KETOCONAZOLE IN THE TREATMENT OF CRYPTOCOCCOSIS OF THE CENTRAL NERVOUS SYSTEM

*P. C. TREVISOL-BITTENCOURT * — J. W. A. S. SANDER ** — C. S. SILVADO *** E. O. WITTIG ****

SUMMARY — Two patients with cryptococcosis of the CNS were treated with ketoconazole (KTZ), an imidazole derivative with fungistatic properties; they had either failed standard therapy (Amphotericin-B + 5-Flurocytosine) or suffred intolerable side-effects to it. Both patients were administered KTZ 800 mg/day as monotherapy for six months without interruption and both responded. One month after KTZ therapy was withdrawn, however, a relapse of the infection was seen in one case. Side-effects were minimal during the trial of treatment. KTZ could be a useful drug in some cases of neurocryptococcosis.

Ketoconazole no tratamento da neurocriptococose

RESUMO — Dois pacientes com neurocriptococose foram tratados com ketoconazole (KTZ), um derivado imidazólico de propriedades fungostáticas. Ambos foram tratados inicialmente com o esquema terapêutico tradicional (anfotericina-B + 5-flurocitosina) porém em um dos casos para-efeitos intoleráveis obrigaram a suspensão do tratamento e, no outro caso, não houve resposta ao esquema terapêutico. KTZ foi administrado regularmente por via oral em regime de monoterapia na dose de 800mg diárias durante 6 meses com ótimos resultados. Todavia, um mês após a suspensão do tratamento, houve recorrência da infecção em um paciente. Efeitos colaterais foram mínimos durante o curso do tratamento. KTZ pode ser útil no tratamento de alguns casos de neurocriptococose.

Cryptococcosis is a rare but grievous affliction caused by the fungus *Cryptococcus* neoformans, an agent which in humans exhibits a special tropism for the central nervous system (CNS). In nearly 50% of patients affected there is an underlying immunological deficiency (AIDS, diabetes mellitus, hematopoietic diseases, leprosy, neoplasias, prolonged steroid therapy or other immunosupressive agents). It is generally accepted that the simultaneous use of amphotericin-B (AB) intravenously and of 5-flurocytosine (5FC) orally is the treatment of choice [5,6]. This regimen, however, is far from ideal; almost one third of patients do not respond to the combination of AB+5FC and there is a high incidence of side effects that sometimes leads to the temporary or permanent interruption of the therapy. The pursuit for a less toxic and more efficacious drug as an alternative treatment is thus a necessity. Ketoconazole (KTZ) is an imidazole derivative with fungistatic properties, which is effective in the treatment of systemic mycosis and other fungal infection of the CNS. In addition, KTZ seems to be less toxic than the standard therapy with AB+5FC [1,2,4], despite its potentiality to provoke liver damage [3] and inhibit steroid synthesis [7]. We treated two patients suffering from cryptococcosis of the CNS with KTZ at a dose of 800mg/day orally for six months uninterrupted and the results obtained are presented here.

Departamento de Clínica Médica, Hospital de Clínicas, Universidade Federal do Paraná, (UFPR) Curitiba: * Neurologist, Universidade Federal de Santa Catarina (UFSC); ** Neurologist, Institute of Neurology, Queen Square (London WC1N 3BG, UK); *** Neurologist, Associate Professor, UFPR.

Dr. P. C. Trevisol-Bittencourt — Hospital Universitário, UFSC - Caixa Postal 173 - 88001 Florianópolis SC - Brasil

CASE REPORTS

Two male inpatients of the neurological department of **Hospital de Clinicas, Universidade Federal do Parana,** Curitiba, in whom a diagnosis of cryptococcal meningitis was made, were treated with KTZ for six months. Both received 800 mg/day orally (400 mg bd.) and were assessed on a monthly basis.

