LEADING ARTICLE

DEPOT NEUROLEPTICS

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The discovery of neuroleptics, a term coined by Delay and Denikar, led to tremendous impact in psychiatric research and treatment. Its true antipsychotic action particularly in both schizophrenia and mania is unquestionable, resulting often in the clear normalisation of the disturbed behaviour and bizarre symptoms.

Its main dopaminergic blocking activity of the Dopamine D2 receptors (1) and to a lesser extent the noradrenergic effects besides other influences on cholinergic, GABAergic, serotonergic and peptidergic systems are considered to be important for its antipsychotic properties (2). The dopamine neuronal pathways affected are the nigrostriatal pathway, the mesolimbic systems and the tuberoinfundibular system (3-6).

The first depot neuroleptic introduced in 1964 was fluphenazine enanthate. Fluphenazine decanoate followed; it was longer acting with fewer side-effects. Others subsequently introduced were perphenazine enanthate, flupenthixol decanoate, pipothiazine undecylenate and palmitate, haloperidol decanoate, and zuclopenthixol. The hunt is on for more potent neuroleptics which are longer acting and with minimal side-effects.

A depot neuroleptic is one which can be administered in a single dose and yet maintain therapeutically efficient tissue concentration of at least a week's duration. The active neuroleptic is released at a constant slow speed so that the maximum/minimum plasma level fluctuation in the depot interval is kept at a minimum (7).

In its preparation, the neuroleptic is esterified with heptanoic–decanoic – or palmitic acid to increase its lipophilicity and solubility in the oil vehicle. The oil vehicle (sesame oil or viscoleo) is chosen for its stability, neutrality in reaction, non reactivity with the drug, rapid absorption, no antigenic properties and its suitability as solvent (8). It should flow readily through the needle. The depot, once in the body, is hydrolysed into free fatty acid and the free active neuroleptic. The longer the fatty acid chain chosen, the higher the lipophilicity and therefore a longer depot effect.

It is with the growing recognition of patients' noncompliance with oral neuroleptics that increasing recognition and appreciation of depot neuroleptics followed. This guaranteed method of medication delivery accounted for lowering the risk for relapse, rehospitalisation (9) and de-institutionalisation (10) of the schizophrenic. It is often said that as the patient improves with medication, the memory of the initial psychotic drama fades away and with it the need to continue in treatment. With depot neuroleptics, bioavailability is increased 4-10 times. The often extremely varying absorption phase and the hepatic first-pass metabolism that occurs with oral dosage is avoided. The antipsychotic effect is no different from oral neuroleptics.

Other advantages of depot neuroleptics include a decreased need to discuss daily with the patient about medication. Less time and resource are consumed. The clinician maintains a regular contact with the patient without him feeling a conscious loss of control or associating it with compulsory treatment. The risk of an overdose is avoided. As a result, much time can be subsequently devoted to the equally important psychosocial aspects of treatment.

Numerous clinical studies have been carried out to compare the efficacy of the various depot preparations. The results, in summary, show that there is no significant difference between the preparations (11-14). However, individual preferences must be considered in choosing the suitable depot. There are small profile differences as the clinical comparative study of pipothiazine by Leong O K et al in this issue of SMJ highlighted.

Most patients respond favourably to the depot neuroleptics, both those with positive symptoms (delusions, hallucinations, etc) and to a lesser extent, the negative symptoms (blunted affect, withdrawal, etc) (14, 15). The depot neuroleptics share the same propensity as the oral for causing side effects like parkinsonism, akinesia, akathisia and numerous others, the most serious being tardive dyskinesia. Whether patients are more at risk with depot than oral preparations to developing side effects remains inconclusive (16). Most of the side effects are dose related except for tardive dyskinesia for which there is no effective remedy. It is recommended that the clinician can favourably influence the benefit to risk ratio by minimizing the potential side effects through the use of a low dose strategy – the lowest possible effective dose. This, together with careful management of dose adjustment when required, would usually be sufficient in preventing psychotic relapses (9,16,17).

There is a need to increase our knowledge of the pharmacokinetic properties of the various depot neuroleptics. Improved plasma level estimations with assay methods and the determination of safe therapeutic ranges would contribute to better clinical management (18,19).

A relapse would mean disrupted family ties, compromised living arrangements, lost jobs, social adjustment needs and many other psychosocial problems. This risk far outweighs the disadvantage of potential side effects from drugs. Drug therapy with the many forms of psychosocial therapy helps stabilise the chaotic life situations of our many psychotics (21,22). The future will see methods for identifying drug responders and non-responders, better drugs, and even more effective and safe methods of ascertaining adequate dosages.

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