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.

[1] T de Boer et al (1995) Human Psychopharmacology 10(2): s107–s118.
[2] JMS Sitsen, M Zivkov (1995) CNS Drugs 4(1): 39–48.
[3] C de Montigny et al (1995) CNS Drugs 4(1): 13–17.

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