Choice of neuroleptics in epilepsy

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The decision to use a neuroleptic in people with epilepsy (PWE) depends on the nature of the psychosis being treated. In some cases a neuroleptic is not required and an adjustment of the antiepileptic drug therapy may be all that is necessary. Antiepileptic drug therapy itself can cause psychosis and this, as well as other aetiologies, should be considered. The choice of neuroleptic in PWE depends on: the nature of the patient's psychosis, including the temporal relationship with seizures and/or any relationship to antiepileptic drug therapy; the epileptogenicity of the neuroleptic; antiepileptic drugs; the efficacy of the neuroleptic; and individual tolerability of side-effects.

There are few data pertaining to comparative efficacy of individual neuroleptics specifically in PWE and it is often difficult to predict individual tolerability of a neuroleptic. We will focus on the effects on choice with respect to type of psychosis, effect on seizure threshold and neuroleptic-antiepileptic drug interactions.

The psychoses of epilepsy may be divided into *peri-ictal* and *interictal*, depending on the temporal relationship of the symptoms to the occurrence of seizures. Peri-ictal psychoses are further divided into *ictal* (occurring as a manifestation of the seizure e.g. non-convulsive status epilepticus) and *post-ictal* (occurring after a seizure or flurry of seizures). Neuroleptics are not indicated in the case of ictal psychotic symptoms as their effect on lowering seizure threshold may exacerbate the seizures and worsen the psychosis. The treatment of choice is optimisation of antiepileptic drug therapy. Post-ictal psychosis is much more common than ictal psychosis and may also be made worse in the long-term by continued neuroleptic treatment, but in the short-term often does require neuroleptics or benzodiazepines. In-patient admission to hospital is usually required for post-ictal psychosis for the patient's safety. The combined risk of recurrent seizures (and thus of recurrent psychosis) and extrapyramidal symptoms do not justify the long-term use of neuroleptics in post-ictal psychosis.

Unlike peri-ictal psychoses, the treatment of interictal psychosis (occurring independently of seizures) usually does require long-term neuroleptic treatment. The interictal psychoses are more common than the peri-ictal psychoses. The selection of neuroleptics for these patients must take into account their efficacy, their effect on seizure threshold and interactions with the patients' antiepileptic drugs. Other causes of psychosis not temporally related to seizures in PWE, such as antiepileptic drug therapy itself (e.g. vigabatrin), should also be considered (see review of McConnell & Duncan, 1997).

The effect of neuroleptics in lowering seizure threshold may be related to the total dose, or to changes in doses during initiation, titration, and withdrawal of medication (Itil & Soldatos, 1980). Neuroleptics which are more sedative or antihistaminic, antiserotonergic, and antiadrenergic have been postulated by some to have a greater effect on lowering seizure threshold (Marks & Luchins, 1991). Although animal studies have suggested that neuroleptics with more anticholinergic activity have fewer epileptogenic effects, this has not been borne out in clinical practice. Clozapine and chlorpromazine have very high degrees of anticholinergic activity but are perhaps the two most epileptogenic neuroleptics clinically (see review of Marks & Luchins, 1991). Effects on dopaminergic, somatostatin and endorphin systems have also been implicated but the mechanism of the epileptogenicity of these agents remains controversial.

Seizure-rate estimates for those on neuroleptics vary between 0.5 and 1.2% (Whitworth & Fleishhacker, 1995) and all drugs may lower seizure threshold. Seizures are more likely to occur in those with predisposing risk factors such as head trauma, a previous seizure history, or concomitant use of other drugs which lower seizure threshold. Lower doses of all neuroleptics should be used in PWE and these should be titrated more slowly than in people without epilepsy.

Comparative studies are few but in one *in vitro* study using hippocampal slices, Oliver *et al* (1982) looked at the relative epileptogenicity of seven neuroleptics. They found chlorpromazine, pimozide and thioridazine enhanced spike activity at low doses, but not at higher doses; haloperidol and fluphenazine increased spike activity as doses increased before plateauing; and molindone, butaclamol, pimozide and fluphenazine caused the least increase in excitability. Combining neuroleptics produced synergistic effects on lowering seizure threshold.

