ANXIETY REDUCTION AND SEDATION: PSYCHOPHYSIOLOGICAL THEORY

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Introduction

THE commonest unwanted effect of drugs used to alleviate anxiety is drowsiness which ensues in so many patients and so intensively that it might seem an unavoidable disadvantage. A belief that such a pessimistic conclusion is premature has led to the institution of research programmes to dissociate the two properties of anxiety reduction and sleep induction so that tranquillizers with minimal hypnotic properties (and *vice versa*?) might be developed. Is this a wild-goose chase? Are there theoretical or practical reasons why such a compound cannot exist? The purpose of my presentation is to explore this topic with respect to three aspects: the semantic differentiation between sedation and tranquillization; possible quantitative differences; and most important, possible qualitative differences. The discussion will concentrate on human studies. Despite the development of animal models which purport to distinguish between anti-anxiety effects and sedation (File & Hyde, 1978), the validity of animal models of fear reduction to human pathological clinical anxiety remains unestablished. Of course, biochemical and neurophysiological approaches remain essential.

Semantics

The term 'sedative' originally meant to make sedate, which the Oxford English Dictionary defines as 'tranquil, equable, composed, settled, not impulsive or lively'. Drowsiness is mentioned neither here nor in the definition for 'sedative' itself – 'tendency to soothe'. However, medical usage has increasingly equated sedation with the induction of feelings of torpor, sluggishness, apathy, drowsiness and fatigability, that is, with what was earlier deemed 'over-sedation'. Such effects are traditionally ascribed to the barbiturates.

The term 'tranquillizer', a drug to render the individual calm, serene, unruffled and not agitated, has usurped the function of the older term 'sedative'. This appropriation of terms has been encouraged in the past 20 years by the pharmaceutical industry, wishing to see its newer drugs such as meprobamate and the benzodiazepines oust the older compounds such as the barbiturates. Whatever the antecedents of the change, and however much one may deprecate the needless in-

troductory of new pseudo-technical terms, current usage favours a clear distinction between sedation and tranquillization (or 'anxiolysis').

Subjective and objective sedation

Sedation is generally defined and detected in subjective terms – the patient's reports of drowsiness, sluggishness and apathy. Such reports should have objective concomitants, that is, be measurable as behavioural responses. Simple psychomotor, perceptual and cognitive tasks in normal subjects will detect sedation, as the large literature on both immediate and residual (hang-over) effects of these drugs testifies. However, tranquillization by drugs is only demonstrable in normals (that is, 'non-patient-labelled' individuals) in stress conditions and in individuals with high trait anxiety (Barrett & DiMascio, 1966). Sedatives can stupefy anyone, whereas tranquillizers can still only the unquiet.

In unquiet patients, however, the inverted U-shaped curve, the so-called Yerkes–Dodson 'Law', complicates matters. Anxious patients have patchy behavioural impairments. For example, in one of our studies (Bond *et al.*, 1974a), 30 chronically anxious patients were compared with 30 age-, sex- and social class-matched normal controls with respect to many behavioural tests. The anxious patients completed fewer items on the Digit Symbol Substitution Test (mean of 51 as against 64 for the normals) and on the Symbol Copying Test (129 against 152). Sorting cards into separate categories and dealing into simple piles both took longer in the patients and they completed fewer simple arithmetic sums (mean = 8.1) than the controls (mean = 10.9). Auditory reaction times, tapping rate, the Gibson Spiral Maze times and errors, and cancellation task times did not differ significantly between the groups.

Twenty of these patients subsequently completed a multi-crossover clinical trial comparing medazepam, diazepam and chlordiazepoxide with amylobarbitone and placebo, each given in flexible dosage (Lader *et al.*, 1974). Amylobarbitone did not differ clinically from placebo but both were distinctly inferior to the three benzodiazepines which did not differ among themselves. In general, behavioural performance was not impaired although amylobarbitone tended to increase error scores (Bond *et al.*, 1974b). The allevia-

tion of anxiety tends to improve anxiety-related impairments in performance and only when high doses with sedation are used does performance again become impaired.

Similarly, it is difficult and sometimes misleading to extrapolate from acute single dose studies in normal volunteers to repeated doses in anxious insomniac patients when investigating the residual hang-over effects of hypnotics. The limited literature on this topic suggests that psychological impairment in patients is less than one would predict from single dose volunteer studies and, indeed, better psychological functioning may occur (Malpas *et al.*, 1974; Tansella *et al.*, 1974).

