

LETTER TO THE EDITOR

Combined clozapine and valproic acid treatment-induced agranulocytosis

R. Madeb^b, S. Hirschmann^{a,b*}, R. Kurs^b, A. Turkie^b, I. Modai^{a,b}

^a Bruce Rappaport Faculty of Medicine, Technion, Haifa, Israel; ^b Sha'ar Menashe Mental Health Center, Mobile Post Hefer 38814, Hadera, Israel

(Received 2 January 2002; accepted 5 March 2002)

Sir,

Valproic acid (VPA) is increasingly used in psychiatry. Hematologic adverse reactions to VPA reported in the literature include aplastic anemia, cytopenia and myelodysplastic syndromes, [1,4,6,7]. Our report describes a patient who developed agranulocytosis after VPA was added to ongoing clozapine therapy. Mr. C., a 51-year-old patient with chronic paranoid schizophrenia and EEG abnormalities (frontal and central teta waves, and landa waves after hyperventilation) was successfully treated with 325 mg/day of clozapine for 3 years, but did not adhere to his treatment regimen after discharge. Six months later he was re-admitted in an acute psychotic state, and clozapine (325 mg/day) was resumed. He was hostile and aggressive, with mood shifts. Addition of lithium carbonate reduced his aggressiveness. Two months later Mr. C developed signs of diabetes insipidus, which remitted after lithium discontinuation. Augmentation with VPA 1000 mg/day was initiated 10 weeks after admission and Mr. C. steadily improved, with reduction of physical aggressiveness, mood shifts, flight of ideas, and paranoid state.

Throughout 3 years of routine clozapine follow-up, Mr. C.'s white blood cell (WBC) count fluctuated between 7500–12 000 cells per mm³ (normal range). His pre-VPA WBC count was 8100 cells per mm³, neutrophils 5580 cells per mm³ with a normal differential. During the first month of VPA treatment rou-

tine serial WBC counts revealed normal but decreasing WBC and differential count. One month after initiation of VPA, Mr. C. complained of general weakness. His WBC count was 1600 cells per mm³, 50 neutrophil cells per mm³ and Mr. C. was transferred to a general hospital.

GMC-SF was administered. The patient's total WBC count surged to 56 000 cells per mm³, neutrophils 48 000 cells per mm³ then settled to normal levels (WBC 7650 cells per mm³; neutrophils 4230 cells per mm³).

Mr. C. then received olanzapine (20 mg/day), and clonazepam (0.5 mg/day); his mental status remained stable and his hematological indices remained normal. Twenty-one weeks later his WBC count was 8000 cells per mm³, neutrophils 4200 cells per mm³.

The incidence of clozapine induced agranulocytosis is 1–2%; with 80% of the cases occurring within the first 18 weeks of therapy. Co-administration of clozapine and some aromatic anticonvulsants (i.e. carbamazepine) has been reported in increased combined toxicity on blood precursor cells [5].

VPA, a simple branched chain carboxylic acid, is an anticonvulsant chemically different from carbamazepine, and suppression of haematopoietic cells is most probably dose related [6,7]. Thrombocytopenia, cytopenia and other forms of hematological toxicity is

*Corresponding author.

E-mail address: shrrrena@matat.health.gov.il (S. Hirschmann).

increasingly encountered in connection with VPA administration, and in some cases has proven fatal [1,7].

Coadministration of clozapine and VPA may slightly increase serum concentration of clozapine metabolites [2]. Reports of efficacy and safety of combined clozapine and VPA are contradictory [3,8]. In our case, 3 years of clozapine monotherapy revealed no hematological side effects, however, agranulocytosis developed after augmentation with VPA, and required GMC-SF treatment. We report a single case and must be cautious against generalization and misapplication of our observation. Further investigation of combined clozapine and VPA therapy is needed.

REFERENCES

- 1 Acharya S, Bussel JB. Hematologic toxicity of sodium valproate. *J Pediatr Hematol Oncol* 2000;22(1):62–5.
- 2 Facciola G, Avenoso A, Scordo MG, Madia AG, Ventimiglia A, Perucca E. Small effects of valproic acid on the plasma concentrations of clozapine and its major metabolites in patients with schizophrenic or affective disorders. *Ther Drug Monit* 1999; 21(3):341–5.
- 3 Kando JC, Tohen M, Castillo J, Centorrino F. Concurrent use of clozapine and valproate in affective and psychotic disorders. *J Clin Psychiatry* 1994;55:255–7.
- 4 Kishi T, Fujita N, Kawaguchi H, Ishimae M, Watanabe K, Tanaka T. Bone marrow suppression induced by high dose valproic acid. *Arch Dis Child* 1994;71(2):153–5.
- 5 Luchins DJ. Fatal agranulocytosis in a chronic schizophrenic patient treated with carbamazepine. *Am J Psychiatry* 1984; 141(5):687–8.
- 6 MacDougall LG. Pure red cell aplasia associated with sodium valproate therapy. *J Am Med Assoc* 1982;247(1):53–4.
- 7 Watts RG, Emanuel PD, Zuckerman KS, Howard TH. Valproic acid-induced cytopenias: evidence for a dose-related suppression of hematopoiesis. *J Pediatr* 1990;117(3):495–9.
- 8 Wilson W. Do anticonvulsants hinder clozapine treatment. *Biol Psychiatry* 1995;37:132–3.