Patient 1 — OB, a 50 year old farmer, with tuberculoid leprosy, presented with) reduced visual acuity in the right eye, headache, fever, vomiting and weakness in his left arm and leg. These symptoms had commenced 30 days before and had been gradually increasing in severity. The neurological examination on admission demonstrated signs of meningeal irritation, left hemiplegia and right optic nerve atrophy. Cerebral angiography indicated occlusion of rigth middle cerebral artery (RMCA); CT scan displayed an ischemic infarction in the territory of the RMCA; cerebrospinal fluid (CSF) examination showed a lymphocytic pleocytosis (148 cells/mm3), low glucoce (19mg%) and raised protein (295mg%); **Cryptocoecus neoformans** in Indian ink preparations was positive and the culture was also positive. The patient was treated with systemic AB (0.3 mg/Kg per day) and 5FC (150 mg/Kg/day). Due to the perseverance of symptoms, after a cumulative dose of 4.6 grams of AB intravenously was reached, the administration of AB intrathecally was instituted, with 0.5 mg being given every 2 days. This therapy, however, was abandoned after a cumulative dose of 10 mg, because of the development of urinary retention! land diffuse pain in both legs. An Omaya reservoir was then inserted for the intraventricular administration of AB and the patient received 0.5 **mg** every other day to a cumulative dose of 15 mg. Despite improvement in CSF parameters treatment was discontinued due to transitory and bilateral oculomotor palsies after each application **and** the occurrence of a tonic-clonic seizure of few seconds after the last dose. In spite of the treatment, the patient presented continuous evidence of active fungal infection and complained of fierce headache. Consequently, due to the failure of the conventional treatment, a KTZ trial was started with a daily dosage of 800 mg. Clinical improvement was noticed during the follow up period. The symptoms gradually lessened and simultaneously CSF examination showed progressive normalisation and after 6 month of treatment KTZ was tapered off. Recurrence of the clinical symptoms and a positive microscopy were seen a month after the suspension of KTZ therapy. Treatment was restarted and his condition steadily improved from then on. The patient remained well for a further 9 months when he was lost to follow-up having moved to another State.

Patient 2 — MLF, **a** 66 year old cabinet maker, with 3 year history of diabetes mellitus treated with chlorpropamide, presented with frontal headache and brief episodes of diplopia. Clinical examination on admission recordedi paresis of the right lateral rectus muscle, absence of ankles reflexes **and a** background diabetic retinopathy. CT scan was normal and the CSF indicated **a** lymphocytic pleocytosis (129 cells/mm3), low glucose (46 mg%), and raised protein (190 mg%). The Indian ink preparation revealed **Crytococcus neformans** and the culture was positive. A course with systemic AB (0.3mg/Kg/da,y) combined with 5FC (150mg/Kg/day) was started. After **a** cumulative dose of 1.6 grams of AB, a persistent and progressive impairment of renal function was noticed, requiring the withdrawal of the drug in spite of the clear-cut clinical improvement. The patient was asymptomatic and the CSF examination showed 18 cells/mm3, glucoses 65 **mg%** (blood 148 mg%), protein 78 mg%. **Cryptocoecus neoformans** was seen on microscopy but the culture was negative. No further medication was prescribed and the patient was re-evaluated monthly. After a 5 months follow up period in which no symptoms were noted, the patient started again to complain of frontal headache and episodic diplopia. The clinical examination was unchanged. The CSF analysis at this occasion revealed 26 cells/mm3, glucose 55mg% (blood 132mg%), protein 93mg%. **Cryptocoecus neoformans** was seen on microscopy but culture was again negative. In spite of the culture result, his symptoms were suggestive of a reactivation of the fungal infection and a trial of KTZ was therefore **initiated.** There was progressive clinical improvement and the patient became asymptomatic after 2 months from commencing KTZ therapy. Treatment was withdrawn after 6 months and recurrence was not observed during a 3 year follow up period.

COMMENTS

In patient 1 the evidence of a positive response of KTZ was clear. The patient became asymptomatic and despite the residual signs (left hemiparesis and decreased visual acuity in the right eye), he returned to a normal daily life. However, indication of persistent CNS infection was detected 30 days after the stoppage of therapy.

This was construed as a consequence of the fungistatic action of KTZ and this may necessitate the administration of the drug for an indefinite period of time.

Patient 2 was given KTZ on clinical grounds alone having a relapse of his symptoms 5 months after the cessation of AB+5FC therapy. The CSF examination before the initiation of KTZ showed similar changes to those noticed when the AB+5FC treatment was interrupted and the Indian ink test was postive but culture was negative. As this diabetic patient already presented signs ot peripheral neuropathy (absence of Achilles reflexes), the visual complaint due to paresis of right lateral rectus muscle could also be interpreted as an aftermath of a diabetic VI nerve palsy. This, however, would not account for the prevailing symptom of headache and it was felt that both symptoms were brought about by the reactivation of the fungal infection. The disappearance of these symptoms and the normalisation of the CSF during the therapy with KTZ further supports this hypothesis. It cannot be certain that the cure was effected by the drug, because the microscopy for *Cryptococcus neoformans* in the Indian ink test was positive but the cultures were negative from the commencement.

Only patient 2 suffered any side effects. He complained of nausea during the first two weeks of his treatment, however, this did not require the reduction or suspension of the drug. Monthly liver function tests were within normal parameters in both patients.

On the basis of our experience we suggest that KTZ could be useful in CNS cryptococcosis in the event of either failure of the standard therapy or when intolerable toxic side effects do not allow the continuation of conventional treatment. Its fungistatic action, however, may render the administration of the drug imperative for an indefinite period of time.

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