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Is Generic Prescribing Acceptable in Epilepsy?

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Abstract

There is considerable debate about the role of generic prescribing for people with epilepsy. The arguments go beyond simple considerations of cost on one hand and the possibility of toxicity or loss of seizure control on the other. The concepts of bioavailability and bioequivalence require further consideration. The measures that are currently used may not apply equally well to all situations. For example, additional measures may be needed for controlled-release preparations and in the other special cases. There is an extensive literature on the bioequivalence of various phenytoin preparations. This anticonvulsant drug is poorly soluble in water, has nonlinear kinetics and has a narrow therapeutic range, implying that problems with bioequivalence are likely to occur. This is borne out by clinical experience. There are a few published investigations on carbamazepine. The systematic studies, on the whole, fail to show major differences in bioequivalence between the various formulations. There is sparse information on the comparison between generic and proprietary formulations of other anticonvulsant drugs. Whatever arguments might be put forward supporting brand name or generic prescribing, there are strong reasons for recommending tight control on the consistency of anticonvulsant drugs, both generic and proprietary. There is also a strong case for ensuring that the physician who signs the prescription remains in control of the situation and that any decisions that the physician makes should be based on accurate and reliable information.

1. The Advantages and Disadvantages of Generic Prescribing

Why do opinion leaders in the field of epilepsy appear to adopt totally opposing views on the issue of generic prescribing of anticonvulsant drugs? For example, Richens,[1] in an excellent review, has concluded that 'the problems that have been reported with generic substitution, while real, have now been adequately taken into account by regulatory bodies and manufacturers . . . it would be surprising if further substantial examples of bio-inequivalence emerged in the future . . . in a healthy climate of fair competition, the role of generic products is undeniable'. Some years earlier, Trimble,[2] in contrast, stated: 'The lack of quality control for the introduction of generics is startling . . . as prescribers, we should all be wary of attempts to force upon us generic prescribing and resist, for our patients' sake, any substitutions that are made without informing our patients and seeking our permission first'. There are clearly advantages and disadvantages in prescribing generic products but the question of whether the advantages outweigh the disadvantages seems to be open to interpretation. What are the advantages and disadvantages? Although the main advantage might

be seen as cost saving, because generic products are usually cheaper, and the main disadvantage might ultimately be seen as the risk to the patient through loss of seizure control or drug toxicity, the argument is broader than that.

The following summary of the advantages and disadvantages is based on the review by Richens.[1] The advantages may be summarised as follows.

- Generic names usually give more indication of the chemical class, and therefore the therapeutic use, of the compound than the brand name does.
- Generic names are usually standard worldwide and so their use avoids confusion. In contrast, brand names often differ from country to country.
- The use of generic name in a prescription allows the pharmacist to select the most suitable formulation, bearing in mind quality and cost. In this way, the pharmacist can limit his/her stock.

The disadvantages may be summarised as follows.

- The rate and extent of absorption, i.e. the bioavailability of the product, may differ between generics and branded products.
- Generics usually differ in appearance from the branded equivalent, and many differ among themselves if there is more than 1 generic. Not only may the colourants and excipients be different, but the size, shape and delivery form of the generic product may contrast substantially with the branded product. This can cause anxiety and uncertainty in patients and occasionally can result in a patient taking 2 formulations simultaneously, not realising that they are one and the same drug.
- Once a generic product has been dispensed, it is often not possible to identify the manufacturer or supplier should a problem arise.
- Although generic names are more helpful in that they usually indicate the chemical class to which a drug belongs, they are often not as euphonious as brand names.
- While an increase in generic prescribing can save healthcare systems considerable sums of money, the research-based pharmaceutical companies are the losers. The effect that this may have on innovation in the industry has been stressed repeatedly.

Bioavailability becomes a particular issue if a drug has any of the following characteristics: it is relatively insoluble in water; it has a narrow therapeutic range, implying that a serum concentration that falls slightly lower than expected might lead to loss of seizure control and a serum concentration higher than expected might readily lead to toxicity; and/or it exhibits nonlinear kinetics.

Phenytoin has all these characteristics. Carbamazepine has the first 2 of these 3 characteristics: it is relatively insoluble in water and has a relatively narrow therapeutic range.