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In another study, Satoh *et al* (1987) looked at the effects of tiapride and sulpiride on several seizure models in mice compared to haloperidol, chlorpromazine and reserpine. They found tiapride and sulpiride, unlike the others, did not affect seizure threshold in a variety of seizure models.

The largest study addressing the question of epileptogenesis in humans is that of Logothetis (1967) who followed 1528 patients with no previous history of epilepsy, taking phenothiazines for four and a half years, during which time 10 developed seizures. The overall incidence of seizures was 1.2%, with a markedly higher incidence noted for those on higher doses (9%) compared to low to moderate doses (0.5%). Overdose data also provide estimates of relative epileptogenicity. In the review by Marks & Luchins (1991), seizure rates for neuroleptics varied between 4.4 and 60% with the highest rate being for loxapine. However, these data are far from conclusive as there are a relative paucity compared with, say, antidepressants (see review of McConnell & Duncan, 1997).

Looking at specific neuroleptics, chlorpromazine has the highest seizure risk of the phenothiazines with a 9% seizure incidence found in patients taking more than 1000 mg/day. This compares, however, with a much lower incidence of 0.5% with doses below 1000 mg/day (Logothetis, 1967). In a study by Toone & Fenton (1977), chlorpromazine was the psychotropic most associated with seizures, occurring at a mean daily dose of 266 mg. If a sedative, anticholinergic neuroleptic is required, thioridazine has been suggested to have a much lower epileptogenic potential (Remick & Fine, 1979). This however may, in part, be because lower doses are often used clinically for reasons independent of its epileptogenicity (Markowitz & Brown, 1987).

Although the piperazine phenothiazines (fluphenazine, perphenazine and trifluoperazine) have all been associated with dose-related seizures, the incidence is relatively low (Trimble, 1985). Pimozide has also been recommended as a neuroleptic of choice in PWE (Trimble, 1985; 1991), but its use is limited by its adverse cardiac effects (Larkin, 1983). The neuroleptic molindone, appears to be less epileptogenic and may be a neuroleptic of choice in this population (Markowitz & Brown, 1987) but it is not available in the UK.

Compared with the phenothiazines, butyrophenones have similar, but less severe, effects on the electroencephalogram (EEG). Even though seizures have been reported with haloperidol, it appears to have a lower epileptogenic potential (Markowitz & Brown, 1987) and may be one of the antipsychotic drugs of choice in PWE (Fenwick, 1995).

There is the greatest amount of data available for clozapine, which is well known for its epileptogenic potential, with a cumulative seizure risk of approximately 10%. The occurrence of seizures is related both to titration and to total dosage, with a seizure risk of 4.4% on high-dose treatment (>600 mg/day), 2.7% on medium doses (300–600 mg/day), and 1% with doses under 300 mg/day (Toth & Frankenburg, 1994). EEG changes occur in 75% of people on clozapine, with up to 40% having paroxysmal spike and wave discharges. These changes do not, however, correlate well with seizure activity and are thus not useful in predicting risk clinically. Pacia & Devinsky (1994) reviewed the incidence of clozapine-induced seizures in 5629 patients. Seventy-one of their patients had generalised tonic clonic seizures, representing a frequency of 1.3%. Of their 16 patients with epilepsy, eight had seizures on low-dose, three on medium-dose, and five on high-dose therapy.

Risperidone has the advantage of having fewer extrapyramidal side-effects and may have a lesser effect on lowering seizure threshold than other standard neuroleptics. Pre-marketing trials found a seizure incidence of 0.3% (9 of 2607 patients) suggesting that this may be a relatively safe neuroleptic in PWE, but more data are needed.

