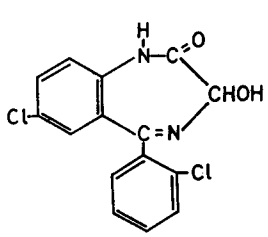
LETTERS TO THE EDITOR

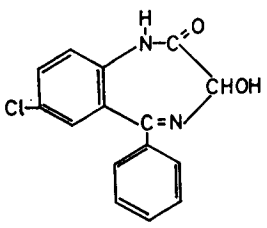
Brain concentrations of lorazepam and oxazepam at equal degree of anticonvulsant activity

Lorazepam (I) is an analogue of oxazepam (II) with a powerful anticonvulsant activity (Bell, McCaully & others, 1968; Gluckman, 1971; Schillings, Schrader & Ruelius, 1971; Owen, Hatfield & others, 1971).

Since we have established a correlation between antileptazol activity and brain levels of oxazepam (Marcucci, Fanelli & others, 1970) we have compared the effective brain concentrations of oxazepam and lorazepam on leptazol-induced convulsions.



I



II

Male Albino Swiss mice (body weight 20–25 g) were used in all experiments.

Lorazepam and oxazepam were administered intravenously at doses corresponding to ED50 measured by their antileptazol effect. Drugs were dissolved in a mixture of propyl glycol–glycofurol–benzyl alcohol–water (30 : 30 : 2 : 48) in concentrations to give a constant dose volume of 5 ml/kg. Each calculation of the ED50 was made on 60 male Albino Swiss mice. ED50 is the dose (mg/kg, i.v.) protecting 50% of the mice from the mortality induced by leptazol, 120 mg/kg (i.p.).

The method of Litchfield & Wilcoxon (1949) was used to calculate the fiducial limits.

Brain extracts were prepared as described by Garattini, Marcucci & Mussini (1969). The analyses were made using a gas chromatograph Model G I (C. Erba, Milan) equipped with a Ni63 electron capture detector (Voltage 42 V). The stationary phase was OV17 3% on Gas Chrom Q (100–120 mesh) packed into a 1 m glass column (i.d. 2 mm). The flow rate of the carrier gas (nitrogen) was 42 ml/min and the column temperature was 255°. The limit of sensitivity for lorazepam was about 1 ng per ml of blood or per g of tissue. Its recovery from blood and brain was respectively 78 $\pm$ 2·5 and 71 $\pm$ 3·6%.

During the gas chromatographic analysis, lorazepam loses a water molecule and it is rearranged to form 6-chloro-4-(2′-chlorophenylquinazoline)-2-carboxaldehyde, checked by mass spectrometry according to a previous study on the dehydration mechanism of oxazepam (Forgione, Martelli & others, 1971). The quantitative analysis of the samples was made by using the internal standard technique with 2-*N*-benzyl-amino-5-chlorobenzophenone as internal standard. The calculation of the peak area was by using an Infotronic digital readout system, Model CRS-104.

A linear relation between the gas chromatographic peak area and lorazepam concentrations was observed between 0·01 and 0·25 ng.

Table 1 summarizes the results obtained. It is evident that depending on the

time of administration, the antileptazol activity of lorazepam is from 3 to 12 times higher than that of oxazepam. The brain concentrations necessary to obtain a comparable degree of this activity are, however, 3–4 times lower for lorazepam than for oxazepam. These data clearly indicate that lorazepam is more potent than oxazepam not only in terms of dose but also in brain concentrations required for exerting an anticonvulsant action.

A slower disposition and/or a lower degree of binding to aspecific sites in the brain may explain the observed higher activity of lorazepam than oxazepam.

Table 1. *Brain concentrations of lorazepam and oxazepam after administration of the ED50 on leptazol in mice.*

Drug	Time*	ED50 mg/kg, i.v. (and 95% fiducial limits)	Brain concn ng/g ± s.e. †
Lorazepam	30	0·031 (0·035–0·027)	19 ± 1
	180	0·255 (0·337–0·193)	27 ± 2
	720	0·640 (0·768–0·533)	31 ± 2
Oxazepam	30	0·380 (0·429–0·336)	98 ± 2
	180	0·690 (1·035–0·460)	94 ± 1
	720	4·850 (6·160–3·819)	95 ± 6

* Minutes between drug and leptazol administration (120 mg/kg, i.p.).

† Each figure is the mean of 5 mice.

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