The only published attempt to study the effects of generic substitution on a large population appears to be the paper by Crawford et al.[3] They screened 48 general practice populations. 2285 people were identified as being treated for epilepsy with carbamazepine, phenytoin and valproic acid (sodium valproate). 1333 people with epilepsy responded to a questionnaire. 70.5% reported no problems. 10.8% reported validated problems such as increased seizures or adverse effects after the 'switch'. 9.9% reported unproven problems and 8.8% reported problems but follow-up was incomplete. They concluded that the costs saved by generic prescribing were outweighed by the negative effects on the person with epilepsy, increased work in general practice and increased social costs. However, it should be pointed out that there was no control group of patients who experienced problems despite having had no drug changes. The difficulty with this type of study is that unless careful measures are taken to make a valid comparison with a control group, the results are very liable to bias.

The debate continues with many proponents of generic prescribing claiming that the cost benefits are considerable, while the opponents quote individual cases of patients in whom seizure control has been lost or intoxication has resulted when changing between proprietary and generic products or even between 1 generic product and another. This suggests that if the question of bioequivalence could be resolved satisfactorily then the case for generic prescribing would be irrefutable. However, valid measures of bioequivalence are needed to ensure

that various forms of the drug do not differ in the clinical situation. What measures should be used?

2. Measures of Bioavailability and Bioequivalence

There is a fundamental difficulty with the terminology. It is quite possible to provide an operational definition of equivalence of bioavailability on the basis of standard parameters. These are usually the area under the curve of concentration against time, extrapolated to infinity, (AUC), the peak concentration of the drug (C_{max}), and the time taken to reach this maximum (T_{max}). Using such parameters it is, at least in theory, easy to state whether 2 formulations are 'bioequivalent' in the sense used in most publications, namely that the formulations achieve similar blood-concentration profiles over time. However, true 'bioequivalence' implies that 2 different formulations have the same effect on an individual patient. This is really what the physician wants to know but it is not what is usually measured. The term 'bioequivalence' as used in most publications implies equivalence of bioavailability, not equivalence of effect on the patient. There may be some circumstances in which 2 products might be equally bioavailable but not bioequivalent. A practical and important example is the use of the use of decarboxylase inhibitors given with levodopa in patients with Parkinson's disease. The combination of levodopa and carbidopa prevents the conversion of the former to dopamine in the peripheral system but because the carbidopa does not enter the central nervous system, the conversion of levodopa to dopamine is not inhibited in the brain. The true bioequivalence of levodopa with and without carbidopa is clearly very different from the bioavailability of the levodopa, as measured by the usual peripheral blood-profile parameters. It should be pointed out that there are no known situations in which this example is relevant to current anticonvulsant drug treatment. Another example of the difference between bioavailability and bioequivalence would be if 1 formulation of a drug were contaminated by a poisonous chemical or metabolite. The 2 drugs would be equivalent in terms of bioavailability of the parent compound but would certainly not be equivalent in terms of the effect on the patient. Good quality control should prevent such situations occurring. For many years, European countries and the US have had subcommittees that scrutinise pharmaceutical data very carefully. In most cases the measures used to confirm equivalent bioavailability probably also indicate true bioequivalence in terms of the effect on the patient, at least in those countries that ensure strict regulation of pharmaceutical products.

Bioavailability studies are carried out on healthy volunteers using single doses of the drug. This is very different from the clinical situation in which the aim is to achieve 'steady-state' conditions for the patient. It is conceivable that an apparently inert chemical compound used in the formulation of an anticonvulsant drug might affect distribution, metabolism or absorption in the steady-state situation without producing obvious differences as a single dose. For example, if the preparation happened to contain another compound that progressively impaired renal excretion of the drug, the absorption characteristics might be the same but the elimination characteristics might eventually become very different from the proprietary preparation. Patients taking anticonvulsant drugs are usually receiving maintenance therapy and it is the steady state situation that is relevant, not the serum concentration after a single dose.

The serum concentrations reached in steady-state conditions in patients are generally much higher than those reached after single dose studies in healthy volunteers. The situation could partly be overcome by using much larger doses in the single dose studies but the adverse effects of large doses might raise additional ethical issues. In addition to acute adverse effects, such as dizziness or ataxia, which are usually avoided by introducing a drug slowly, there is a possibility that more serious adverse effects such as rash might be produced by a large single dose. The incidence of rash certainly appears to be related to the initial dosage regimen and the rate of dose escalation for drugs such as lamotrigine,[4] and almost certainly carbamazepine,[5] but there are insufficient data to state whether patients would be particularly at risk after a single large dose.

