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PROLONGED PARKINSONIAN REACTION AFTER HALOPERIDOL IN A PATIENT WITH MONOCLONAL IgM

Dear Sir,

The binding of drugs to plasma proteins is an important determinant of drug concentration and therapeutic efficacy (Dayton *et al*, 1973). Studies thus far have pertained to patients with normal concentrations of plasma proteins and the albuminopathies (Koch-Weser and Sellers, 1976). The pharmacokinetic significance of clinical entities involving elevations of paraproteins (i.e. monoclonal immunoglobulins), e.g. multiple myeloma, Waldenström's macroglobulinemia, benign monoclonal gammopathy (BMG) has not hitherto been studied. These paraproteins, in contrast to polyclonal immunoglobulins found in normals, are homogeneous in structure and function. They possess antibody and non-immunologic binding properties (Farhangi and Osserman, 1976; Seligmann and Brouet, 1973; Thomas *et al*, 1974). A drug-binding capacity for paraproteins would enhance drug storage and prolong pharmacologic effect.

An 82-year-old woman was admitted to the psychiatric unit for treatment of a senile psychosis characterized by behavioural and sensorial changes, delusions, and auditory hallucinations. Treatment was initiated with haloperidol, starting at 1 mg/per day with gradual increase to 9 mg chlorpromazine 50 mg was given at bedtime. A moderately positive response permitted her discharge from the hospital, reduction of haloperidol to 3 mg per day, and discontinuation of chlorpromazine. About four weeks later, she developed a severe Parkinsonian reaction manifested by hypokinesis, bradykinesis, rigidity, and sialorrhea. The haloperidol was then discontinued, but the reaction persisted for 12–14 days thereafter. A remarkable symptomatic improvement of several weeks' duration was noted after its clearance.

Blood drawn one day after initiation revealed a sedimentation rate of 104 mm/hr (normal 0–15) and an alkaline phosphatase of 110 mu/ml (normal 30–85). Diagnostic studies revealed no evidence of malignancy. Serum viscosity was 1·97 (normal 1·4–1·7). Immunoelectrophoresis revealed abnormal values for IgM. The first study, done 20 days after initiation of haloperidol, revealed an IgM level of 4200 mg percent (normal 100); second and third determinations, done at 22 and 34 days, showed IgM levels of 4200 and 2800 mg per cent respectively. The levels of IgG and IgA were within normal range. Bone marrow aspirations were negative for myeloma and a diagnosis of BMG was made. In all probability these abnormalities pre-dated treatment with haloperidol, but the remote possibility of drug antigenicity was considered. Pre-treatment studies were not performed.

Data suggestive of an hypothesis of paraprotein binding are the binding affinity of haloperidol (92 per cent), its serum half-life of 12–22 hours, and the half-life of IgM being 6–7 days with 75 per cent metabolism in 12–14 days. Discontinuation of haloperidol usually results in prompt subsidence or brief duration of dyskinesias but persistent Parkinsonism of 12–14 days is not common.

In order to ascertain if the monoclonal IgM had any haloperidol-binding property 25 ng of tritiated haloperidol (a gift from McNeil Laboratories, Inc, Fort Washington, Pa) was incubated for 1 hour with 0·1 ml of serum of patient and normal control respectively. Ouchterlony (double gel diffusion) analysis in 1 per cent agar was performed with anti-IgM. Radioactivity of the precipitin line was determined by autoradiography over a period of 14 days. No evidence of binding of haloperidol to IgM was found in either patient or normal control serum.

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