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Communications

Tetrabenazine as a Cause of Neuroleptic Malignant Syndrome

To the Editor:

Neuroleptic malignant syndrome (NMS) is an uncommon complication of treatment with neuroleptics or with abrupt withdrawal of various antiparkinsonian drugs. We report the third described case of NMS consecutive to the administration of tetrabenazine used for treatment of Huntington's disease.

A 52-year-old man has been suffering for 8 years from Huntington's disease, proved by PCR technique (size of allele b corresponding to 44 CAG trinucleotide repeat on the short arm of chromosome 4). His usual treatment consisted of tetrabenazine (82.5 mg/day) and clonazepam (2.5 mg/day). He was first admitted for an accidental intoxication, 6 days before, with 500 mg, more or less, of tetrabenazine. At home, overdosage was characterized by falls, low blood pressure, nauseas, vomiting, diarrhoea, hallucinations, and worsening of confusion. On admission, general examination showed only mild dehydratation signs. Neurological examination showed an important generalized chorea and cognitive impairment. Laboratory test showed only a moderate increase of urea to 62 mg/dl. Analysis of CSF was unremarkable. Brain CT scan revealed severe cortical atrophy with involvement of caudate nuclei. EEG showed a diffuse slowing (4–5 Hz). Tetrabenazine was stopped during 3 days after admission. Progressively, the patient recovered his usual state. He was discharged on day 17. His treatment included tetrabenazine 100 mg/day and clonazepam 4.5 mg/day.

Two months later, he was readmitted for major hyperthermia resistant to administration of acetylsalicylic acid and paracetamol. Two weeks before, tetrabenazine had been slightly increased to 131 mg/day. On admission, the patient presented an hyperpyrexia to 41°C, an hypomimic facies, a moderate stiffness and complete disappearance of choreic movements. Haematological examination showed a white cell count of 15,040 cells/mm^3 (84.1% neutrophils) without inflammatory syndrome. CPK were increased to 3,108 U/l. CSF examination was normal. Blood, urine, and CSF cultures remained sterile. Chest x-ray was normal.

The next day CPK rose to 42,350 U/l. As NMS was suspected, treatment with parenteral sodium dantrolene (2 mg/kg/h), mild doses of bromocriptine (3 × 10 mg/day) and alkaline diuresis was started. Temperature and CPK decreased quickly with the treatment. Bromocriptine was stopped 4 days later because reappearance of important choreic movements. Sodium dantrolene was stopped after 10 days when CPK were normalized.

Unfortunately, the patient died 2 months later of a bacterial pneumonia and a septicemia caused by *Staphylococcus aureus*. In this case, clinical and biological features were consistent with the diagnostic of NMS and comparable with two other cases described after treatment by tetrabenazine for Huntington's disease (1,2).

In our case, the syndrome occurred 2 weeks after a moderate increase of a chronic treatment with tetrabenazine (100–131 mg/day), and 2 months after a clinical picture consistant with an accidental overdosage as described by Kidd and McLellan (3). In the first described case (1), the NMS occurred 7 months after the introduction of a high dosage of tetrabenazine (350 mg/day) in association with the dopamine synthesis inhibitor alpha methyltyrosine. In the case of Mateo et al. (2), the NMS occurred 3 weeks after the beginning of a moderate dose (100 mg/day) of tetrabenazine simultaneously with interruption of haloperidol.

In all three cases, early evolution of NMS was good without treatment in Burke et al.'s (1) patient, with parenteral sodium dantrolene in Mateo et al.'s (2) patient, and with parenteral dantrolene and bromocriptine in our case. The outcome of the other patients was good after a more progressive rechallenging of tetrabenazine at a lower dosage.

One of the main pathogenic mechanism of NMS is probably a blockage of dopaminergic receptors at many levels in the central nervous system (striatum, hypothalamus, spinal cord) (4).

Tetrabenazine is a dopamine storage blocking agent and cause a depletion of presynaptic dopamine. In several rare conditions (association with a neuroleptic, inadequate dosage), this mechanism of action may explain the occurrence of NMS.

Tolerance of tetrabenazine during long term-treatment seems to be quite safe (5). Because NMS triggered by tetrabenazine is a very rare entity, we believe that the risk at developing NMS is not a limitating factor for the appropriate use of this drug.

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