S-44-03

Sleep EEG and HPA axis regulation changes under antidepressant treatment and prediction of long-term outcome

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Objective: In acute depression characteristic changes in EEG sleep measures are well documented findings. However, the course and the predictive value of these alterations for long-term course of depression still warrants clarification. Therefore, we examined whether the previous clinical course of depression, and the long-term outcome in follow-up are associated with abnormal EEG sleep parameters. Since the hypothalamic-pituitary-adrenocortical (HPA) system seems to play a crucial role in treatment outcome and course of depression, we evaluated HPA system function as well.

Methods: 15 patients with depression were enrolled in the study. HPA system assessment using the combined DEX/CRH test and sleep EEG studies were conducted at baseline, after a 6 week antidepressant treatment period (trimipramine), and at follow-up (after 2 to 10 years of the index episode).

Results: The previous clinical course as reflected by the number of episodes until baseline correlated significantly with EEG sleep measures i.e. sleep continuity values and slow wave sleep (SWS). During treatment sleep continuity values improved and the correlation with the previous long-term course disappeared. However, the correlation with SWS persisted. In the prospective long-term outcome SWS and REM density variables were related to the occurrence of recurrences in follow-up. These identified sleep EEG markers correlated closely with HPA system regulation.

Conclusion: In conclusion, the previous and the prospective long-term course of depression are related to sleep EEG variables during the acute depressed state. Among them SWS and REM density measures seem to reflect predictive markers for the long-term course of depression. These markers are associated with HPA system regulation.

S-44-04

Sleep EEG alterations as surrogate markers of serotonin and noradrenaline neurotransmission in healthy subjects: Relationship to the neurobiology of depression

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Objective: Dysfunctions of the central monoaminergic system have been implicated in the neurobiology of depression and since both serotonin and noradrenaline are involved in sleep regulation processes, it has been proposed that sleep EEG alterations observed during major depression could reveal these monoaminergic dysfunctions. In the present study, we investigate whether the effects of a serotonergic antidepressant (citalopram) on sleep EEG parameters could be differentiate from those of a noradrenergic antidepressant (reboxetine). These effects were compared relative to those of placebo and of a non antidepressant drug enhancing noradrenergic transmission (yohimbine).

Methods: 16 healthy male volunteers aged 27 +/-6.3 years were included in a double-blind placebo-controlled 4-way cross-over study including 4 sessions each separated by at least a 8-day wash-out period. Each subject received either citalopram 40mg, reboxetine 8mg, yohimbine 40mg or placebo. Difference from baseline values were analyzed on the per protocol set allowing for subjects, sequence, periods and treatment.

Results: The results of the present study demonstrated the dramatic effects of a single administration of citalopram or reboxetine on sleep -continuity, - architecture and -profile in comparison to those induced by yohimbine. Both antidepressant drugs displayed REM suppressing properties but differed in terms of their effects on wake propensity. The effects of yohimbine were modest and consisted of a sleep disrupting effect comparable to those of reboxetine but without influence on REM sleep.

Conclusion: The present results study bring some support to the idea that polysomnographic recordings could distinguish noradrenergic from serotonergic reuptake blocking properties of an antidepressant drug.

Tuesday, April 5, 2005

S-47. Symposium: Relationship between dose and response in trials of antidepressants

Chairperson(s): Per Bech (Hillerod, Denmark), Lars F. Gram (Odense C, Denmark)
08.30 - 10.00, Holiday Inn - Room 2

S-47-01

Pharmacokinetics and -dynamics in dose-response trials with antidepressants

L. F. Gram. *Univ. Southern Denmark IST, Clinical Pharmacology, Odense C, Denmark*

Objective: Dose-effect studies with antidepressants define, in groups of patients, the probabilty of a certain degree of therapeutic response and/or tolerability problems for different doses and duration of drug therapy. Such studies thus describe the inter patient variability and the therapeutic range of the drug.

Methods: Systematic reviews and a 5-dose study with clomipramine (DUAG 1999) have shown that for both tricyclic and SSRI antidepressants, the dose effect curves for therapeutic response and tolerability are flat and overlapping. High doses yield better response, but with higher risk of tolerabilty problems.

Results: The clomipramine study (DUAG 1999) suggested that all doses may be effective, but that high doses (125 - 200 mg/d) result in faster reponse than the low doses (25 - 50 mg/d). Genetic polymorphism and dose dependent kinetics for clomipramine enhanced the inter patient variation from a factor 8 for dose to a factor 100 for steady state blood concentrations (clomipramine + desmehtylclominpramine). However the correlations for dose versus rating score and concentration versus rating score were not significantly different (R(S) about - 0.25, p= 0.01 - 0,05).

Conclusion: In conclusion clinical dosing should be based on a judgement of the individual patient's need for rapid and effective cure against the importance of good tolerability. Dose is an important, but not the only determinant of the clinical effects of antidepressant drugs. However, for further studies on the other factors of importance including pharmacokinetics, the dose-effect study design remains essential.

