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A NEUROENDOCRINE APPROACH TO BENZODIAZEPINE TOLERANCE AND DEPENDENCE

Tolerance to the subjective effects of benzodiazepines is well-recognized clinically: most patients reporting initial drowsiness find it wanes over a few days. Normal subjects given a single dose of a long-acting benzodiazepine report progressively fewer subjective effects of drowsiness over the next few hours despite plasma concentrations of the drug hardly diminishing (Greenblatt & Shader, 1979). Tolerance also develops rapidly to the characteristic electroencephalographic effects, such as increase in fastwave activity and decrease in auditory evoked responses (Lader, Baker & Curry, 1980). Animal work shows that the benzodiazepine-induced depression of active social interaction wears off after a few days (Vellucci & File, 1979). Further support for a non-pharmacokinetic tolerance comes from case studies of acute overdosage (Greenblatt, Woo, Allen, Orsulak & Shader, 1978). Finally, there is cross-tolerance between the benzodiazepines and barbiturates and alcohol.

It is well-known that excessive doses of benzodiazepine over prolonged periods of time can lead to physical dependence and a characteristic withdrawal syndrome (Hollister, Motzenbecker & Degan, 1961; Fruensgaard, 1976; Preskorn & Denner, 1977). In such documented cases, the patients have escalated the dose thus giving a clear indication of tolerance and of probable physical dependence. We have withdrawn patients from high- and low-dose, long-term benzodiazepine treatment and all have experienced some form of withdrawal reaction. More importantly, the changes on withdrawal of normal doses were indistinguishable from those on withdrawal of high doses, both in quality and quantity (Hallstrom & Lader, 1981). It would, therefore, seem that physical

dependence on benzodiazepines does not necessarily lead to escalation of dosage and, hence, it would be useful to look for a biological marker of tissue tolerance to these drugs.

We investigated this possibility using a neuroendocrine strategy. The intravenous injection of 10 mg diazepam is a potent stimulus to the secretion of growth hormone (GH) (Syvalahti & Kanto, 1979). These authors found that after an intravenous administration of 10 mg diazepam to ten, drug-free, healthy volunteers, the content of serum GH rose significantly from 7.5 ± 0.9 ng/ml to 17.1 ± 3.8 ng/ml in 15 min ($P < 0.05$) and to 19.6 ± 2.9 ng/ml in 30 min ($P < 0.01$) before returning to pre-test levels at 120 min. The GH response probably involves the stimulation of GABA-ergic mechanisms as a similar GH response follows the administration of other GABA-mimetic drugs such as γ -hydroxybutyric acid (Takahara, Yunoki, Yakushiji, Yamauchi, Yamane & Ofuji, 1977), γ -amino β -hydroxybutyric acid (Fioretti, Melis, Paoletti, Parodo, Caminiti, Corsini & Martini, 1978), muscimol (Tamminga, Neophytides, Chase & Frohman, 1978), and baclofen (Koulu, Lammintausta & Dahlström, 1979).

We measured GH responses to diazepam in patients who had received diazepam in normal therapeutic doses (15-30 mg/day) for at least 1 year (range 4-12 years). All patients were admitted to a metabolic ward for the study. All were male and their age range was 32-38 years. Their psychiatric diagnoses were of anxiety neurosis and/or personality disorder and none were alcoholic or took other drugs. Following an overnight fast and the insertion of an intravenous cannula, patients were infused intravenously with diazepam (10 mg/75 kg body weight) over 3 min.

Figure 1 Plasma growth hormone concentrations (ng/ml) following diazepam infusion (10 mg/75 kg body weight) at time 0, pre-withdrawal (O— —O) and post-withdrawal (●——●) from long-term benzodiazepine treatment.

Blood samples were taken at the time shown in Figure 1 for estimation of GH levels by radioimmunoassay. The procedure was performed for the first time when patients were receiving diazepam regularly. Diazepam was then withdrawn over 2 weeks, and 4 days after complete withdrawal a second diazepam infusion was given, using the same dose.

As shown in Figure 1 all patients tested so far have had normal GH responses to diazepam after diazepam withdrawal whereas none have had a normal GH response while they were taking diazepam regularly. Patient No. 4 fainted 1 h prior to the pre-withdrawal test and his GH had not returned to basal

levels at the time of the infusion. As in the other cases, however, the GH response to diazepam was impaired. A post-withdrawal test was not performed in patient No. 3, but his pre-withdrawal results are in agreement with those of the others. The post-withdrawal GH responses were all greatly enhanced in spite of the fact that the diazepam peak plasma levels were substantially lower than those resulting from the pre-withdrawal infusions.

Our preliminary data appear to offer a simple measure of benzodiazepine tolerance. They also demonstrate a relatively simple neuroendocrine model which could be used in experimental animals

for investigating the pharmacological mechanisms underlying this tolerance. However, the mechanisms underlying benzodiazepine tolerance and dependence are ill-understood. Although experimental work indicates that simple quantitative or qualitative changes in benzodiazepine receptors do not seem to be involved (Möhler, Okada & Enna, 1978), it is possible that some form of receptor hypersensitivity may have played a role in the post-withdrawal GH responses. It is likely that uncovering the mechanism

involved in the suppression of the GH response would elucidate the general mechanisms of tolerance to benzodiazepines.

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LOCAL BUCCAL MUCOSAL EFFECTS OF ASPIRIN, INDOMETHACIN AND ISOXEPAC; THEIR RELATIONSHIP TO GASTROINTESTINAL DAMAGE

It has been established that non-steroidal anti-inflammatory drugs (NSAID) produce gastrointestinal bleeding in man and in animals (Mann & Sachdev, 1976; Pemberton & Strand, 1979). This damaging effect seems intimately associated with the ability of these weakly acidic agents to antagonise physiologically protective prostaglandins (Garner, Flemstrom & Heylings, 1979; Robert, Nezamis, Lancaster & Hanchar, 1979). The mechanism by which the damage is mediated may be the production of relatively ischaemic areas of mucosa by antagonism of prostaglandin-induced vasodilation (Whittle, 1977) or by inhibition of bicarbonate secretion under the protective layer of gastric mucus (Garner *et al.*,

1979) the character of which may itself be changed by NSAID (Allen & Garner, 1980). It has also become apparent that the mucosal injury with consequent haemorrhage produced by NSAID can be potentiated by combination with agents with strong local emulsifying or lipolytic effects such as bile salts (Whittle, 1977) or ethanol (Goulston & Cooke, 1968) even though these agents have no effect on prostaglandin synthetase activity.

It seems probable that all the acidic NSAID in current use for the treatment of the inflammatory arthritides produce full blockade of physiological prostaglandins at their site of absorption in the gastrointestinal tract due to high local concentration at