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Phase I study of single ascending doses of befloxatone, a new reversible MAO-A inhibitor antidepressant

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Key words: Befloxatone; MAOI; Antidepressant; Phase I study

Befloxatone (MD370503) is a new reversible, selective, and competitive MAO-A inhibitor, very active in several antidepressant animal models, more potent compared to reference MAOI's and monoamine reuptake blockers studied. The safety and pharmacokinetics of single ascending doses of befloxatone (0.25, 1, 5, 10, 20, 40, 80, 160 mg capsules) were tested in 2 groups of 12 healthy volunteers in a double-blind placebo-controlled design. Results showed a remarkable tolerance of befloxatone at all levels of doses, with a complete lack of reported side-effects, as well as laboratory and EKG abnormalities. Moreover, befloxatone was totally devoid of negative effect on vigilance and memory, as assessed by rating scales (visual analogue scales, POMS) as well as sophisticated computerized tests (alert function, continuous recognition, semantic facilitation). The pharmacokinetics of befloxatone were linear in the whole range of doses, with T max of 2-4 h and apparent elimination $t_{1/2}$ of 5-6 h. Moreover, befloxatone induced a reversible dose-dependent reduction of free DHPG and DOPAC plasma levels, with maximal reduction of respectively 70 and 60% already obtained 2-4 h after the 10 mg dose and a marked effect on DHPG (60%) already found after the 5 mg dose. All these findings encourage further developments of befloxatone as a promising antidepressant.

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Prospective evaluation of the 'Serotonin Syndrome' in depressed patients treated with clomipramine

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Key words: Myoclonus; Side effects; Serotonin; Tricyclic antidepressants

Antidepressant-induced myoclonus (Lejoyeux et al., In press), defined as an involuntary and repetitive contraction of a muscle or a group of muscles has been related to the perturbation of the balance of acetylcholine and serotonin. The association of myoclonus to agitation, hypomania, confusion, hyperreflexia, diaphoresis, shivering, diarrhea, incoordination, fever and hyperreflexia could, in patients receiving MAOI or tricyclic antidepressants, (Stembach, 1991) constitute a serotonin syndrome. To assess the frequency of this newly described depressed inpatients answering to DSM III R criteria of major depression and treated with a serotoninergic agent, 'serotonin symptoms'. In all patients, a scale of depression (MADRS), a scale of dyskinesia and parkinsonism (Smith Scale), a scale of side effects (Asberg et al.) and an additional check-list of 'serotoninergic signs' were used before treatment and weekly during the first month of treatment. All patients (18 female and