THE CLINICAL SIGNIFICANCE FOR CONVULSION THERAPY OF TRACE METAL INTERACTIONS WITH SODIUM VALPROATE

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Sodium valproate (Epilim) has proved an effective anticonvulsant in the treatment of epilepsy and, more recently, in initial therapy of neonatal lead-induced convulsions (Fernando et al 1981). The incidence of adverse reactions to the drug is low in comparison with other anticonvulsants, but still affects about 30% of patients. Epilim and most of its metabolites contain a labile carboxylate anion or carbonyl moiety. Any compounds formed with trace metals in vivo will affect solubility and, possibly, the side reactions of the drug.

We have performed in vitro metathetical reactions between Epilim and salts of copper(II), iron(II) and (III), manganese(II), magnesium(II), nickel(II), zinc(II) and calcium(II), as well as the toxic metals mercury, cadmium and lead. Magnesium and calcium gave products of only slightly lower solubility than the initial sodium compound. Iron(II) spontaneously and rapidly oxidised to iron(III) with absorption of atmospheric water. These compounds were not further examined. All other salts precipitated. The products analysed to better than 1% for the appropriate oxidation state of the metal. Nickel(II), iron(III) and lead(II) valproates contained one molecule of water. Mass spectra for the metal fragments of two representative compounds are listed in Table 1. The infrared asymmetric and symmetric stretching vibrations for (COO^-) are given in Table 2.

Table 1. Nickel and copper mass spectral metal containing fragments.

m/e	Intensity	Species	m/e	Intensity	Species
545	100.0	$Ni_2(val)_3^+$	413	90.9	$Cu_2(val)(valH)^+$
402	30.7	$Ni_2(val)_2^+$	341	15.7	$Cu_2(val)(H_2C{=}CHCO_2H)^+$
262	18.9	$Ni(CH_3(CH_2)_3CO_2H^+$	269	100.0	$Cu_2(val)^+$
200	53.8	$Ni\ (CH_3CH_2CH_2)_2C{=}CO_2^+$	227	33.8	$Cu_2(CH_3CH_2CH_2CH{=}CO_2H)^+$
			205	23.3	$Cu(CH_3CH_2CH_2)_2C{=}CO_2^+$

Table 2. Infrared asymmetric and symmetric (C-O) stretching vibrations (cm^{-1}).

	asym	sym		asym	sym		asym	sym
sodium	1550	1415	manganese	1560	1420	nickel	1570	1410
mercury	1545	1406	copper	1578	1419	iron(III)	1580	1420
cadmium	1567	1413	zinc	1590	1429	lead	1525	1380

Mass spectra show oligomeric structures for several of the metal valproates with infrared data indicating bonding ranging from ionic to bidentate coordination.

If reaction occurs with similar facility in vivo then, at the typical dose level for the drug of 30mg/kg/day for a child and 1.8g/day in adults, trace metal chelation could occur. Thus, for example, zinc and copper deficiencies give rise to, inter alia, alopecia and wavy hair syndrome respectively. Such symptoms are observed in about 11% of patients undergoing valproate therapy. Other correlations can be drawn: for example, between manganese and the incidence of ataxia.

The scope of the reactions between sodium valproate and trace metals demonstrated in vitro indicate this is a likely contributing factor in the observed side effects of the drug. It is hoped that metal balance studies of patients taking valproate will test this hypothesis, and with the aid of dietary supplements may lead to a reduction in side effects.

Fernando, N.P., Healy, M.A., Aslam, M., Davis, S.S. and Hussain, A. (1981) Public Health, London, 95; 250-260.

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