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Time-related effects of benzodiazepines on intestinal motility in conscious dogs

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The effects of diazepam and GABA on intestinal motility were investigated in fasted dogs fitted with strain-gauge transducers. Injected intravenously at 9.00 and 16.00 h, diazepam (0·5 mg kg^{-1}) affected intestinal motility only during darkness i.e. from 19.00 to 7.00 h. These jejunal motor effects which were mimicked by GABA, (0·3 mg kg^{-1} i.v.) corresponded to a disruption of the migrating myoelectric complex (MMC) with an increased contractile activity. These results demonstrate that benzodiazepines affect the intestinal motility in dog and suggest that the effects are related to sleep-stages.

Benzodiazepines have been used in the treatment of gastrointestinal and colonic motor disturbances (Haubrich 1976) however, few experiments have been conducted to analyse their effects on intestinal motility in healthy or ill subjects.

Controversial effects of intravenous diazepam on human lower oesophageal sphincter pressure have been reported (Hall et al 1975; Weihrauch et al 1979) showing that the effects are related to the dose used and the duration of the treatment (Weihrauch et al 1979).

There is now substantial evidence that benzodiazepines act on γ-aminobutyric acid (GABA)-ergic pathways enhancing GABA-ergic transmission by a postjunctional membrane action (Costa & Guidotti 1979) with an interaction between the respective receptors (Tallman et al 1980). In addition, an enhanced binding of [^{3}H] diazepam is obtained when either GABA or one of its analogues is included in the binding assay (Tallman et al 1978; Wastek et al 1978).

GABA is known to stimulate intrinsic inhibitory and excitatory nerves in the guinea-pig intestine (Krantis et al 1980) inducing a contractile response (Inouye et al 1960). Consequently the present work was undertaken to analyse in conscious dogs the effects of diazepam injected intravenously on the motility of the small intestine and to compare these effects with those of GABA.

* Correspondence. This work was supported by I.N.R.A.

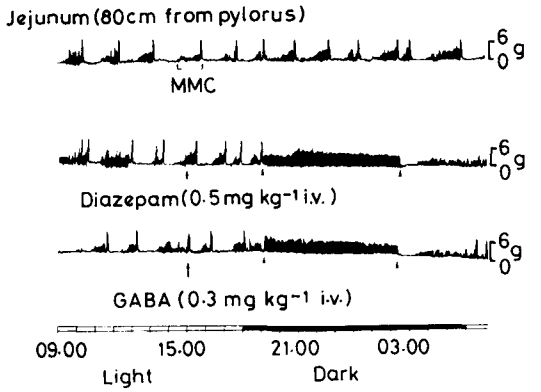

FIG. 1. Effects of diazepam and GABA on the motor profile of the jejunum in fasted dog. The normal pattern of intestinal motility consisted of cyclic migrating myoelectric complexes (MMC); they were disrupted as indicated by triangles only during darkness after treatment by diazepam or GABA independently of the injection time.

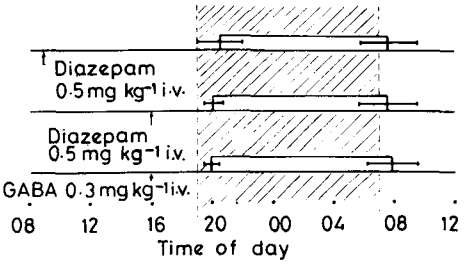

FIG. 2. Comparative jejunal motor response following administration of diazepam at 9.00 or 16.00 h or GABA at 16.00 h. Note that in all cases the disruption of the MMC pattern (open columns) occurred (mean ± s.d.) during darkness (hatched area) independently of the time of injection.

Material and methods

Four mongrel dogs, 15–25 kg, were used. Under halothane anaesthesia (fluothane N.D.), strain gauge transducers constructed in our laboratory according to Pascaud et al (1978) were sutured on the jejunum 40 and 80 cm from the pylorus. Strain gauge wires were exteriorized at the back of the neck and the dogs were then allowed to recover for 10–15 days after surgery.

The animals were placed in modified metabolic cages and housed in a dark room with artificial lighting from 7.00 to 19.00 h; the mechanical activity from the two transducers was recorded continuously by connecting the strain gauges to a 4 channel Wheatstone bridge amplifier (VT 2100, Vishay, France) connected to a potentiometric recorder (RK4, Rikadenki, Japan). Each strain gauge was calibrated before implantation with the establishment of individual calibration curves (Pascaud et al 1978).

The dogs were fed once daily (500 g canned food Fido) at 17.00 h except the day of experiments, and the drugs to be tested were injected intravenously at 9.00 and 16.00 h i.e. 16 and 23 h after the last meal. The effects of intravenous administration of diazepam (Valium N.D.), 0·5 mg kg^{-1}, were compared with those of i.v. injection of γ-GABA (SIGMA, USA) at 0·3 mg kg^{-1}.