A further problem with single dose studies is that they give no indication of possible effects of accumulation of active metabolites that may occur in continuing treatment.

Bialer et al.[6] have challenged the use of the classical pharmacokinetic measures. They have pointed out that if the maximum in the plot of drug concentration against time is very flat, as typically occurs for slow release preparations, then it is not possible to estimate either C_{max} or T_{max} accurately. They have proposed the measurement of additional parameters to take account of these difficulties. The choice of appropriate pharmacokinetic criteria to assess the rate of absorption of controlled release formulations remains a matter of controversy.

Most studies on bioavailability use AUC, C_{max} and T_{max}. Provided these are measured properly, with adequate time being allowed for serum concentrations to reach sufficiently low values to attain a good measure of the area under the curve, they probably give a reasonable estimate of bioavailability which allows comparison between different products.

What limits should be set on the parameters in order to allow a manufacturer to state that 2 products are equally bioavailable using these parameters?

3. Regulatory Requirements and Issues

The US Food and Drug Administration (FDA) and the Medicines Control Agency in the UK are among the regulatory bodies most often quoted in studies on pharmacological agents. The established FDA guidance (1992 guidance) and the new proposals are now readily available through the FDA website.[7] The criteria for bioequivalence for a single dose of a reference drug and the test drug given to healthy, normal adults in a crossover design are that, at a 90% confidence interval, the ratios of the AUC, C_{max} and T_{max} must fall between 0.8 and 1.25, when log-transformed data are used. This has been termed 'The –20%/+25% rule'.

The criteria already stated do not cover all situations. For example, further uncertainty can arise if there are differences in bioavailability between different batches of a drug. Even the parent proprietary drug may vary in this way. Furthermore, the actual content in the formulation may vary. For example, Brown[8] has quoted the situation for generic carbamazepine tablets which are required to contain from 92% to 108% of the labelled quantity of the drug, implying that a 200mg tablet could have as little as 184mg or as much as 216mg of carbamazepine and still fulfil the requirements.

Richens[1] has pointed out that different preparations of a proprietary drug may appear to offer the same amount of pharmacological agent while systematically providing quite different amounts. This situation arises with the proprietary preparations of phenytoin. 'Epanutin Infatabs' contain 50mg of phenytoin acid but the 'Epanutin' capsules and the generic tablets contain the sodium salt, which is equivalent to 92% or 46mg of the phenytoin acid.

Cloyd[9] has highlighted a number of other confounding factors that may affect anticonvulsant drugs. These include storage in unsuitable conditions, diurnal changes in gastrointestinal physiology affecting the break-up of enteric-coated tablets, interactions between drugs and pathological conditions such as hypoalbuminaemia. Cloyd has also pointed out that stress may activate hepatic drug metabolism. Testing is carried out in healthy volunteers and most papers are published on relatively young patients. These results do not necessarily apply to the elderly in whom many drugs, including anticonvulsant drugs, need to be given in lower doses because of an extended half life and, in some cases, because of greater sensitivity to the effects of the medication.

4. Literature Review of Bioavailability Studies of Specific Anticonvulsant Drugs

4.1 Phenytoin

Phenytoin provides an outstanding example of the importance of bioavailability considerations in clinical practice. It is now understood that phenytoin has all the characteristics, listed in section 1, that would indicate that bioavailability issues would be important: poor solubility in water, a relatively narrow therapeutic range, and nonlinear kinetics.

These statements are made with the wisdom of hindsight. In practice, the problems were not predicted; they emerged as clinical difficulties requiring explanation.

The example that has been most widely quoted is the sudden emergence of phenytoin toxicity in Australia in the late 1960s, as reported by Tyrer[10] and Bochner.[11] Appleton et al.,[12] Sansom et al.,[13] Manson et al.,[14] Stewart et al.[15] and Tammisto et al.[16] showed differences in bioavailability of phenytoin between different formulations of this drug. Further studies carried out in European countries such as those of Rambeck et al.,[17] Chen et al.[18] and Hodges et al.[19] broadened the debate. There are now over 100 papers and reports on the bioavailability of phenytoin. Only a small number of representative papers can be reviewed in this article.

