevalence of paradoxical reactions

Although the first reports of paradoxical reactions to benzodiazepines date back over 40 years (Boyle & Tobin, 1961), the incidence of this adverse effect remains uncertain. Some small studies in well-defined homogeneous patient groups report high rates of paradoxical reactions. In a placebo-controlled study of alprazolam in the treatment of panic disorder, 13.7% of patients randomised to alprazolam experienced paradoxical reactions compared with none given placebo (O'Sullivan *et al*, 1994). In a further study of the efficacy of alprazolam in borderline personality disorder, 58% of patients randomised to alprazolam experienced paradoxical reactions compared with 8% with placebo (Gardner & Cowdrey, 1985).

While these studies, numerous case reports and published case series suggest that paradoxical reactions are common, large studies and systematic reviews have



generally found them to be rare. For example, published case series report that disinhibition occurs in 10–20% of patients treated with alprazolam but Cassano *et al* (1994) found no difference in the incidence of aggressive behaviour between imipramine and alprazolam in 1168 patients treated for panic disorder. Similarly, when Greenblatt *et al* (1984) reviewed 45 controlled trials, they found no difference in the incidence of behavioural disinhibition between patients given triazolam, flurazepam and placebo. In a review of this subject, Dietch & Jennings (1988) conclude that, in the general population, the incidence of aggressive dyscontrol after administration of a benzodiazepine is less than 1%, similar to the incidence with placebo, and because overt rage reactions are rare, they are difficult to quantify. These apparently contradictory findings may be explained by the differences in the populations exposed (see below).

## Who is most at risk?

Genetic factors may be important. Short *et al* (1987) reported similar disinhibitory reactions to benzodiazepines in monozygotic twins and Dietch & Jennings (1988) reported that a mother and daughter both experienced behavioural disinhibition with temazepam.

Mood and environment may also contribute, as may the presence of neurological disorders, being young (Litchfield, 1980; Hawkridge & Stein, 1998) or over 65 or having a learning disability or CNS degenerative disease (Bond, 1998). Perhaps the single most important factor is underlying personality, as those with a history of aggression and poor impulse control may be more prone to experiencing paradoxical reactions to benzodiazepines. This association has been demonstrated with alprazolam in borderline personality disorder (Gardner & Cowdrey, 1985) and flunitrazepam in subjects with high scores on boredom susceptibility and verbal aggression (Dåderman & Lidberg, 1999). Animal studies also provide support for this association. Chlordiazepoxide has been shown to increase aggressive behaviour in pre-selected aggressive male mice but not in control mice (Ferrari *et al*, 1997).

## Mechanism of paradoxical reactions

The mechanism by which paradoxical reactions occur is not completely understood, but several theories exist.

The most likely explanation is that the anxiolytic and amnesic effects of benzodiazepines lead to a loss of the restraint that governs normal social behaviour and a reduced ability to concentrate on the external social cues that guide appropriate behaviour. This is supported by the observation that children and those with learning disabilities are at increased risk of disinhibitory reactions. These patient groups may not have developed the skills to control their behaviour in adverse circumstances. Benzodiazepine-induced inhibition of neurotransmission may result in a decrease in the restraining influence of the cortex, leading to excitement, agitated toxic psychosis, increased anxiety, hostility and rage. Ingestion of alcohol, which also binds to GABA<sub>A</sub> receptors, would be expected

to, and indeed can, increase the severity of this reaction (Medawarn & Rassaby, 1991). Several randomised placebo-controlled clinical studies provide support for the above: Blair & Curran (1999) found that when diazepam was administered to healthy volunteers, it selectively impaired the ability of subjects to recognise angry facial expressions. Recognition of other emotions was not impaired. The authors suggested that failure to recognise anger could lead to failure to moderate behaviour to conform to social rules. Weisman *et al* (1998) reported that healthy volunteers who had taken diazepam 10 mg were more likely to behave aggressively under low levels of provocation than those who had taken clorazepate, oxazepam or placebo. All were equally aggressive when subject to a high level of provocation. Bond *et al* (1995) found that patients who received alprazolam were more likely to respond to provocation than those who received placebo. The alprazolam group rated themselves as more tolerant and friendly, the same dissociation between behaviour and feelings that is found after alcohol consumption.