Quantitative differences

The general consensus is that barbiturates produce sedation at doses only a little above those necessary to assuage anxiety, whereas the benzodiazepines permit a much wider dosage latitude. As a corollary, there should be a lower incidence of sedation in patients treated with benzodiazepines than in those given barbiturates. This is generally found (see review by Greenblatt & Shader, 1974), but the differences can sometimes be trifling. For example, in the cross-over trial comparing three benzodiazepines with amylobarbitone and placebo, all given in flexible dosage, sedation was reported by five of the 20 patients when on diazepam, in two on chlordiazepoxide, in eight on medazepam and in nine on amylobarbitone. However, there were six such reports from the patients when administered placebo, an incidence of almost one-third (Lader *et al.*, 1974). Nevertheless, patient preferences clearly favoured the benzodiazepines.

Other studies have disclosed larger differences

which are interpreted in terms of the barbiturates having steeper dose-effect curves than the benzodiazepines (Figure 1). This is supposed to allow a greater latitude in attaining a dose adequate to combat symptoms of anxiety but insufficient to promote drowsiness. This inference is tautologous and unsupported by adequate data. The circular argument arises because it is the clinical impression that an optimal dosage is more easily reached with the benzodiazepines which leads to the assumption of a less steep dose-effect curve which implies a large dosage range.

The facts to support such an explanation are lacking because of very few attempts to construct dose-effect curves in human subjects. In a two-dose comparison of chlordiazepoxide (7.5 and 15 mg three times daily) with amylobarbitone sodium (50 and 100 mg three times daily) and placebo, both the dose-effect curves for anti-anxiety effects and the incidences of sedative effects were similar for the two drugs (Lader & Wing, 1966; Figure 2). Despite this, patients favoured chlordiazepoxide.

Might a more tenable hypothesis for the greater acceptability and effectiveness of the benzodiazepines as compared with the barbiturates concern their relative pharmacokinetic properties? The barbiturates, other than phenobarbitone, have plasma half-lives of about 24 hours. From this one can calculate that in 'steady-state' conditions and 8-h dosage intervals, the plasma concentration will fluctuate within each dose interval by about 20%. With many benzodiazepines, such as diazepam's major metabolite *N*-desmethyldiazepam, half-lives are much longer, say 72 hours. With 8-h dosage intervals the fluctuations between doses will average about 10%, but with once-nightly dosage, preferred by many patients, fluctuations of

Figure 1 Schematic representation of supposed dose-effect curves for a typical barbiturate (a) and benzodiazepine (b).

about 20% will still occur. Furthermore, for some benzodiazepines, mainly the 3-hydroxy derivatives, oxazepam, temazepam and lorazepam, the plasma half-lives are less than 24 h and yet these drugs still seem superior to the barbiturates. Of course, plasma concentrations are only a crude reflection of the biologically relevant concentration, that at the site of the action. That there are definite time-effect differences between diazepam and amylobarbitone, for instance, is evidenced by the different time-course of withdrawal phenomena. The withdrawal syndrome with a typical barbiturate occurs within 48 h of discontinuance; that for a long-acting benzodiazepine is delayed for several days.

Qualitative differences

So far, it has proved difficult to ascribe the apparent therapeutic contrasts among sedatives or tranquillizers to differences in quantitative aspects such as dose-effect relationships and pharmacokinetics. One fact at least suggests that a fundamental qualitative difference exists between the barbiturates and the ben-

zodiazepines. Overdoses of barbiturates are notoriously dangerous (Mathew, 1971). Severe poisoning is likely when more than ten times the full hypnotic dose has been taken. The shorter-acting lipophilic barbiturates are more toxic than phenobarbitone and patients taking them with suicidal intent are more likely to be found dead. The signs and symptoms of barbiturate overdosage reflect profound depression of the central nervous system with minimal or absent reflexes, periods of electrical silence in the EEG, and diminution in respiratory minute volume with hypoxia. Blood pressure drops partly due to barbiturate effects on medullary vasomotor centres, partly to a direct action of the drug on the myocardium, sympathetic ganglia and vascular smooth muscle. The patient goes into shock with hypothermia and the danger of respiratory and renal complications.

Contrast this serious medical emergency with benzodiazepine overdose. To echo Hollister's (1976) words (p829): 'It is probably impossible to commit suicide with benzodiazepines alone; almost all reported fatalities include other drugs'. (Children, however, are at definite risk with benzodiazepine overdosage.) Usually drowsiness or stupor is the most that

Figure 2 Dose-effect curves for amylobarbitone (A) 50 and 100 mg three times daily (●) and chlor-diazepoxide (C) 7.5 and 15 mg three times daily (○). *a*, Patients' self-ratings; *b*, psychiatrists' ratings; *c*, number of patients reporting drowsiness; *d*, sum of rank preferences of patients. P, Placebo.

occurs, with muscle relaxation and a mild drop in blood pressure. The patient recovers after 24 h or so asleep and is then awake and apparently functioning despite high plasma concentrations of benzodiazepines.

