INTERACTION OF ETHOSUXIMIDE AND SODIUM VALPROATE IN MICE

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The combination of ethosuximide (Esx) and sodium valproate (Val) is claimed to be useful in some severe types of petit mal seizures which are refractory to monotherapy (Rowan et al 1980). With reference to this practice, it has been proposed that Val inhibits the metabolism of Esx because both drugs are extensively metabolized by the liver (Pisani et al 1984). The interaction of these two drugs has now been examined in male albino mice.

The drugs, dissolved in saline, were administered i.p. at doses (Val 200 mg/kg, Esx 150 mg/kg) that were submaximally-protective against leptazol (100 mg/kg i.p.)-induced seizures. Val (or saline) was administered 30 min before injection of Esx (or saline). In some experiments SKF525-A (50 mg/kg) replaced Val. Blood was collected under ether anaesthesia at 1 and 3 h after Esx and Esx plasma levels were determined by EMIT assay (Syva). Convulsant activity (seizure score) of leptazol was also determined 1 h after Esx administration. The results (Table) show that SKF525-A caused only a small potentiation of Esx's antileptazol activity. Val was a less effective antileptazol agent than Esx: in combination, a slight potentiation of their antileptazol activity occurred. The small potentiation of Esx activity in these cases may be related to the shallow slope of the plasma level/antileptazol activity relationship for Esx. Thus in mice receiving Esx orally (150, 225 and 300 mg/kg) the 1 h plasma levels of 49, 60 and 132 µg/ml were associated with 45, 50 and 60% protection respectively against leptazol. Consistent with the in vivo data, both compounds competitively inhibited O-demethylation of 4-nitroanisole by the 10,000 xg supernatant of mouse liver, Esx being less potent than Val. Therefore it is possible that these two drugs may compete with each other at this site and that Val, being a more active inhibitor, would inhibit Esx metabolism. As Esx exhibits no serious toxicity at plasma concentrations above the therapeutic range (Oellerich et al 1980), the interaction with Val should not indicate a potential hazard but may well represent a therapeutic advantage.

Table. Interaction of Esx and Val in mice

Group	Esx plasma level (µg/ml)		% protection
n = 10	1 h	3 h	against leptazol
Esx	53±17	8±4	40
SKF525-A + Esx	137±17	68±8	50
Val	-	-	20
Val+Esx	94±12	20±4	65

Val and Esx were gifts from Sanofi and Parke-Davis respectively

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