Results

In fasted dog, the motility of the small intestine is organized in cyclical sequences of contractions, considered as migrating motor complexes (MMC) (Szurszewski 1969; Buéno et al 1975) comprising two phases: a phase of small amplitude (0·5–3 g) contractions occurring irregularly and lasting 40–80 min (phase II) followed by a short (6–8 min) phase of high amplitude (6–8 g) regular contractions (phase III) which migrated aborally from the duodenum to the ileum at a rate of 2–5 cm min^{-1} (Fig. 1). The phases were separated by period of mechanical inactivity (phase I). This 'fasted' pattern was disrupted for 8·4 ± 1·2 h after the meal but was omnipresent in fasted animals independently of the sleep-stages and the day/night rhythm (see Fig. 1).

When injected 23 h after the last meal, i.e. at 16.00 h, diazepam (0·5 mg kg^{-1}) did not modify significantly the duration of the migrating myoelectric complex (118 ± 23 min for the 1st MMC after injection vs 127 ± 31 min for the last MMC before injection); however in 87% of cases a strong increase in intestinal spiking activity was observed during the following period of darkness i.e. from 19.00 to 7.00 h.

This hyperactivity corresponded to a disruption of the MMC pattern, resembling that induced by feeding, it started between 19.00 and 20.40 h and lasted 11·3 ± 1·2 h (Fig. 2).

This response also occurred during the period of darkness after an injection of diazepam in the morning at 9.00 h corresponding to a delay of 10 to 13 h after the injection.

GABA injected intravenously (0·3 mg kg^{-1}) at 9.00 or 16.00 h produced a similar motor response of the small intestine also occurring between 19.00 and 21.00 h and lasting 10·3 ± 1·5 h, a duration similar to that observed for diazepam.

Discussion

This work demonstrates that intravenous administration of diazepam affects the intestinal motility only under unusual physiological conditions.

The fact that, independently of the injection time, both diazepam and GABA affect the intestinal motility when the dogs are in darkness and/or at night, suggests that these effects are related to sleep-stages.

In addition, these effects can occur more than 12 h after i.v. injection whereas the half life of diazepam injected intravenously is about 7 h with a rapid conversion into desmethyldiazepam and a very high plasma binding (Klotz et al 1976; Löscher & Frey 1981).

However, this retarded effect is in agreement with the fact that in mice pharmacological activity (anticonvulsant effect) and receptor occupancy still occur 48 h after a single i.p. injection of diazepam when total brain concentrations of drug and metabolites are no longer detectable (Garattini et al 1973).

In 1971, Birnhaum et al have shown that intravenous diazepam decreases nocturnal basal (unstimulated) gastric secretion in man. This result has been partially reproduced by Stacher & Stärker (1974) using bromazepam and more recently it has been shown that diazepam inhibits pentagastrin-stimulated acid secretion during nocturnal tests, suggesting that it acts by inhibition of the secretory stimuli arising centrally during sleep (Roberts & Oldrey 1975).

These changes in gastric acid secretion do not appear as a possible factor mediating the diazepam or GABA-induced intestinal hyperactivity, since blockade of gastric acid secretion by cimetidine, a H_2 antagonist, does not affect the MMC pattern in the fasted dog (Buéno & Garcia-Villar 1979).

Recently it has been shown that some neuropeptides such as somatostatin and cholecystokinin octapeptide (Buéno & Ferré 1982) or calcitonin (Buéno et al 1983) act at picomolar level within the brain to affect the intestinal motility, consequently it may be suggested that the release of these substances during sleep (NREM or REM sleep) is emphazised under diazepam, the GABA-ergic neuronal system being implicated in these effects.

Benzodiazepines are largely employed in the treatment of digestive disorders such as irritable bowel syndrome (Haubrich 1976) and sometimes in anxious patients with peptic ulceration (Roberts et al 1975), this work shows that they affect the intestinal motility probably in relation to the sleep-stages but it does not explain the mechanism involved.

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Suppression of laxative action of phenolphthalein by orally-administered indomethacin or aspirin

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Oral administration of phenolphthalein produced a dose-dependent increase of wet faeces excreted by mice. The response to phenolphthalein was reduced by pretreatment with indomethacin, aspirin or polyphloretin phosphate (PPP), but not with benoxaprofen. These findings support the view that the effect of phenolphthalein may be suppressed by PG synthetase inhibitors (indomethacin, aspirin) and by PPP.

The mechanism by which phenolphthalein and other contact laxatives exert their cathartic effect has long been a matter of controversy but, there is now a substantial literature that argues that these drugs stimulate PG biosynthesis and release PGE_2-like material in the gut (Beubler & Juan 1979; Cohen 1982). So it has been suggested that the PG may mediate the cathartic action of phenolphthalein and other laxatives. However, the contribution of these mechanisms to the cathartic effect in-vivo still remains to be established. The present paper demonstrates that treatment with indomethacin or aspirin reduces the incidence of the laxative effect of phenolpthalein in-vivo.

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