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Congress report

Tardive dyskinesia: preclinical and clinical aspects*

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Tardive dyskinesia (TD) is a common adverse effect of neuroleptic therapy. The mean prevalence in neuroleptic-treated neuropsychiatric patients is about 20%, increasing considerably with age. Whereas 33% of the TD cases are reversible or improve markedly after neuroleptic discontinuance, in a high proportion of patients the symptoms are neither persistent or may last for several years.

The first part of the symposium dealt with preclinical experiments with rodents and nonhuman primates. Emergence of TD during long-term neuroleptic treatment remains a major clinical and ethical issue in psychiatry, and a scientific enigma; despite it's sometimes striking manifestation, extreme difficulty has been encountered in developing a homologous animal (rodent or nonhuman) model thereof. The development of an adequate animal model would potentially allow the preclinical investigation of the causes and prevention of TD. *John Waddington* (Royal College of Surgeons in Ireland) presented some criteria for the validation of such models. There is a multitude of studies on the effects of chronic neuroleptic treatment on brain dopaminergic (DAergic) function in animals, but seeking to relate these to TD presumes a particular pathophysiology, usually in the absence of appropriate phenomenology. Animal models should first seek to reproduce the (predominantly orofacial) phenomenology of TD; this can then be evaluated against putative criteria for isomorphism: spontaneous emergency during or after very prolonged rather than acute/subacute administration of neuroleptics; extent of persistence following neuroleptic withdrawal; extent of response to acute anticholinergic and neuroleptic challenges; effect of ageing and/or preexisting organic brain dysfunction on neuroleptic-free baseline and neuroleptic-associated emergent behaviour. Animals showing appropriate behaviour(s) can then be investigated for putative pathophysiological correlates. Application of this strategy to animal studies over the past decade (Waddington, Psychopharmacology 101:431–447, 1990) does not provide strong support for the DAergic hyperfunction/DA receptor supersensitivity hypothesis of TD and refocuses attention on an interaction between neuroleptic drugs and other endogenous cerebral processes.

Jes Gerlach (St. Hans Hospital, Roskilde, Denmark) presented human and monkey data on the relationship between clozapine and TD. One of the main advantages of clozapine is that it rarely produces extrapyramidal syndromes (EPS) and TD. Bradykinesia, tremor and akathisia may occur, whereas dystonia is absent. Clozapine is particularly interesting in relation to the prevention of TD. Clinical experience over 15–20 years suggests that very few patients develop TD. However, no controlled studies have been carried out. Gerlach and his group performed a retro- and prospective video-controlled study of 100 schizophrenic patients treated with clozapine for up to 20 years compared to 100 controls treated with traditional neuroleptics. The results concerning EPS and TD were presented. The advantageous EPS/TD effect of clozapine appears to be linked to the low and balanced blockade D1 and D2 dopamine receptors. Gerlach and collaborators observed in drug-naive Cebus monkeys that a D1 antagonist (NNC 756) can be given in extremely high doses (1 mg/kg) without causing dystonia and with less acute TD than a D2 antagonist (raclopride, 0.01 mg/kg). This, together with the low D2 receptor blockade, seems to explain the favourable EPS/TD profile of clozapine.

V. L. Coffin and collaborators (Shering-Plogh Research Institute, New Jersey, USA) further investigated the role of dopamine D1 and D2 receptors in cebus monkeys with regard to TD. They demonstrated that dopamine D1 antagonists given acutely, weekly or daily by the oral route do not produce these abnormal movements in nonhuman primates to any significant degree. The authors hypothesised that the mechanisms underlying neuroleptic-induced abnormal movement is a D2-receptor-mediated phenomenon resulting from acute and chronic administration of typical neuroleptics. Chronic exposure of neuroleptics to cebus monkeys involves a sensitization

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process to abnormal movements. Monkeys frequently exposed to the neuroleptics progressively develop more severe and diverse symptoms. The sensitization process associated with neuroleptics may be linked to the eventual appearance of TD. In this regard, Coffin and collaborators showed that co-administration of SCH 39166 (10 mg/kg po) with haloperidol (0.3 mg/kg po) for 12 days in cebus monkeys prevents the sensitization process to abnormal movements. Thus, in contrast to studies in which haloperidol was given alone, an increased in severity and diversity of abnormal movements was not observed. Furthermore co-administration of SCH 39166 with haloperidol over 12 days greatly diminished the production of abnormal movements in previously sensitized monkeys. These are the first findings to show that a dopamine D1 antagonist can prevent and reverse abnormal movements produced by a typical neuroleptic and thus may prove useful in the treatment of dyskinesias.

