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S37. New strategies with antiepileptics

THE NEW ANTICONVULSANT DRUGS

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During the last decade, four new anti-epileptic drugs have entered the market, namely oxcarbazepine, vigabatrin, lamotrigine and felbamate. Of all these, vigabatrin has two outstanding properties: it was specifically designed to exert one mechanism of action (inhibition of GABA transaminase), and it is equally efficacious against partial and generalized seizures; as most adult patients with intractable suffer from (complex) partial seizures, the importance of this aspect is evident.
Oxcarbazepine is clinically equal to carbamazepine, but the side-effects and potential for drug interactions are significantly less pronounced; hence, it is justified to label it a major new drug.
Both above-mentioned drugs are effective against partial and secondarily generalized seizures. They are of little or no use against specific age-related epileptic syndromes, e.g. childhood absence epilepsy and juvenile myoclonic epilepsy. Lamotrigine seems promising in these conditions, although no controlled studies have corroborated this expectation. Felbamate has as the first drug been shown efficacious(against astatic seizures), in Lennox-Gastaut's syndrome a childhood epileptic syndrome particularily resistant to all drug regimens. Both drugs are also - even in monotherapy - effective against partial seizures (felbamate probably most); thus, their spectrum of efficacy is rather broad.
All these drugs have few side-effects, and, with the exception of felbamate, have low potential for drug interactions.

THE RELEVANCE OF ANTICONVULSANT DRUGS FOR PSYCHIATRY

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Anticonvulsant drugs have been used by psychiatrists for many years for the treatment of various forms of psychiatric illness. Historically f.e. bromides and barbiturates were used far more frequently for psychiatric conditions than for epilepsy. The introduction of the benzodiazepines represented another group of drugs with multiple CNS functions.

In this presentation the interesting data on carbamazepine, both with regards to it's effects in partial seizures arising from the temporal lobes, and as a mood stabiliser will first be presented. An up-date on the position with regards to carbamazepine in the management of psychiatric disorders will be given.

The newer anticonvulsant drugs, with different chemical actions, have also provided substantial interest for psychiatrists and psychopharmacology. The behavioral effects of vigabatrin, lamotragine, gabapentin and felbamate will be reviewed, and the relevance for these in terms of their biochemical profiles discussed. One observation, again which overlaps epilepsy and psychiatry, relates to the phenomenon of forced normalisation. With this, patients who suddenly stop having epileptic seizures can develop a variety of psychiatric states including psychoses.

The role that anticonvulsant drugs play in this phenomenon, and the association between this and the effects of a seizure in resolving a psychosis in psychiatric patients (ECT), will emphasise the close neurobiological links between anticonvulsant drugs, epilepsy, psychopharmacology and psychiatry.

SEIZURES IN THERAPY OF PSYCHOSES

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Convulsive therapy in the form of ECT in the treatment of psychotic disorders has been in current use since 1938. Although the main indication is severe melancholia convulsive therapy is useful in the therapy of a variety of psychotic conditions such as mania, catatonia and delirium. Also in the therapy of epileptic psychoses has proven useful.

There is no unitary hypothesis concerning the working action of convulsive therapy but it seems as if it is mainly the anticonvulsant action of ECT which is the main mechanism behind the therapeutic efficacy. This is understandably in the light of the kindling hypothesis for the development of psychotic conditions, especially bipolar manic depressive illness, and based on both clinico-chemical analyses of new peptides in depressive disorder and animal experiments the expression of immediate/early genes and the subsequent expression of neuropeptide Y (NPY) points to an understanding of this anticonvulsant action which is demonstrated in the increase of seizure threshold during an ECT series as a necessary prerequisite for the therapeutic action of ECT.

The role of ECT has for many years been underestimated due to negative professional and public opinion but an abundance of clinical and experimental evidence now points to re-evaluation of the rationale for ECT in the treatment of various psychotic conditions.

LITHIUM AND ANTICONVULSANT DRUGS IN THE THERAPY OF MOOD DISORDERS

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The majority of patients with bipolar manic-depressive illness benefit considerably from prophylactic pharmacotherapy with lithium. However, in a proportion of bipolar patients lithium is not effective, is not accepted or not tolerated. For such patients additional or alternative treatments with other psychotropic drugs is needed. Several anticonvulsant drugs are promising candidates. Among these carbamazepine is the best investigated but also valproate and clonazepam seem effective. Unfortunately it is true for all the new treatment modalities that sufficient long-term experience is lacking. Only for carbamazepine have controlled long-term trials been performed and even these trials are difficult to interpret due to methodological short-comings.

ANTIDEPRESSANT DRUGS AND CONVULSIVE SEIZURES: CLINICAL AND EPIDEMIOLOGICAL CONSIDERATIONS

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Convulsive seizures are uncommon but important unwanted effects of antidepressants. They are distressing to the patient and rarely life-threatening. The word seizure is sometimes used inaccurately to describe non-epileptic phenomena, while many medical illnesses can cause loss or clouding of consciousness and be erroneously diagnosed as epilepsy. The most important aspect of the investigation of a suspected antidepressant-induced seizure is the clinical assessment - taking a detailed history, carrying out a thorough physical examination and assessing the causal connection between the drug and the attack. Without this clinical assessment, subsequent electroencephalographic and other investigations may be of limited value.

The incidence of seizures occurring during treatment with antidepressants has been assessed by overviews of published trials in which adverse reactions have been reported, studies of large clinical trial data bases and drug surveillance programmes, such as the Boston Collaborative Drug Surveillance Program. The incidence of fits has also been investigated by Prescription Event Monitoring (PEM) carried out in the Drug Safety Research Unit in Southampton. Cohorts in excess of 10,000 patients who have received new antidepressants are studied. A recent PEM study suggested that the incidence of seizures occurring during treatment with fluvoxamine (1.2 per 1,000) is similar to that previously reported during treatment with tricyclic antidepressants (1 per 1,000). The incidence in patients treated with fluoxetine was 0.6 per 1,000; that in subjects receiving other selective serotonin reuptake inhibitors is currently being investigated. Because of the low incidences and methodological problems in assessing drug-related seizures, differences between drugs may be more apparent than real.