S-47-02

Receptor binding problems in dose-response trials of antidepressants

B. Leonhard. *National University of Ireland Pharmacology Dept., Galway, Ireland*

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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they are implemented too late during the time course/ progression of the somatic illness. Our own findings from a large population based study not only show significant associations of depression subtypes with coronary heart disease but also demonstrate a major role for somatic comorbidity, that has as yet been neglected. If, at all, antidepressive treatments are expected to have an influence not only on depressive symptoms, but also on the progression of a chronic and complex somatic disorder, they probably must be implemented as early and as powerful as possible.

S-52-03

Major depression in the general hospital: Critical appraisal of different strategies to improve its treatment at the University Hospital of Lausanne

A. Berney, L. Michaud, R. Voellinger, B. Burnand, F. Stiefel. *Lausanne, Switzerland*

Objective: Major Depressive Disorders (MDD) remains under-treated in the general hospital despite a high prevalence, major impact on health, and effective therapeutic possibilities; no consensus exists to date as to what strategies would be effective to improve this situation.

Methods: Over the past few years, several efforts targeting MDD were conducted at Lausanne University Hospital: i) a general agenda was established, identifying major difficulties in the management of MDD in the physically ill (1), ii) studies aimed at demonstrating the importance of MDD in specific clinical settings, (i.e. post-stroke depression, Parkinson disease patients) were conducted (2), iii) clinical practice guidelines for the management of MDD in the general Hospital were developed (3) and iv) implementation of guidelines in different somatic services were evaluated.

Results: Preliminary evaluation of the impact of the guideline approach shows very limited effects of a minimal implementation intervention. Focused studies conducted in the service of neurology, seem to be followed by greater changes in clinical practice, with the limit to be circumscribed to very specific settings.

Conclusion: There is a dilemma between the feasibility of large scales brief interventions and time consuming, highly adapted interventions. The minimal requirement for an intervention to improve the management of depression in the General Hospital is an unresolved issue that will be discussed-where possible-by means of scientific evidence. References: 1) Stiefel F et al. Journal of Supportive Care in Cancer (2001), pp: 477-88 2) Berney A et al. Neurology (2002), pp: 1427-29 3) Voellinger R et al. Gen Hospital Psychiatry (2003), pp: 185-193

Tuesday, April 5, 2005

S-53. Symposium: Sleep deprivation: Neurobiological basis and therapeutic aspects

Chairperson(s): Ulrich Hemmeter (Marburg, Germany), Dieter Riemann (Freiburg, Germany)
14.15 - 15.45, Gasteig - Lecture Hall Library

S-53-01

Daytime microsleep, GABAergic mechanisms and neuroendocrine secretion in relation sleep deprivation response in patients with major depression

U. Hemmeter, M. Hatzinger, E. Seifritz, E. Holsboer-Trachsler. *Department of Pscychiatry, Uni, Marburg, Germany*

Objective: Sleep deprivation (SD) has an antidepressive, but temporary efficacy in 60% of depressed patients. Characteristic sleep EEG alterations of depression are improved after SD in the recovery night due to an increase of NonREM sleep pressure. Naps and short sleep-episodes (microsleep) during extended wakefulness reduce NonREM sleep pressure in the recovery night. Furthermore, early morning naps and microsleep during SD can prevent the antidepressant effect of sleep deprivation. The GABA-A-benzodiazepine receptor antagonist flumazenil reduces daytime sleep and increases vigilance. In addition, flumazenil is able to suppress NonREM sleep pressure and NonREM sleep associated growth hormone secretion in early morning recovery sleep after SD in healthy subjects, which is the critical time for a detrimental effect of microsleep and naps on sleep deprivation response.

Methods: Therefore, 27 patients with major depression were subjected to a partial sleep deprivation (PSD). In a double blind randomized design either flumazenil or placebo was orally applied during the initial hours of PSD. A Sleep-EEG was registered continuously for 60 hours by a portable device.

Results: Flumazenil significantly suppressed microsleep during PSD. In the recovery night sleep continuity and slow wave sleep were increased and stage 1 reduced in patients treated with flumazenil compared to placebo. Antidepressant efficacy of PSD was not different between flumazenil and placebo during PSD, but better after the recovery night in patients treated with flumazenil.

Conclusion: It is concluded that GABAergic mechanisms are substantially involved in the regulation of MS and NonREM-sleep during PSD and may be associated with the antidepressant efficacy of PSD.

S-53-02

Sleep deprivation in depression: Involvement of the Renin-Angiotensin-Aldosteron system?

H. Murck, M. Uhr, M. Ziegenbein, H. Kuenzel, K. Held, I. Antonijevic. *Laxdale Limited, Medical Direc, Stirling, United Kingdom*

Objective: Changes in the activity of the renin-angiontensin-aldosterone system (RAAS) in depression have recently been reported. Renin and aldosterone secretion are coupled to sleep in healthy subjects. As total sleep deprivation (TSD) leads to a rapid mood improvement in patients with depression it is of interest to investigate its effect on the response of the RAAS in this population. Additionally we explored HPA-system and the sleep-EEG-changes.

Methods: We compared the sleep related activity of the RAAS before and after TSD in seven depressed patients. After an accommodation night a polysomnographic examination was performed between 23.00 h and 7.00 h. This was followed by 40 h of TSD and the second polysomnography. During the examination nights blood samples were taken every 20 min for analysis of renin, aldosterone, ACTH and cortisol.

Results: During recovery-sleep renin was significantly increased ($p<0.05$). Aldosterone showed no change. ACTH and cortisol were decreased by trend in the first half of the night. REM-density and intermittent wakefulness was significantly decreased ($p<0.05$), whereas slow wave sleep increased by trend in the first half of the night.

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