efficacy is superior to that of the tricyclic antidepressants. This raises the question of whether there is a common mechanism of antidepressant effects that may be activated via different neurochemical processes. Some of the possible mechanisms whereby chronic administration of antidepressants may elicit adaptive changes in serotonergic, noradrenergic and other neurotransmitter systems are discussed against the background to the biochemical basis of depression. Finally, the need to improve the efficacy of antidepressants, possibly by utilising mechanisms other than those involving direct modulation of monoamine neurotransmitters (e.g. by changes in prostaglandins, cytokines and neuropeptides such as corticotrophin-releasing factor) will be considered.

MIRTAZAPINE

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There are three established mechanisms that produce clinical defined antidepressant activity; blockade of monoamine reuptake, prevention of monoamine breakdown by monoamine oxidase inhibition, and blockade of monoamine receptors. The prototype of this third class of antidepressant is mianserin, whose mode of action was thought to be due to blockade of presynaptic inhibitory α_2-adrenoceptors and postsynaptic 5-HT_2 and 5-HT_3 receptors. Mirtazapine represents the next generation of this class of drug, having the same actions at these three classes of receptor but being free of the other unwanted actions of mianserin, namely the sedative ones that came from blockade of histamine and α_1-adrenoceptors. Thus, mirtazapine increases the availability of noradrenaline in the brain by disinhibiting tonic activity at presynaptic autoreceptors. In addition, mirtazapine blocks similar inhibitory α_2-adrenoceptors on 5-HT terminals, it also increases the release of 5-HT. However, as it also inhibits 5-HT_2 and 5-HT_3 receptors, mirtazapine should be free from some of the side effects that emerge from a more general increase in brain 5-HT, such as produced by the SSRIs.

Clinical studies comparing mirtazapine with placebo and comparator antidepressants confirm the predictions from the preclinical studies. It is effective against placebo and equivalent to comparator drugs; it has good tolerability in general and shows a low propensity to provoke anxiety or agitation, or the sleep disruption that can be a feature of treatment with SSRIs. It thus appears, that mirtazapine is a pharmacologically novel antidepressant that represents a useful addition to the formulary.

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S52. Mood disturbances, psychoses and epilepsy

Chairmen: F Monaco, EH Reynolds

THERAPEUTIC ASPECTS OF DEPRESSION IN EPILEPSY: THE IMPACT OF DRUG INTERACTIONS

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The impact of drug interactions on the rational treatment of depression in epilepsy is quite relevant, both from the pharmacokinetic and the pharmacodynamic point of view. It must also be remembered that some anticonvulsants (i.e., carbamazepine, valproic acid and, more recently, lamotrigine) are also used in the therapy of depression in association with other antidepressants (AD).

In general, antiepileptic drugs (AED) cause a reduction of AD plasma levels (chlomipramine, imipramine, nortriptiline, amitriptyline, mianserine, nomiphensine), with the consequent risk of an insufficient therapeutic effect.

On the other hand, classic tricyclic AD usually cause an increase of AED plasma levels.

Some of these potential interactive effects are also shared by the SSRI-AD, which, though in different ways for each different drug (fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram) may cause an increase of concomitant tricyclic AD and AED, through the inhibition of the isoenzyme P50 IID6.

An area of particular interest is the one concerning the phenomena of potentiation and/or antagonism at the drug's site of action in the CNS. Coadministration of AD and AED, infact, may exert severe neurotoxic effects in some cases, with possible impairment of cognitive functions. Therapeutic drug monitoring of plasma AED and AD levels, whenever available and indicated, allows the clinician to evaluate the kinetic modifications in the course of such combined therapies thus tailoring the posology to individual needs.

THERAPEUTIC ASPECTS OF DEPRESSION AND EPILEPSY: NEW VS. OLD ANTIEPILEPTIC DRUGS

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The symptom depression is frequently associated with epilepsy and, therefore, the problem rises on how this symptom can be prevented and/or adequately controlled. Among traditional antiepileptic drugs, phenobarbital and primidone are known to induce depression, while valproic acid and, especially, carbamazepine have proved to exert beneficial effects on mood disturbances. In recent years, a number of new antiepileptic drugs have entered the marketing and are now available for clinical use. Some of these new drugs, especially vigabatrin and lamotrigine, have been seen to influence mood in some way.

Whether or not the observed effects of all these antiepileptic drugs are secondary to their effect on epileptic seizures or are independent from this is not fully elucidated at the present.

The main pharmacokinetic and pharmacodynamic properties of some conventional and new drugs together with their effect on mood will be reviewed briefly with the aim of facilitating a more rational use in clinical practice.