Dåderman & Lidberg (1999) reported that, in a population of young violent offenders, flunitrazepam-abuse led to self-reported feelings of power, overwhelming self-esteem and increased suggestibility. Rickert & Wiemann (1998) reported that flunitrazepam (Rohypnol), particularly when used with alcohol, renders women more likely to be victims of sexual assault due to diminished ability to respond to social cues.

Antisocial personality disorder is associated with a high prevalence of aggressive behaviour, possibly mediated through underactivity of serotonin (5HT) neurotransmission (Fava, 1997). Benzodiazepines can reduce 5HT neurotransmission, which may in turn precipitate aggressive behaviour. It therefore follows that people with antisocial personality disorder may be at increased risk of paradoxical reactions to benzodiazepines (Bond, 1998). There is evidence that acetylcholine (ACh) is involved in the paradoxical excitement seen in some patients. The cholinesterase inhibitor physostigmine has been used to reverse benzodiazepine-induced delirium (Van der Bijl & Roelofse, 1991). A similar reversal has been reported with flumazenil, a benzodiazepine antagonist (Soderpalm & Svensson, 1999; Fulton & Mullen, 2000).

Dose is also likely to be important. The majority of case reports of behavioural disinhibition are in patients treated with high doses of high-potency benzodiazepines, such as alprazolam, clonazepam, flunitrazepam and triazolam (Bond, 1998), particularly when they are administered intravenously or intranasally. There is also an increased risk from drugs with a short half-life. Very high and/or rapidly fluctuating plasma levels may be responsible (Van der Bijl & Roelofse, 1991; Bond, 1998).

Bond *et al* (1995) highlighted four factors associated with benzodiazepine-induced aggression: it occurs in response to provocation; it is recognised by others but not by the patient; it usually occurs with high doses; and high-potency drugs cause particular problems. Blair & Curran (1999) postulated that disinhibition may be



drug  
information  
quarterly

mediated via GABA<sub>A</sub> pathways in the right orbitofrontal cortex.

## Clinical management of paradoxical reactions

The patient should be kept safe, with constant nursing supervision, until their behaviour returns to normal. In extreme cases, flumazenil may be used, but its half-life is much shorter than that of lorazepam, clonazepam or diazepam and the patient is likely to require repeated doses.

Paradoxical reactions may not always be recognised at the time of occurrence, but may be suspected in retrospect. It is important that this suspicion is documented, along with the dose of benzodiazepine used and its route of administration, in order that the patient can be protected from future reactions of this type.

## Implications for practice

The association between benzodiazepines and behavioural dyscontrol has important implications for practice. We need to be able to predict who is at risk, as benzodiazepines are widely used as the first line to control acute behavioural disturbance.

True paradoxical reactions to benzodiazepines are probably uncommon, but are not completely unpredictable. Known risk factors include high-potency drugs, high doses being administered by parenteral routes to the very young, elderly, those with pre-existing CNS damage and those with a history of aggression or impulsivity.

It is important to be aware of the ability of benzodiazepines to cause behavioural disinhibition and to maintain a high degree of vigilance when these drugs are administered to patients known to be at risk. Failure to recognise such a reaction could lead to the administration of higher doses of benzodiazepines in an attempt to control the behavioural disturbance. In patients who have experienced a paradoxical reaction to benzodiazepines, future behavioural emergencies should be managed with antipsychotic drugs.

## Declaration of interest

None.

