In the rabbit cardiac purkinje fiber model we found the following rank order for prolongation of the APD (lowest statistical effective concentrations in nM): risperidone (100), haloperidol (100), sertindole (300), olanzapine (1000) and clozapine (3000). EAD's were induced with risperidone (7/7), haloperidol (3/6), olanzapine (1/6) and clozapine (1/6), but not with sertindole (0/7).

Conclusions: Our data indicate that the prolongation of APD and the development of proarrhythmia in rabbit cardiac purkinje fibers can not be positively correlated with the blocking effect on Ikr. This suggests that other cardiac ion channels or receptor blocking properties are opposing the effect on Ikr. For sertindole, we found a complete lack of proarrhythmic activity in rabbit cardiac purkinje fibers, supporting the presence of an important counter-regulatory mechanism(s) against arrhythmogenic events.

P.2.035 The antipsychotic potential of the anandamide transporter inhibitor AM-404 in rodents

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The endogenous cannabinoid anandamide has been suggested to regulate dopaminergic activity by strengthen signalling via dopaminergic D2 auto-receptors and to inhibit post-synaptic D2 receptor-mediated transmission. In line with this hypothesis, anandamide transporter inhibitors have been reported to normalise hyperactivity in spontaneously hyperactive SHR rats, as well as antagonising yawning induced by apomorphine in rats (Beltramo et al., J. Neurosci., 2000, 20(9): 3401–3407). Consequently, the anandamide transporter has been suggested as a drug target for treatment of various CNS disorders associated with hyperdopaminergia such as schizophrenia (Piomelli et al., TiPS, 2000, 21: 218–224). Thus, we aimed to investigate the effect of blocking the anandamide transporter in three animal models predictive of antipsychotic action.

We studied the effect of acute treatment with the anandamide transport inhibitor N-(4-hydroxyphenyl)-arachidonamide, AM-404 (Beltramo et al., Science, 1997, 277: 1094–1097) on d-amphetamine-induced hyperactivity and disruption of prepulse inhibition (PPI) in rats, two models with high predictive validity for positive symptoms. We also tested its effect in a model related to glutamatergic hypoactivity, i.e. PCP-induced hyperactivity in mice. Finally, its motor depressant effect in rats and mice, as well as its cataleptic potential in rats were investigated. AM-404 (2.5–40 mg/kg) partially reversed d-amphetamine-induced hyperactivity in rats. However, AM-404 did neither reverse d-amphetamine-disrupted PPI, nor PCP-induced hyperactivity within the dose range tested. AM-404 did not induce motor depressant effect nor catalepsy at the doses tested. Consequently, these results indicate that AM-404 affects certain behaviour mediated by dopaminergic activity, but does not seem effective against NMDA mediated behaviours. Taken together, our results suggest that AM-404 on its own has a limited therapeutic potential in the treatment of schizophrenia.

P.2.036 The effect of quetiapine on aggresive/hostility symptoms in patients with schizophrenia

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Objective: Aggressive behavior of psychotic patients impacts all aspects of their clinical care. Better treatments are needed, and atypical antipsychotics, such as clozapine, risperidone, and perhaps quetiapine, have shown promise (Volavka,1999). Preliminary data indicate that quetiapine has an antihostility effect which is independent of the antipsychotic effect (Hellewell,1999). The purpose of this report is to evaluate the effect of quetiapine on hostility symptoms in a large sample of patients with schizophrenia and in the subgroup of patients with schizophrenia with prominent hostility symptoms.

Methods: After obtaining written informed consent, patients aged 18 or over meeting DSM-IV criteria for schizophrenia and for the whom the participant psychiatrists had decided to prescribe quetiapine as part of their normal clinical practice were included in this naturalistic, non-comparative, prospective study. The study was reported to the Ministry of Health. Efficacy measures consisted of Brief Psychiatric Rating Scale and Clinical Global Impression. Tolerability was monitored with a modified-UKU scale. The effectiveness analysis includes the intention-to-treat population. Response was defined as a reduction of at least 20% in the hostility cluster or hostility factor. The subgroup Prominent Hostility Symptoms (PHS) included patients with a score of at least 4 in the hostility item of the BPRS. All patients were included in the analysis of tolerability.

Results: In the global sample, 686 patients, the response rates at month 6 on the Hostility Cluster and the Hostility Factor were 70,3% and 68,4% respe ctively, and 78,4% and 78,8% in the subgroup patients with PHS, (249 patients).

In the global sample the percentage of patients with high level of hostility (score of 6 or 7 in the Item 10 of the BPRS), fell from 9,9% at baseline to 2,0% at month 6 and from 26,3% at baseline to 4,6% in the subgroup PHS.

In addiction a multivariate analysis using a stepwise forward selection logistic regression model was performed, The model does not suggest that prominent hostility increase antipsychotic response in the overall sample (n=666 evaluable patients), however it does in the female sample (n=265) (OR:2.2, 95%CI:1.2–3.9).

Conclusions: Our results suggest that long-term quetiapine treatment was effective in the improvement of aggression and hostility regardless the criteria used, comparable to that of clozapine (Volavka,1993) and suggest that quetiapine is a suitable antipsychotic for the hostile schizophrenic patient in the clinical practice setting. The clinical relevance of the gender differences we found is uncertain; further research is needed to clarify this issue.

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