One such paper is a study by Rosenbaum et al.[20] In August 1987, the US Veterans Administration hospital pharmacies changed from a branded phenytoin product 'Dilantin', manufactured by Parke Davis, to a generic phenytoin preparation manufactured by Sidmak Laboratory. Sidmak Laboratory recalled their generic phenytoin preparation in December 1987 after 'some batches failed dissolution specification'. This occurrence gave Rosenbaum et al.[20] the opportunity to examine the issue of bioequivalence systematically in a relatively large number of patients. The study population consisted of 36 patients for whom there was at least one serum concentration measurement made while receiving the generic phenytoin as well as 'Dilantin' before or after generic substitution. There was a subgroup of 10 patients taking phenytoin monotherapy 'who were judged to have excellent compliance'. In this subgroup, the mean serum phenytoin concentration was 31% lower during the period of generic use than it was when the patients were receiving 'Dilantin'.

According to Rosenbaum et al.[20], the generic formulation in question apparently met FDA standards at the time of manufacture but underwent a change in dissolution characteristics while in storage. There were no data on retesting of the product after storage and it was consequently not possible to state whether the product still fulfilled the FDA requirements, although the presumption was that it did not. Based on their study, Rosenbaum et al.[20] recommended that standards for certification of therapeutic equivalence should be improved. They stressed that not only was the variation in bioavailability allowed too wide, but that there should also be a regulation stipulating more regular and frequent *in vitro* testing of stability during storage. However, they cautioned that, 'although the potential for harm to patients from therapeutic inequivalence is real, its extent can be evaluated only by adequately documented studies'.

Rosenbaum et al.[20] were highly critical of earlier reports of bioinequivalence. An American Academy of Neurology position statement[21] on the generic substitution of anticonvulsants cited four 'well known published reports of clinical nonequivalence with breakthrough seizures or increased seizure frequency upon generic substitution'. Rosenbaum et al.[20] pointed out that 3 of the 4 reports[22-24] were letters to the editor or other nonrefereed communications. There were other problems with these reports. Serum concentrations were not available for 2 of them[22,23] and the third report showed swings of serum concentrations that suggested the possibility of noncompliance.[24]

Most of the investigations into the bioavailability of phenytoin have been comparative single dose kinetic studies. Steady state data, which reflect the clinical situation more closely, have often arisen through accident rather than design. A good example would be the paper by Rosenbaum et al.,[20] already quoted, in which a phenytoin preparation apparently deteriorated in storage and was no longer equivalent to the proprietary product. The investigations of Chen et al.[18] and Hodges et al.[19] used steady-state plasma concentrations in patients rather than volunteers. 18 of 20 patients completed the study by Chen et al.[18] The baseline generic phenytoin preparation, manufactured by Boots, was compared with another lot of the same brand, 3 other generic preparations and 'Epanutin' capsules manufactured by Parke Davis. The 18 patients took each of the 6 preparations in turn. The mean phenytoin concentrations varied from 39.2 ± 18.0 to 45.9± 20.8 μmol/L. A

small but significant difference was found between the baseline Boots tablets and a different lot produced by the same manufacturers (t-test, $p < 0.01$). There was also a significant difference between this preparation and another generic brand (t-test, $p < 0.05$). Chen et al.[18] concluded that the differences they found between the generic formulations and proprietary 'Epanutin' capsules were generally 'unlikely to be of much clinical significance'. They also pointed out that some of the effect may have reflected varying compliance and may consequently not have represented genuine differences in the preparations.

Hodges et al.[19] were able to demonstrate a significant difference between 1 generic product and a proprietary formulation; they also showed a difference between 2 generic brands of phenytoin. Over a 12-week period 30 new patients aged 3 to 15 years were entered into the study; data from 19 were included in the final analysis. The patients were treated with phenytoin alone and took each preparation (a proprietary formulation made by Parke Davis, a generic product made by Boots and a generic product made by Evans) for 4 weeks. The Parke Davis capsules and Boots tablets produced significantly higher mean serum concentrations of phenytoin than the Evans tablets (t-test, $p < 0.001$). However, it was not possible to correlate any differences in adverse effects or seizure control with the differences in serum concentration.

