limbic as compared to striatal DA receptors in vivo. At low doses, amisulpride facilitates DA transmission via a selective blockade of presynaptic D_2-, D_3-receptors. Ami is active anti-psychotic compound effective at low doses for negative symptoms and at high doses for positive symptoms of schizophrenia. The CNS profile of multiple doses of a low dosage regimen of Ami (50 mg OD for 4 days) was assessed in a randomised, double-blind, 3-way crossover, placebo-controlled study carried out in 12 young sleep-deprived (for 36 h) subjects, using EEG and various measures of psychomotor and cognitive functions. Caffeine (slow release, 600 mg) was used as a positive reference.

Multiple doses of Ami 50 mg OD was devoid of any detrimental effects on EEG, psychomotor performance and cognitive function after total sleep deprivation (TSD). Trends and significant increase in EEG beta (12–40 Hz) power and decrease in subjective sedation, more pronounced at the end of the TSD suggest possible alerting effects of amisulpride. Caffeine significantly antagonizes the detrimental effects of TSD (increase in EEG beta waves, speed of reaction, sustained attention and reduction of subjective sedation) peaking 3 to 4 h after dosing.

In conclusion, the present results demonstrate that Ami 50 mg is able to partially antagonize the deleterious effects of TSD on EEG and subjective sedation. In addition, Ami 50 mg is devoid of any detrimental effects on psychomotor and cognitive performance after TSD, a situation well-known to amplify such effects if they exist. Moreover, some data suggests possible alerting effects of this slow dosage of Ami.

Wed-P67

AMISULPRIDE IN SCHIZOPHRENIA: POST-MARKETING SAFETY PROFILE

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Amisulpride is an atypical antipsychotic drug which selectively blocks mesolimbic dopaminergic D2/D3 pre and post-synaptic receptors. It proved efficacy in acute exacerbations of schizophrenia at doses from 400 to 800 mg/d and in patients with predominant negative symptoms at dose from 50 to 300 mg/d.

The case reports of adverse reactions collected spontaneously either by the manufacturer from 1986 to June 30th, 1997 or by French Health Authorities from 1995 to June 30th, 1997 are analysed. The total number of treatment days for this period is estimated to be more than 150 million.

425 cases were analysed using the most medically relevant reaction (395 directly reported to the manufacturer, 30 reported by Health Authorities). These cases concerned mostly expected reactions which are related to endocrine system (n = 116, usually due to hyperprolactinaemia), to nervous and psychiatric systems (n = 98, one third being extrapyramidal symptoms and tardive dyskinesia being exceptional) and to nutritional disorders, mainly weight increase (n = 26). In no cases of liver, haematological, cardiac nor skin disorders, a causal relationship with amisulpride could be definitively established: either another cause was identified or no sufficient information was available. Acute overdosage (n = 11, 4 leading to death) often with concomitant psychoactive drugs, led to disturbances of consciousness and various cardiac rhythm disorders. No relevant drug interaction was observed as expected from the absence of hepatic metabolism of amisulpride.

In conclusion, the available post-marketing surveillance data confirm that amisulpride appears as a very safe drug.

Wed-P68

IMPROVEMENT OF NEGATIVE SYMPTOMS IN ACUTE SCHIZOPHRENIA WITH AMISULPRIDE

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Negative symptoms are very disabling in chronic patients and one of the main limiting factors for rehabilitation. They are also apparent to a considerable degree in schizophrenic patients with acute exacerbations, where they are associated with positive symptoms and probably mainly secondary in nature. Newer antipsychotics and, to a lesser degree, standard neuroleptics improve these negative symptoms in acutely ill patients. Amisulpride, a D2/D3 specific antipsychotic with preferential limbic affinity, was efficacious in improving predominant negative symptoms in chronic schizophrenic patients.

Three studies in acutely ill schizophrenic patients (DSM III-R/IV) designed to prove antipsychotic efficcay, were analysed with respect to improvement of negative symptoms measured with the PANSS Negative subscale. A total of 738 patients were included in these short-term studies (4 to 8 weeks duration), 465 received amisulpride (AMI 400–1200 mg/d), 160 haloperidol (HAL 15–20 mg/d), and 113 risperidone (RIS 8 mg/d). The baseline PANSS Negative scores were between 23.8 $\pm$ 4.9 and 27.8 $\pm$ 8.1 across studies. AMI improved the PANSS Negative subscale scores from 6.9 to 9.6 points, HAL from 5.1 to 7.4, and RIS 5.3. When data from the 3 studies were pooled, AMI, at antipsychotic doses of 400 to 800 mg/d, was superior to the reference compounds: mean change from baseline AMI 7.9 (CI 95%: 7.0; 8.7), HAL + RIS 5.7 (CI 95%: 4.8; 6.6), difference between groups: 2.2 (CI 95%: 0.9; 3.4, $p < 0.05$).

These results indicate that amisulpride not only improves primary negative symptoms at low doses, but also negative symptoms in acute exacerbations at antipsychotic doses. This is a unique therapeutic profile with a broad spectrum of efficacy on positive and negative symptoms of schizophrenia.

Wed-P69

MAINTENANCE OF ANTIPSYCHOTIC EFFICACY WITH AMISULPRIDE: RESULTS OF A LONG-TERM STUDY VERSUS HALOPERIDOL

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Maintenance drug treatment in schizophrenia is of utmost importance for the management of the disease and the social functioning of the patients. New antipsychotics with good efficacy on positive and negative symptoms and good tolerability will be well accepted by patients, increase compliance and decrease relapse rates. The long-term efficacy and safety of amisulpride (AMI), a specific D2/D3 dopamine receptor blocker with limbic selectivity, was assessed in a 12-month open randomised study versus haloperidol (HAL) in schizophrenic patients with acute exacerbations (DSM III-R). A total of 488 patients was included in the study (AMI 370, HAL 118), 67% were male, mean age was 36.8 (AMI) and 39.6 years (HAL), mean duration of illness was 12 years.

A total of 322 patients (AMI 253, HAL 69) having reached at least a 20% improvement of their BPRS baseline total score after one month, were analysed with a survival method to test maintenance of efficacy. Patients having a response <20% BPRS baseline score on one of the following visits, dropouts and patients with missing data were considered as failures. Using this conservative

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