DEPRESSION IN PEOPLE WITH EPILEPSY

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Depression is a common complication in people with epilepsy (PWE). It has been shown that the depression is associated with both psychosocial and neuroepilepsy variables. Thus, in some instances, psychosocial stressors such as increased life events, poor adjustment to seizures and financial stresses may contribute to depression in PWE. Other aetiological factors include a family history of depression and/or suicide. Several investigations have found that the depression appears to be associated with complex partial seizures (CPS) and temporal lobe epilepsy (TLE), when compared to generalised epilepsy (GE). Moreover left sided lesions may be particularly implicated. Depression may also be associated with the duration of epilepsy and a past history of depression. Finally, antiepileptic drugs (AEDs) have a significant effect on mood, with phenobarbitone being

implicated in depressive symptomatology, parasuicide and suicide; a similar association with depression has been found with vigabatrin. In contrast, carbamazepine (CBZ) has been shown to ameliorate depression and reduce anxiety in PWE. Valproate and lamotrigine may also be associated with less depressed mood. It is also important to note that both parasuicide and suicide are significantly more common in PWE than in the general population. Treatment of depression in PWE may be problematic as the majority of antidepressants lower the seizure threshold. Thus, rationalising AEDs with the reduction of polypharmacy, and prescription, where possible, of monotherapy (with special reference to CBZ) may well be the first step. After that, the judicious prescription of "safer" antidepressants (with respect to both lowering the seizure threshold and safety in overdose) may be indicated.

THERAPEUTIC ASPECTS OF DEPRESSION AND EPILEPSY: NEW VS. OLD ANTIDEPRESSANT DRUGS

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Depressive symptoms can affect clinical prognosis of epilepsy and increase risk of suicide: therefore antidepressant drugs (AD) have to be frequently used in depressed epileptic patients. Nevertheless data obtained in vitro and in animals indicate that most tricyclic antidepressants (TCA) exert anticonvulsant, proconvulsant or convulsant effects in relationship with the dose used: higher doses are related with more common convulsant effect. Particularly some old AD are characterized by an intrinsic proconvulsant activity (i.e amoxapine, maprotiline, etc.), others show a lower seizure risk (nomifensine, trazodone, viloxazine, etc.). At last, in some cases, pro- or anticonvulsant properties seem to be dose related. A significant proportion of drug-related seizures occurs in patients with an identifiable predisposition such as previous history of epilepsy, an abnormal EEG, the presence of cerebropathy, an alcohol abuse, concomitant medications.

The effects of Selective Serotonine Reuptake Inhibitors (SSRI) have to be well defined, even if experimental studies show interesting results about an antiepileptic activity for some of these compounds. Particularly fluoxetine exerts anticonvulsant actions against maximal electroshock convulsions in genetically seizure-prone rodents and enhances the anticonvulsant effects of phenytoin and carbamazepine. A discrepancy is clinically reported in the literature between studies that observe an anticonvulsant action of fluoxetine in epileptic patients and others reporting a lack of potentiation of these antidepressant in drug-resistant epilepsy.

Otherwise some Authors report isolated proconvulsant effects shown by zimelidine, fluvoxamine and fluoxetine or toxic reactions following the combined administration of fluoxetine and phenytoin.

In our depressed epileptic patients, treated with fluoxetine, we observed a statistically significant improvement of depressive symptoms and anxiety, without changes of EEG, seizure frequency and anticonvulsant plasma levels.

FORCED NORMALISATION AND ITS RELEVANCE FOR NEUROPSYCHIATRY

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The relationship between epilepsy and psychiatry has several interesting interfaces. One of these is the clinical observation that suddenly stopping seizures in patients who have habitual seizures may be associated with the onset of an acute behaviour disorder. Landolt, in the 1960's identified the phenomenon of forced normalisation. This was essentially an EEG concept, in which suppression of seizures, with "normalisation" of the EEG was associated with the presentation of a schizophrenia like psychosis. On resolution of the psychosis with a seizure, the EEG abnormalities returned.

The observations on forced normalisation have been confirmed by many anecdotes but the phenomenon has been poorly studied. In part this is because of the necessity to examine EEG data while patients are psychiatrically disturbed. However, the theoretical interest of these observations in relationship to the opposite, namely the resolution of the psychosis in psychiatry following the administration of ECT is obviously of relevance for psychiatry.

In this presentation the background to forced normalisation, and the clinical observations related to it will be presented. This will be followed by some personal examples and then the theoretical underpinnings of this condition will be examined. The relationship between these phenomena in epilepsy and ECT will then be explored.

S53. Recent empirical data informing prevention strategies

Chairmen: R Jenkins, D de Leo

PREVENTION OF DEPRESSION AND SUICIDE IN PRIMARY CARE

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Depression is an endemic disease with high morbidity and a high mortality in depression related suicide. Suicidality, especially amongst males is increasing today in East European countries. General practitioners are considered to have a most important role in the prevention and treatment of depression. Matters of depression are today more openly discussed in the society. Patients refuse today less to see depression as a causative factor behind their symptoms when showing up in primary care. Taboos concerning the stigma of depression and suicidality are reduced. In spite of this still today important problems exist regarding poor diagnostical and treatment routines in primary care and the inability of depressive and suicidal males to seek for help or to be recognized.

In the years 1983–1984, the Swedish Committee for Prevention and Treatment of Depression (PTD) offered an educational program to all general practitioners (GP:s) on the Swedish island of Gotland. During the 80:ies this education has been shown to lead to a significant decrease in inpatient care, morbidity, suicide, mortality and costs caused by depressive illness on the island. Unspecific anxiolytic and sedative medication decreased and specific antidepressive medication increased. Thus, evidence was found that a quality improving educational program in primary care with focus on depression and suicide was effective. A shortcoming was, however, that the number of male suicides was almost unaffected by the education and the GP:s improved ability to diagnose and treat depressions.

The role of the Gotland study as a possible model for preventing depression and depression related suicide is described. Strategies to avoid failures concerning its efficacy on the prevention of male suicides are discussed.

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