Comparative pharmacodynamic studies with the novel serotonin uptake-enhancing tianeptine and - inhibiting fluvoxamine utilizing EEG mapping and psychometry

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Summary. In a double-blind, placebo-controlled study, the encephalotropic and psychotropic effects of tianeptine (TIA) – a new tricyclic antidepressant, enhancing serotonin reuptake – were investigated as compared with the serotonin reuptake inhibiting antidepressant, fluvoxamine (FLU), utilizing EEG mapping, psychometric and psychophysiological measures. 16 healthy volunteers (8 males, 8 females) aged 21–35 (man 27) years received randomized and at weekly intervals single oral doses of placebo, 12.5 and 25 mg TIA and 50 mg FLU. EEG recordings, psychometric and psychophysiological tests and evaluation of pulse, blood pressure and side effects were carried out at 0, 2, 4, 6 and 8 hours; blood sampling, in addition, at hour 1.

TIA plasma levels rose fast to peaks at 1–2 hours and declined rapidly as well, while the MC\textsubscript{5} metabolite peaked in the 4th hour and declined more slowly. EEG mapping demonstrated that both TIA and FLU induced significant changes in brain function between the 1st and 8th hour, which, however, differed in their time course. 12.5 mg TIA exhibited, as compared with placebo, slight activating properties in the EEG (decrease of delta and theta, increase of alpha and beta, acceleration of the centroid), paralleled by thymopsychic improvement (mood elevation). 25 mg TIA showed EEG activation up to the 4th hour, later EEG sedation, accompanied by an initial thymopsychic improvement and differential changes thereafter (improved mood, decreased vigility), with the noopsyche improving at all times (attention, Pauli test). 50 mg FLU induced initially sedation and thereafter activation, accompanied by thymopsychic deterioration and subsequent improvement, the latter also being observed in the noopsyche (attention, memory). In pupillary and skin conductance measures, generally a slight activation occurred after placebo, which was attenuated by 25 mg TIA. Correlation maps between plasma levels and EEG changes demonstrated: the higher the TIA plasma levels, the more absolute and relative beta power, the less alpha power and the faster the centroid of the total power spectrum,
reflecting CNS-activation. Topographically, the correlations were mostly seen over both fronto-temporal regions. In the latter, dominant frequency signalled desactivation in the right and activation in the left hemisphere after both antidepressants, which thereby induced changes in brain function opposite to those observed in depression. Both drugs were well tolerated.

**Keywords:** Human pharmacology, antidepressant, tianeptine, fluvoxamine, serotonin, pharmacokinetics, pharmacodynamics, EEG mapping, psychometry

**Introduction**

There is ample evidence that serotonin influences many areas of the brain involved in psychological, cognitive, sensory, autonomic, neuroendocrine and emotional function, and that serotonin synthesis or function is reduced in the brains of depressed patients (Sandler et al., 1991; Grahame-Smith, 1992). Selective serotonin reuptake inhibitors (SSRI) such as fluvoxamine, fluoxetine, paroxetine, sertraline, citalopram, have been shown to be therapeutically active in depression. However, in recent years, another compound – tianeptine (TIA) – has been found to exert antidepressant properties as well, which in contrast to SSRIs increases the presynaptic reuptake of serotonin in brain platelets after single as well as repeated administration (Mocaer et al., 1988a).

Tianeptine (TIA) – the sodium salt of 7 – [(3 – chloro 6 – methyl 5,5 – dioxy 6,11 – dihydro dibenzo [c, f] (1.2) – thiazepine) 11 -yl] amino] heptanoic acid – is a new tricylic agent with antidepressant properties in animal models (Labrid et al., 1988; Mocaer et al., 1988a) and in humans (Defrance et al., 1988; Loo and Deniker, 1988; Olie et al., 1988; Casacchia et al., 1989; Guelfi, 1992). In two recent, large, multicentre trials, TIA was found to be superior to placebo in major depression and in depressed bipolar disorder (Staner et al., 1994; Costa e Silva and Ruschel, 1994).

The antidepressant activity of TIA has been demonstrated using the classical pharmacological screening tests of antagonism of reserpine-like compounds, rat behavioural despair (Porsolt’s test) and aggressive behaviour induced by isolation in mice (Poignant, 1981; Mocaer et al., 1988a). TIA is active in the bulbectomized rat model of depression (Kelly and Leonard, 1990) and in stress models of depression like immobilization stress (Whitton et al., 1991) and inescapable shocks in the learned helplessness paradigm (Thiebot et al., 1991). In the immobilization stress model of depression, TIA is active both after acute (like buspirone-type anxiolytics) and chronic administration (like classical antidepressants).

Tianeptine has no anxiolytic activity in classical screening tests of benzodiazepine anxiolytics (File and Mabbutt, 1991) and is devoid of sedative effects (Poignant, 1981; Mocaer et al., 1988a,b; Lejeune et al., 1988; Delagrange et al., 1990). It improved learning and memory (Jaffard et al., 1991), showed moderate analgesic activity at high doses, like serotonergic antidepressants, antiemetic activity and a protective effect against experimental ulcers, no anticholinergic effects, nor changes in cardiac and hemodynamic parameters,