

Generic drug use in epilepsy

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Abstract

Most antiepileptic drugs have a narrow therapeutic index. Dosage adjustment is required to provide optimal seizure control while avoiding adverse drug effects. Case reports and retrospective studies indicate that there is a risk of loss of seizure control or toxicity if interchange of generic and innovator antiepileptic drug occurs. The advice of various expert bodies is that a patient with well controlled epilepsy should not have the preparation of drug, whether generic or innovator, substituted. If substitution is undertaken then appropriate clinical monitoring is required.

Standardisation of drug formulations is essential for successful medical treatment of patients. In Australia, the potential danger of bio-inequivalence was first reported in 1970 when a spate of patients suffered phenytoin intoxication.¹ The formulation of phenytoin had been altered which resulted in improved absorption of phenytoin.

When production of a new drug is no longer protected by patent or other legislation, alternative pharmaceutical companies may manufacture this drug. This product is termed a generic drug. The patent protection of a new drug provides the pharmaceutical manufacturer the opportunity to recoup the costs of development and provides an incentive to develop new therapeutic agents. As licensing of a generic drug does not require animal and clinical research regards effectiveness or toxicity to be undertaken, production costs of generic drugs are usually lower than the innovator drug. This reduced cost may result in the generic drug becoming available to patients at a discount relative to the innovator brand.

Generic drugs contain the identical active ingredient(s) as the innovator medicine drug however the excipients (inactive ingredients) may vary. Generic drugs are required to meet the same standards as innovator drugs regards drug amount, purity and quality. Physicochemical characteristics, eg. tablet dissolution rate, must be close to identical between generic and innovator drug.

Generic drugs are closely matched to innovator or reference drugs on the basis of pharmacokinetic parameters (bioequivalence). Comparative dosing studies, usually in volunteers, establish the pharmacokinetic parameters C_{max} , T_{max} and AUC (area under the curve) for the generic (comparator) and innovator (reference) drugs. A generic drug is acceptable if the 90% confidence interval for

C_{max} and AUC is between 0.8-1.25 of the reference drug. T_{max} is assessed if clinically relevant. Bioequivalence studies are carefully planned and meticulously undertaken such that generic drugs can be interchanged with innovator medicines with confidence in most clinical situations. Epilepsy treatment provides an exception.

Most antiepileptic drugs have a narrow therapeutic index. Dosage adjustment is required to provide optimal seizure control while avoiding adverse drug effects. The titration of dose of antiepileptic drugs is guided by target dose², 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 antiepileptic drug dose or plasma drug concentration is often not known.

In many females, drug doses are kept at the lowest feasible level to minimise the risk of teratogenesis. In the elderly and those with intellectual impairment, antiepileptic drug doses are often kept to a minimum to avoid cognitive adverse effects. Where antiepileptic drugs are expensive, the dose may be minimised for economic reasons. There are uncommon patients where seizures are controlled by doses bordering on those that produce toxicity. For these reasons in certain patients with satisfactory seizure control, a slight change in drug bioavailability may produce toxicity or seizure breakthrough. This situation may arise if the antiepileptic drug 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^{3,4} if interchange of generic and innovator antiepileptic drug occurs. Crawford *et al* (1996)⁵

surveyed 2,285 patients with epilepsy and obtained responses from 1333. Of the patients responding 251 reported that their antiepileptic drug brand (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.

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 antiepileptic drugs are not clearly quantified but equally are not clearly established as nil.

Seizure breakthrough can be disastrous for a patient with consequent injury, loss of employment or driver's licence as possible outcomes.

The advice of expert bodies (National Institute for Clinical Excellence, Scottish Intercollegiate Guidelines Network, the German Section of the ILAE, Epilepsy Society of Australia, and American Academy of Neurology) is that a patient with well controlled epilepsy should not have the preparation of drug, whether generic or innovator, substituted. If substitution is undertaken then appropriate clinical monitoring is required. Generic antiepileptic drugs provide patients with the opportunity of economic benefit or, even more importantly, access to previously unaffordable medicines. Essentially the patient needs to take reliable drugs reliably.

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