WHICH PCP-LIKE NMDA-RECEPTOR ANTAGONISTS ARE AVAILABLE FOR CLINICAL USE?

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N-methyl-D-aspartate (NMDA) receptor activation is involved in various pathologic conditions leading to neuronal cell loss. Therefore, development of neuroprotective drugs preventing acute and chronic neurodegeneration like stroke and Alzheimer's disease respectively, is focusing on the inhibition of abnormal excitatory amino acid transmission. Unfortunately, the therapeutic use of potent NMDA receptor antagonists (e.g. MK-801 or phencyclidine) is limited by psychotomimetic side effects and neurotoxicity. However, NMDA receptor antagonists with low potency and associated fast open channel kinetics and strong voltage-dependency (e.g. amantadine or memantine) are well tolerated. Beside *neuroprotective* effects, these agents also have *antiparkinsonian, muscle relaxant, analgesic* and *antidepressive* properties.

Table 1: Therapeutic indications and affinities to the NMDA receptor (given as K_i-values at the PCP binding site) of drugs in clinical use

Substance	Indication	K_i-value (μM)
Amantadine	Parkinson's disease	10
Budipine	spasticity	12
desipramine	major depression	7
Ketamine	pain	0.4
Memantine	dementia	0.5
	Parkinson's disease	
	spasticity	
Orphenadrine	spasticity	6
	Parkinson's disease	
Procyclidine	Parkinson's disease	2

Based on the therapeutic profile of NMDA receptor antagonists binding of drugs with antiparkinsonian, muscle relaxant, analgesic and antidepressive properties at the PCP binding site of the NMDA receptor complex has been investigated, using a [^{3}H] MK-801 binding assay in crude brain homogenates. K_i-values were determined from displacement experiments. K_i-values which were found in the *range of therapeutic concentrations*, are shown in table 1. From the results it can be concluded that therapeutic effects of these drugs are — at least in part — due to uncompetitive NMDA receptor antagonism.

SEROTONIN SYNDROME: 4 CASE REPORTS AND A REVIEW

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Already in the late fifties, in animal experiments a behavioral syndrome consisting of hyperactivity, stereotypies and increase of temperature was described after administration of serotonin (5-hydroxytryptamine; 5-HT) enhancing compounds. Increasingly since the sixties a condition of 5-HT hyperstimulation, originally denoted as agitated delirium, is reported in humans and characterized by various combinations of particularly confusion, restlessness, agitation, myoclonus, incoordination, hyperreflexia, tremor, hyperthermia, shivering and diaphoresis. Such cases of serotonin syndrome have been described especially after the introduction of selective 5-HT reuptake inhibitors (SSRI's), mostly, but not always after administration of a SSRI in higher doses or in combination with other 5-HT enhancing compounds.

Recently, we were challenged by 4 patients who developed the characteristic symptoms of serotonin syndrome shortly after initiation or dose increase of clomipramine (n = 2), paroxetine (n = 1) or fluvoxamine (n = 1) because of a recurrent major depressive episode. In one of the patients treated with clomipramine, biochemical analysis revealed an extremely prolonged half-life and marked elevation of plasmalevels of clomipramine and its metabolite desmethylclomipramine. After discontinuation of the serotonergic agent and symptomatic treatment, symptoms of the serotonin syndrome disappeared in all 4 patients within 1 to 6 weeks, although treatment was complicated in 2 patients due to the clinical differentiation with a delirious state. Thus, the serotonin syndrome is a toxic hyper-serotonergic state, in most cases the result of combining 5-HT agents or the administration of higher dosages, that results most probably from hyperstimulation of brainstem and spinal cord 5-HT_{1a} receptor systems. It is concluded that heightened awareness for potential drug interactions with serotomimetic agents or monotherapy with SSRI's in higher dosages is warranted because of the risk for the development of a potentially lethal serotonin syndrome.

NR20. Child and adolescent psychiatry/eating disorders

Chairmen: C Dare, G Russell

RELATIONSHIP BETWEEN PERSONALITY DISORDERS AND EATING DISORDERS

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In order to assess the prevalence of personality disorders in eating disordered patients, the Personality Assessment Schedule (PAS; Tyrer & Alexander, 1979; Tyrer, 1988) was administered to 54 eating disordered individuals. The PAS is a structured interview schedule with 24 personality attributes rated on a nine-point scale. The scores for each rating are then combined using a computer program based on cluster analysis (Tyrer & Alexander, 1979). Analysis of these results produces diagnoses of personality difficulty, personality disorder, or severe personality disorder according to 13 diagnostic categories which can be further reduced to four major categories (antisocial group, dependent group, inhibited group, withdrawn group). DSM-III personality disorder diagnoses can also be reached with the PAS by using a modified scoring system. The schedule has been demonstrated as having inter-rater and test-retest reliability (Tyrer et al, 1979, 1983). Patients were 54 consecutive female referrals to the Maudsley Hospital Eating Disorder Clinic, referred for eating disorders who met DSM-III-R and ICD-10 criteria for AN and BN and were at or over the age of 18 years (this was stipulated since the PAS is not valid in those under 18). The sample had a mean age of 26 years (range = 18–45). Subjects were divided into 40 (74%) anorexics and 14 (26%) bulimics.

Results: Overall, 19 subjects (35.2%) had no personality disorders on the PAS. Eight subjects (14.8%) met the PAS criteria for personality difficulties, 19 (35.2%) for personality disorders, and 8 (14.8%) for severe personality disorders. Twenty-seven patients (50%) had more than one personality disorder. Anxious personality disorder was most common. A comparison between anorexic and bulimic patients showed that personality type was not significantly associated with eating disorder subtypes. There was a trend for bulimic patients to have more paranoid personality type and more personality disorders than anorexic patients but the difference did not reach levels of statistical significance. The clinical and research implications for these findings are discussed.

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