Any hypothesis concerning the mode of action of tranquilizers and sedatives must account for the lethal consequences of barbiturate overdose and the astonishing safety of the benzodiazepines. Our knowledge of the biochemical and physiological actions of the benzodiazepines and barbiturates has recently burgeoned (Nicoll, 1978; Guidotti, 1978; Haefely, 1978). Hypotheses concerning the actions of the benzodiazepines have implicated several neurotransmitter systems in the brain including cholinergic, noradrenergic and serotonergic pathways. Recently, a wealth of evidence has suggested that gabaminergic mechanisms are primarily involved. γ -Aminobutyric acid (GABA) is a widespread inhibitory neurotransmitter in the mammalian brain, being involved in 50% or more of all inhibitory synaptic influences. Benzodiazepines enhance gabaminergic activity, that is, they increase normal inhibition. Major tracts and actions involved are (Figure 3):

Figure 3 Possible links between gabaminergic inhibition and benzodiazepine actions. NB *Highly speculative*.

Spinal cord

GABA mediates presynaptic inhibition in the spinal cord thereby promoting muscle relaxation by an

action on the primary afferents. Cells in the dorsal column nuclei are also inhibited by GABA but by both pre- and post-synaptic mechanisms. Benzodiazepines increase all these effects offering an explanation for their muscle relaxant actions.

Cerebellum

The only output of the cerebellar cortex is the gabaminergic inhibition of deep cerebellar nuclei by Purkinje cell neurones. Moreover, basket, stellate and Golgi cells also release GABA and modulate afferent excitation to the Purkinje cells. Benzodiazepines can enhance the inhibition of Purkinje cells which could explain the ataxia which occurs at supratherapeutic doses.

Basal ganglia

A gabaminergic pathway runs from the caudate nucleus to the substantia nigra where it inhibits post-synaptically the dopaminergic nigrostriatal pathway. Increased inhibition by benzodiazepines could underlie their propensity to produce tremor at supratherapeutic doses.

Anticonvulsant properties

Isoniazid produces convulsions when the GABA content of the brain is diminished and GABA has a local anticonvulsant action. Benzodiazepines antagonise isoniazid-induced convulsions but have little action against strychnine-induced convulsions which are mediated through glycinergic mechanisms. By contrast barbiturates and phenytoin have equal potency against both types of convulsion. Clinically, the benzodiazepines are useful in status epilepticus and specific forms of epilepsy such as infantile spasms (Bower, 1978), whereas phenobarbitone and phenytoin are more generally useful.

Anti-anxiety and sedative actions

These actions of benzodiazepines are commonly attributed to an effect on the limbic system, a sort of 'chemical amygdectomy'. However, limbic structures are complex and no single overall effect is likely. Both spontaneous and induced activity in the amygdala and hippocampal structures can be inhibited by low doses of benzodiazepines, an effect possibly mediated by way of gabaminergic influences.

Benzodiazepines also seem to affect diffuse projection systems to the cortex, noradrenergic, serotonergic and cholinergic. In particular, the stress-induced increase in noradrenaline turnover is blocked by benzodiazepines, whereas resting levels are unaffected (Corrodi *et al.*, 1971).

Mode of gabaminergic potentiation

Benzodiazepines have no direct action on GABA receptors but only increase the synaptic effects of gabaminergic neurones when these are activated. How they do this is obscure. Further, putative benzodiazepine receptors have been identified widely in the mammalian brain (Braestrup & Squires, 1977; Möhler & Okada, 1977). The affinity of benzodiazepines for these receptors corresponds encouragingly with their clinical potency (allowing for pharmacokinetic factors). Unfortunately, it has so far proved impossible to identify the natural ligand. It is not GABA and it may turn out to be a new neurotransmitter system, (perhaps a polypeptide like adrenal corticotrophic hormone (ACTH)), as was the case with the opiate receptors. Certainly, exciting developments can be expected in the near future.

To return to the benzodiazepines and the barbiturates: both classes of drug increase gabaminergically mediated inhibition. However, at high doses barbiturates but not benzodiazepines progressively suppress neuronal excitation by post synaptic antagonism of excitation (Nicoll, 1978). This neatly explains the lethal nature of barbiturate overdose as compared with that of benzodiazepines where the only major effect is to maximize natural inhibition.

Benzodiazepines themselves must be presumed to have differential effects in various areas as their profiles of action differ appreciably: diazepam is a much more effective anticonvulsant than chlor-diazepoxide. These differences are not primarily pharmacokinetic as animal profiles with single and local dose administrations also vary.