Sulpiride is another neuroleptic that appears to have lower epileptogenic potential than standard antipsychotics as well as the advantage of fewer extrapyramidal adverse effects. To date there have been only four cases of convulsions reported to the manufacturer and it has shown only minimal effects on EEG (Lorex Synthélabo, personal communication, 1997). The animal study of Satoh *et al* (1987), discussed above, also suggests that sulpiride may be a useful neuroleptic in PWE.

Sertindole is another new neuroleptic recently approved in the UK which has the advantage of few extrapyramidal side-effects. It has many interactions with other psychotropics and its possible cardiac effects may also limit its use. An incidence of 1% (22/2194 patients) was noted in clinical studies (Lundbeck, personal communication, 1997). Olanzapine has been noted to have a seizure incidence of 0.88% (22/2500 patients) in pre-marketing studies (Lilly, personal communication, 1996). Although many of these patients had predisposing factors, this early figure is a relatively high rate and there are too few data to recommend its use in PWE at this time.

Less is known about the epileptogenic effects of depot neuroleptics, but fluphenazine decanoate has been recommended by some as being safe in PWE (Trimble, 1991) and zuclopenthixol decanoate has been suggested not greatly to affect seizure threshold (Izmeth *et al*, 1988). Although

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depot neuroleptics have the advantage of ensuring compliance, they also have the disadvantage of not being amendable to delicate dose titration should a patient have an exacerbation of seizures. Oral preparations are thus preferable whenever possible in PWE, as dose changes can occur more easily.

The other important consideration in the choice of neuroleptic in PWE is that of drug interactions. Adverse behavioural effects are frequently due to interactions between psychotropic drugs and antiepileptic drugs. Carbamazepine, for example, may increase the metabolism of haloperidol causing a 50% or greater decrease in plasma levels (Ketter *et al*, 1991) which may subsequently lead to an exacerbation of psychotic symptoms in some patients (Arana *et al*, 1986; Fast *et al*, 1986). The rebound effect of increased neuroleptic levels when carbamazepine is withdrawn may also result in increased extrapyramidal symptoms (Fast *et al*, 1986) or even, in one case report, neuroleptic malignant syndrome (Keepers, 1990). Phenytoin may also have similar effects in some cases (Miller, 1991).

Concomitant use of carbamazepine may similarly lower clozapine levels (Tiihonen *et al*, 1995) and withdrawal of carbamazepine may also cause a marked increase in clozapine levels. Because of their combined haematopoietic toxicity and a possible increased risk of neuroleptic malignant syndrome, carbamazepine is not recommended with clozapine (Toth & Frankenburg, 1994). Other antiepileptic drugs also interact with clozapine, with valproate inhibiting and phenytoin inducing clozapine metabolism. Valproate also has the disadvantage of causing weight gain, as does clozapine. Because of its marked epileptogenic effect, we do not recommend clozapine in PWE.

The data concerning the appropriate neuroleptic drugs to use in PWE are largely anecdotal and there are few well-designed studies looking at the efficacy, epileptogenic potential or antiepileptic drug interactions with these drugs. From the available data, it appears that:

(a) clozapine, chlorpromazine and loxapine should be avoided in PWE because of their clear increased epileptogenic potential;
(b) haloperidol may be the drug of choice in PWE of the standard neuroleptics. If, however, long-term treatment is necessary, risperidone and sulpiride appear at this early stage to have a lesser effect on seizure threshold and have fewer extrapyramidal effects;
(c) trifluoperazine, fluphenazine, zuclopenthixol, molindone (not available in the UK) and thioridazine are other reasonable alternatives in that they probably have a lesser effect on seizure threshold than others;
(d) using more than one neuroleptic at the same time increases seizure risk and should be avoided;
(e) whichever neuroleptic is used, doses should start low and be titrated slowly with monitoring of seizure frequency and severity;
(f) neuroleptic (when possible) and antiepileptic drug levels should be monitored in those receiving both; and
(g) the use of neuroleptics in PWE should be guided primarily by the aetiology of the psychosis and whether the psychosis is ictal, post-ictal or interictal. Psychosis related to antiepileptic drug usage should be treated with switching to an alternative antiepileptic rather than neuroleptic therapy.

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