ESA Position Statement: Generic drug use in epilepsy

Generic preparations of several antiepileptic drugs are available to patients in Australia. Retrospective studies and case reports indicate that there is a small risk of loss of seizure control or toxicity if interchange of generic and innovator antiepileptic drug occurs. Patients with epilepsy should first obtain the advice of their treating doctor before having the preparation of antiepileptic drug interchanged.

Category of evidence Level IV, Strength of recommendation D.

The ESA has no conflict of interest regards this statement.

Rationale

Most antiepileptic drugs (AEDs) have a narrow therapeutic index. Dosage adjustment is required to provide optimal seizure control while avoiding adverse drug effects. The titration of dose of AEDs is guided by target dose [1], plasma drug concentration reference range or seizure response. The first two of these three factors are determined from population studies of treated patients. In the individual patient the range of effective and tolerable AED dose or plasma drug concentration is often not known.

In many females, AED doses are kept at the lowest feasible level to minimise the risk of teratogenesis. In the elderly and those with intellectual impairment, AED doses are often kept to a minimum to avoid adverse cognitive effects. Where antiepileptic drugs are expensive, the dose may be minimised for economic reasons. There are uncommon patients in whom seizures are controlled by AED doses bordering on those that produce toxicity. For these reasons, a slight change in drug bioavailability may produce toxicity or seizure breakthrough. This situation may arise if the AED preparation is changed from innovator to generic, generic to innovator or generic to alternative generic.

Case reports and retrospective studies indicate that there is a risk of loss of seizure control or toxicity [2,3] if interchange of generic and innovator AED occurs. Crawford et al. (1996) [4] surveyed 2,285 patients with epilepsy and obtained responses from 1333. Of the patients responding 251 reported that their AED brand (either carbamazepine, sodium valproate or phenytoin) had been switched with 74 noting increase in seizure frequency or adverse events. Of these patients the investigators considered 27 were due to the switching of brand. Berg et al. (2008) report a retrospective physician survey identifying 50 patients experiencing a seizure after switching to a generic AED. In 26 cases serum AED concentrations were known pre- and post-substitution. Lower concentrations were found in 21 cases at time of seizure breakthrough on generic preparation [5].

Seizure breakthrough can be disastrous for a patient with consequent injury, loss of employment or driver's licence possible outcomes. The cause of seizure breakthrough in a previously well controlled patient cannot always be determined. Failure to take medication reliably, seizure provocation (eg. by sleep deprivation) or the natural

history of the underlying epilepsy appear to be common causes of breakthrough seizures. Change in drug brand may not be reported by the patient nor inquired about by the physician. The risks associated with brand substitution of AEDs are not clearly quantified but equally are not clearly established as nil.

The advice of expert bodies (National Institute for Clinical Excellence [6], Scottish Intercollegiate Guidelines Network [7], the German Section of the ILAE [8], and American Academy of Neurology [9]) is that a patient with well controlled epilepsy should not have the preparation of drug, whether generic or innovator, substituted. Like the American Epilepsy Society [10], the ESA's position is that patients with epilepsy should first obtain the advice of their treating doctor before having the preparation of AED interchanged.

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References

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