Haefely (1978) has speculated that sedation might reflect inhibition of noradrenergic and dopaminergic systems, whereas anti-anxiety effects reflect serotonin and acetylcholine pathway inhibition. I would favour the reverse attribution in view of the effect of benzodiazepines on stress-induced noradrenaline turnover increase. However, we know too little about these diffuse projection pathways to be dogmatic. What is important is that different systems could be differentially sensitive to various benzodiazepines. Different populations of receptors might exist as with noradrenaline and histamine transmission. It is thus theoretically possible that the anti-anxiety and sedative actions of these drugs might be separable.

Other types of tranquillizers

Many other ways of relieving anxiety have been developed, both pharmacological and non-pharmacological. The latter, such as relaxation techniques, biofeedback and meditation, have the advantage that sedation should be avoidable but they are difficult for some patients to learn properly and to apply effectively in anxiety-provoking situations (Shapiro, 1977).

These techniques may be capable of development so that they become widely applicable and efficacious, but at present we must rely on pharmacological methods.

The antipsychotic (major tranquillizer, neuroleptic) agents have been advocated at low dose levels in the treatment of anxiety. The danger of tardive dyskinesia, although probably remote at these sub-neuroleptic dose levels, makes many practitioners reluctant to use these agents in this role. The main advantage is the avoidance of dependence. Many antipsychotic drugs (and some tricyclic antidepressants) have marked sedative activity as a secondary psychotropic property.

The group of drugs which should provide alleviation of anxiety without inducing over-sedation is the β -adrenoceptor blocking agents such as propranolol. Their main site of action is at the periphery where they prevent any symptom mechanisms mediated by β -adrenergic pathways, chiefly palpitations, tremor and diarrhoea. Even here, two complications arise. First, the degree of anxiety alleviation varies greatly from patient to patient. Some, generally those with predominant somatic complaints, are greatly helped; others with mainly psychological symptoms such as tension, apprehension and irritability are not impressed by the administration of a β -blocker and may even feel worse (Tyrer & Lader, 1974).

Secondly, these drugs do actually enter the brain and are consequently capable of producing central effects. The brain entry of β -blockers varies widely: that of practolol is low, that of pindolol high. In our work with sotalol in normal volunteers, subjective reports of drowsiness and muzziness were obtained (Lader & Tyrer, 1972). In one patient, larger doses of sotalol (600 mg daily) were associated with hypnagogic and hypnapompic hallucinations (Tyrer & Lader, 1973). In a survey of about 1500 patients on oral propranolol therapy, Stephen (1966) reported 22 patients with light-headedness or dizziness, 18 with fatigue and 7 with insomnia. Wheatley (1969), in a general practice comparison of propranolol with chlor-diazepoxide, reported that 8% of patients on propranolol complained of drowsiness as compared with 12% on the benzodiazepine.

Thus, while it is possible that β -blockers could be developed devoid of central effects, at present they cannot substitute very extensively for the centrally acting drugs. Even in those patients with somatic anxiety who gain symptomatic relief, drowsiness may still occur. Possibly the most appropriate way to use the β -blockers is as adjuncts to the benzodiazepines.

Conclusions

On theoretical grounds based on recent pharmacological and biochemical work, the anxiolytic and sedative properties of a benzodiazepine could be

mediated through different pathways and perhaps different neurotransmitters. If so, then the ingenuity of medicinal chemists should make feasible the development of a drug which is anxiolytic without being

sedative. The therapeutic advantages of such a divorce hardly need stressing. Nonetheless, the wider social, ethical and political implications of perfect tranquillity should not be entirely ignored.

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Discussion

DR S. FIELDING (New Jersey) asked whether there was any clinical evidence that anti-anxiety effects may be mediated by serotonergic mechanisms.

DR LADER replied that there was no such evidence.

DR W. BOGIE (London) commented on Lader's data which showed a 20% variation in plasma levels of diazepam when it is given as a single dose in the evening. He asked whether there was any difference in clinical efficacy with the once daily or divided daily dosage regimens.

DR LADER replied that the usual three times a day dosage regimen for diazepam was illogical in view of the very long half-life of the active metabolite nordiazepam (72 h or longer). It would be reasonable to

administer the drug only once a day or even every other day; the advantage of the single dose in the evening was that the patient obtained a useful hypnotic effect together with a prolonged anxiolytic action the following day.

DR A. NICHOLSON (Farnborough) commented that his group had carried out studies using potassium clorazepate 15 mg and the N-desmethyl derivative of diazepam (nordiazepam) in a dose of 5–10 mg given at night. EEG studies in healthy male volunteers had shown that sleep patterns were modified for two nights following a single dose and there was therefore a case for using such long-acting drugs on alternate nights only.