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S-47-02

Receptor binding problems in dose-response trials of antidepressants

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The presentation will consider the following problems that arise in correlating the concentration of an antidepressant with the therapeutic response to treatment: 1) Most therapeutically active antidepressants have active metabolites with different pharmacokinetic and pharmacodynamic properties to the parent compound. For example, dual action antidepressants such as amitriptyline and imipramine have metabolites with a high affinity for the noradrenaline transporter; fluoxetine has a potent, long half-life metabolite norfluoxetine; lofepramine produces several metabolites that (unlike the parent drug) show selectivity for the noradrenaline transporter. These metabolites play a major role in the therapeutic actions of the parent drug. 2) There is little evidence that a correlation exists between the transporter or receptor binding properties of an antidepressants in peripheral tissues (for example platelets) and the therapeutic effect. Unless the binding properties of the antidepressants in the brain of the before and following a therapeutic response is known, there seems little value in trying to extrapolate from data obtained from peripheral tissues to the brain. 3) There is now substantial evidence that the therapeutic effects of antidepressants occur "down-stream" from aminergic transporters and receptors. This implies that until methods are available to determine changes in such tertiary messengers and neurotrophic factors such as brain-derived neurotrophic factor from the brains of depressed patients being treated with antidepressants, it seems unlikely that a meaningful relationship between the local drug concentration and the therapeutic effect will be understood. 4) With the limitation of the techniques presently available, it appears that determining the time of onset of an antidepressant response will depend on inexact rating scales. As appropriate ligands become available, imaging methods may be of more value in the future. For example, in schizophrenia research it has been demonstrated that antipsychotic drugs are most likely to cause extrapyramidal side-effects when they occupy more than 80% of D2 receptors in the striatum.

S-47-03

A linear dose-response relationship of venlafaxine in major depression

P. Boyer. *Ottawa, Canada*

S-47-04

Dose-response relationship of other antidepressants using unidimensional depression scales

P. Bech. *WHO Collaborating Centre Psychiatric Research Unit, Hillerod, Denmark*

Among the new generation antidepressants, the first SNRI, venlafaxine, has been investigated intensively concerning dose-response relationship. The results have not been quite clear, because the two depression scales HAM-D17 and MADRS10 showed divergent results when used as indicators of clinical response. However, when looking at all controlled venlafaxine trials it has been shown that the depression factor of HAM-D17 containing the six core depression items (HAM-D6), emerged as being the most sensitive in discriminating between venlafaxine and placebo. For the other SNRI, duloxetine, the HAM-D6 was able to show dose-response relationship in the dose range between 40mg and 120 mg daily (higher dose showing better outcome). HAM-D6 and its counterpart, the MADRS6, were able to demonstrate a dose-response relationship for the two SSRIs citalopram (in the dose range from 10 to 60 mg) and escitalopram (where 20mg was significantly superior to 10mg in severely depressed patients). In conclusion, the gold standard for measuring dose-response relationship both for SNRIs and SSRIs is the HAM-D6 subscale, which is a scale that is unidimensional, indicating that its total score is a sufficient statistic.

Sunday, April 3, 2005

S-52. Symposium: Can we improve treatment for depression in the medically ill?

Chairperson(s): Francis Creed (Manchester, United Kingdom), Volker Arolt (Münster, Germany)
08.30 - 10.00, Gasteig - Lecture Hall Library

S-52-01

Designing trials for the treatment of depression in the medically ill

F. Creed. *University of Manchester, Manchester, United Kingdom*

Objective: To review studies of medically ill patients and assess how depressive disorder predicts poor outcome.

Methods: The review covers medical in and out patients, in whom depression has been measured and which have a prospective cohort design.

Results: Depressive disorder leads to impaired health related quality of life and, possibly, increased healthcare costs. This effect is independent of the effect of the comorbid medical illness. Trials demonstrate that compliance with antidepressants is poor in medical patients and few studies have included sufficient patients to demonstrate the full benefits of treatment of depression in the medically ill.

Conclusion: Trials to demonstrate improved health related quality of life in medical patients following treatment of depression need to be designed with a sufficiently intensive intervention, adequate power and sufficient allowance for confounders.

S-52-02

The importance of early intervention in depression in the medically ill

V. Arolt, B. T. Baune. *University of Münster Dept. of Psychiatry, Münster, Germany*

Depression is very common in the medically ill. Depending on the type and severity of the somatic illness and on the extent of disability, the prevalence of depressive disorders is 20-50%, about half of these being major depression. It is known that psychosocial and pharmacotherapeutic interventions may enhance quality of life in these patients; however, there is only little evidence that, by such interventions, both the progression of disease and the timepoint of premature death can be substantially influenced. These aspects will be explicated for the case of coronary heart disease. The relatively weak influence of psychiatric treatments may be due to the fact that

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