## References

- BLAIR, R. J. R. & CURRAN, H. V. (1999) Selective impairment in the recognition of anger induced by diazepam. *Psychopharmacology*, **147**, 335–338.
- BOND, A. J. (1998) Drug-induced behavioural disinhibition. *CNS Drugs*, **9**, 41–57.
- , CURRAN, H. V., BRUCE, M. S., et al. (1995) Behavioural aggression in panic disorder after 8 weeks treatment with alprazolam. *Journal of Affective Disorders*, **35**, 117–123.
- BOYLE, D. & TOBIN, J. M. (1961) Pharmaceutical management of behavioural disorders: chlordiazepoxide in covert and overt expressions of aggression. *Journal of the Medical Society of New Zealand*, **58**, 427–429.
- CASSANO, G. B., TONI, C., PETRACCA, A., et al. (1994) Adverse effects associated with the short term treatment of panic disorder with imipramine, alprazolam or placebo. *European Neuropsychopharmacology*, **4**, 47–53.
- DÄDERMAN, A. M. & LIDBERG, L. (1999) Flunitrazepam (Rohypnol) abuse in combination with alcohol causes premeditated, grievous violence in male juvenile offenders. *Journal of the American Academy of Psychiatry and the Law*, **27**, 83–99.
- DIETCH, J. T. & JENNINGS, R. K. (1988) Aggressive dyscontrol in patients treated with benzodiazepines. *Journal of Clinical Psychiatry*, **49**, 184–187.
- FAVA, M. (1997) Psychopharmacologic treatment of pathologic aggression. *Psychiatric Clinics of North America*, **20**, 427–451.
- FERRARI, P. F., PARMIGIANI, S., RODGERS, R. J., et al. (1997) Differential effects of chlordiazepoxide on aggressive behaviour in male mice: the influence of social factors. *Psychopharmacology*, **134**, 258–265.
- FULTON, S. A. & MULLEN, K. D. (2000) Completion of upper endoscopic procedures despite paradoxical reactions to midazolam: a role for flumazenil? *American Journal of Gastroenterology*, **95**, 809–811.
- GARDNER, D. L. & COWDREY, R. W. (1985) Alprazolam-induced dyscontrol in borderline personality disorder. *American Journal of Psychiatry*, **142**, 98–100.
- GREENBLATT, D. J., SHADER, R. I., DIVOLL, M., et al. (1984) Adverse reactions to triazolam, flurazepam and placebo in controlled clinical trials. *Journal of Clinical Psychiatry*, **45**, 192–195.
- HAWKRIDGE, S. M. & STEIN, D. J. (1998) A risk–benefit assessment of pharmacotherapy for anxiety disorders in children and adolescents. *Drug Safety*, **19**, 283–297.
- LITCHFIELD, B. (1980) Complications of intravenous diazepam. An overall assessment of 16000 cases and detailed studies of 6000 cases. *Dental Anaesthesia & Sedation*, **10**, 7–24.
- MEDAWARN, C. & RASSABY, E. (1991) Triazolam overdose, alcohol and manslaughter. *Lancet*, **339**, 1515–1516.
- MICZEK, K. A., DEBOLD, J. F., VAN ERP, A. M. M., et al. (1997) Alcohol, benzodiazepine–GABA<sub>A</sub> receptor complex, and aggression. In *Recent Developments in Alcoholism. Vol. XIII. Alcohol and Violence*, pp. 139–171. New York: Plenum Publishing.
- NUTT, D. J. & MALIZIA, A. L. (2001) New insights into the role of the GABA<sub>A</sub>–benzodiazepine receptor in psychiatric disorder. *British Journal of Psychiatry*, **179**, 390–396.
- O’SULLIVAN, G. H., NOSHIRVANI, H., BASOGLU, I. M., et al. (1994) Safety and side-effects of alprazolam: controlled study in agoraphobia with panic disorder. *British Journal of Psychiatry*, **165**, 79–86.
- PILOWSKY, L. S., RING, H., SHINE, P. J., et al. (1992) Rapid tranquilisation. A survey of emergency prescribing in a general psychiatric hospital. *British Journal of Psychiatry*, **160**, 831–835.
- RICKERT, V. I. & WIEMANN, C. M. (1998) Date rape among adolescents and young adults. *Journal of Pediatric Adolescent Gynecology*, **11**, 167–175.
- SHORT, T. G., FORREST, P. & GALLETLY, D. C. (1987) Paradoxical reactions to benzodiazepines – a genetically determined phenomenon? *Anaesthesia and Intensive Care*, **15**, 330–331.
- SODERPALM, B. & SVENSSON, A. I. (1999) Naloxone reverses disinhibitory aggressive behaviour in 5,7-DHT lesioned rats: involvement of GABA<sub>A</sub> receptor blockade? *Neuropharmacology*, **38**, 1851–1859.
- VAN DER BIJL, P. & ROELOFSE, J. A. (1991) Disinhibitory reactions to benzodiazepines: a review. *Journal of Oral and Maxillofacial Surgery*, **49**, 519–523.
- WEISMAN, A. M., BERMAN, M. E. & TAYLOR, S. P. (1998) Effects of clorazepate, diazepam, and oxazepam on a laboratory measure of aggression in men. *International Clinical Psychopharmacology*, **13**, 183–188.

**Carol Paton** Chief Pharmacist, Oxleas NHS Trust, c/o Pinewood House, Pinewood Place, Dartford, Kent DA2 7WG