The second part of the symposium dealt with clinical aspects of TD. *Wagner F. Gattaz* (Central Institute of Mental Health, Mannheim, Germany) presented a new device for the automatised assessment of TD. The clinical assessment of TD is usually performed by means of operationalised rating scales such as the AIMS (abnormal involuntary movement scale). Such scales provide a convenient means for cut-off assessments of TD, but they are to a considerable extent subject to observers' bias and experience, thus producing an appreciable inter- and intra-rater variability. Gattaz and his collaborators developed a wireless device and the necessary software for the assessment of TD by means of digital imaging processing. Four skin-cream dots placed around the subjects' mouth are recorded by a video camera. The image is passed to a framegrabber with a signal processor, where it is converted from analogue to digital. A fast spot-detecting algorithm implemented in the signal processor tracks the dots and passes the information to a personal computer, where a Fourier transformation is performed to calculate the frequency spectrum of the movements. The device provides detailed information on the magnitude and frequencies of the involuntary movements. It showed a higher sensitivity and reliability than conventional rating scales in detecting and evaluating abnormal perioral movements. In a longitudinal study, Gattaz and collaborators examined with their device 20 TD patients who were recorded before and after a 2-week interval in which medication was kept constant. They found a clearly higher test-retest correlation for their device assessments ($r = 0.84$) as compared to two conventional rating scales ($r = 0.63$ for AIMS and $r = 0.61$ for ADRS). The authors concluded the device might be useful for the early detection, for the longitudinal assessment (i.e. clinical trials) and in some cases for the differential diagnosis of TD.

Robin G. McCreadie (Crichton Royal Hospital, Dumfries, Scotland) reported on the results of an epidemiological study on TD related to neuroleptic plasma levels. Of all known schizophrenics living in Nithsdale, southwest Scotland, 146 (88%) were examined for the presence of TD. Of these, 29% had TD and 8% persistent TD. Neuroleptic plasma levels at the time of clinical assessment were measured by the radioreceptor technique. The authors found that the correlations between dose and plasma level were low and that the ratio of mean plasma concentration to mean dose was greatest with fluphenazine decanoate and lowest for sulpiride. The concentration-dose ratio was higher in the elderly. In this study, no relationship was found between neuroleptic plasma levels and TD.

Daniel E. Casey (VAMC, Portland, USA) reported on the long-term outcome of TD. The potential irreversibility of TD has led to the suggestion that neuroleptic drugs should be discontinued in patients with this disorder. However, such an approach leaves patients who have benefited from neuroleptics at great risk for psychotic exacerbation. Recent studies have indicated that TD may be reversible in many patients, even in those remaining on neuroleptic drugs. Casey reviewed the literature concerning long-term outcome of TD. A consistent finding is the negative correlation between age and good prognosis. Many, but not all, studies find that patients not receiving neuroleptics have a more favourable TD outcome. However, the negative aspects of continued neuroleptic treatment are modest. Length of follow-up is also associated with greater improvement. Fluctuations in TD severity make repeated long-term assessments necessary to properly evaluate the long-term course of TD.

Paulo Dalgalarrondo and collaborators (Central Institute of Mental Health, Mannheim, Germany) investigated the relationships between brain anatomical abnormalities and neuropsychological deficits in TD. The authors assessed the computed tomography (CT) parameters and the Luria-Nebraska Neuropsychological Test Battery in 30 psychiatric patients with TD as compared to 30 psychiatric patients matched by sex, age, psychiatric diagnosis and duration of illness (psychiatric controls), as well as to a sex and age-matched group of healthy individuals. The authors found that both patients with TD and psychiatric controls differed significantly from healthy individuals with regard to several CT parameters. However, these differences were more pronounced in the patients with TD, who differed significantly from psychiatric controls and from healthy individuals in CT measures related to the basal ganglia (frontal horn, Huckman number and caudate head). Moreover, patients with TD showed significantly more neuropsychological deficits in the score "intellectual processes" as compared to the psychiatric controls. These results confirm previous neuropathological and neuroradiological reports of structural brain abnormalities, mainly related to the basal ganglia, in patients with TD. The authors suggest that such abnormalities may underlie the neuropsychological deficits observed in these patients.

In the last presentation of the symposium, *Miklos F. Losonczy* (VAMC, Montrose, USA) reported on a positron emission tomography (PET) scan evaluation of dopamine supersensitivity in TD. It has been hypothesised that the abnormal movements characteristic of TD are associated with increases in striatal DA-receptor concentrations (Davidson et al. 1987). To examine this hypothesis, a group of 15 RDC-positive chronic schizophrenic

male subjects with TD was compared to a group of eight schizophrenic subjects without TD. All subjects were at least 4 weeks drug-free, had stable AIMS scores during withdrawal of neuroleptics, but showed a wide range of psychotic symptoms. The two groups did not differ significantly in mean age and weight. All subjects underwent a 4-h study by PET to evaluate striatal neuroleptic binding using F-18 N-methylspiroperidol (NMS). Scan times ranged from 60 s to 20 min as the study progressed. NMS metabolite levels in plasma were evaluated at 1, 5, 20 and 60 min post-injection. Regions of interest were manually drawn around both the left and right striatal areas, with the boundaries approximately 80% of peak uptake. DA-receptor concentrations were presumed to be proportional to the asymptotic slope of the metabolite-corrected Patlak curve for the rate of uptake of NMS, averaged over the left and right striata. For most subjects, the Patlak curve closely approximated a straight line between 20 and 220 min post-injection. This model produced estimates of striatal DA-receptor concentrations which were slightly higher in the subjects *without* TD than in subjects with TD, providing no support for the supersensitivity hypothesis of tardive dyskinesia.

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