One of the more comprehensive attempts to test for differences in bioavailability between phenytoin preparations was the study conducted by Soryal and Richens.[25] They used a single-blind crossover study, consisting of seven 4-week treatment periods in 14 patients. The treatments were: Parke Davies 'Epanutin' capsules, Evans Medical phenytoin BP tablets, APS phenytoin BP tablets, Parke Davies 'Epanutin Infatabs', AH Cox phenytoin BP tablets, Thomas Kerfoot phenytoin BP tablets and Regent Laboratories phenytoin BP tablets. Serial blood samples were taken over a 12-hour period. The sequence of formulations was randomised. The usual parameters, namely C_{max}, T_{max} and AUC were calculated, the last being over a 12-hour period. The relative bioavailability, compared with 'Epanutin' capsules, ranged from 76% for the Regent Laboratories tablets to 121% for the 'Epanutin Infatabs'. The mean bioavailability for the 7 preparations was 93%. The AUC varied from 132.8 to 210.7 mg/L•h. They found that the 'Epanutin' capsules did not differ significantly from the generic formulations. However the 'Epanutin Infatabs', in which the phenytoin is in the acid form, effectively contain 8% more phenytoin than the 'Epanutin' capsules or the generic tablets. This may have accounted for the fact that these did yield different results. Two of 5 generic formulations differed significantly from each other in C_{max} and AUC. However, the less bioavailable of these generic preparations was subsequently withdrawn from the market 'following technical difficulties'. There were no significant differences in seizure control during the 7 treatments. However, Soryal and Richens[25] concluded that substitution of 1 generic formulation of phenytoin for another could potentially cause problems with seizure control or adverse effects and that inhouse testing by the manufacturers using *in vitro* techniques might not be sufficiently sensitive to predict clinically important differences in patients.

In a randomised, double-blind, crossover study, Mikati et al.[26] compared a brand name phenytoin preparation, 'Dilantin', with a generic version of phenytoin in patients with well controlled seizures who were receiving phenytoin monotherapy. 13 patients were randomised but 3 did not complete the study because of adverse effects that were not attributable to the change between the preparations. Only 1 of the remaining 10 patients experienced adverse effects that were clearly due to changing from 1 preparation to the other. The serum phenytoin concentration at the time of the adverse effects was 30.2 μg/ml on the generic and the steady-state baseline concentration had been 20.5 μg/ml on the proprietary preparation. For the patients who completed the study there was an increase in serum concentration with the generic preparation: from a mean concentration of 11.9 μg/ml with 'Dilantin' to a mean concentration of 14.2 μg/ml with the generic drug. This difference was not statistically significant. However,

there was a statistically significant difference between the free phenytoin concentrations: 0.93 μg/ml with 'Dilantin' and 1.14 μg/ml for the generic drug (Wilcoxon rank sum test, $p < 0.005$). Because seizures were generally well controlled in these patients it is not surprising that there were no statistical differences in seizure control.

4.2 Carbamazepine

'Tegretol', the proprietary preparation of carbamazepine, was provided on patent until 1986. A number of generic products have been marketed since then. There are several individual case reports suggesting that problems can arise when switching from one form of carbamazepine to another. However, there are relatively few systematic, prospective studies.

One of the few early systematic studies was that of Jumao-as et al.[27] In a crossover study of 10 patients with epilepsy they compared steady-state serum concentrations of proprietary 'Tegretol' with a generic formulation and found no differences in the mean concentrations.

Hartley et al.[28] also compared 'Tegretol' with generic carbamazepine in 12 children with epilepsy and found similar bioavailability. They had previously considered that breakthrough seizures might have been of the result of differences in bioavailability but their testing did not confirm this.[29]

Pedersen and Dam[30] described the case of a 16-year-old boy who was treated with 'Tegretol' and reached stable concentrations of 34 to 42 mmol/L. 'Tegretol' was replaced by the generic preparation 'Karbamazepin-DAK' and the plasma concentration of carbamazepine fell by around 10 mmol/L. This was associated with a recurrence of seizures after he had been seizure-free for 8 months. When 'Tegretol' was reinstituted in the same dose he developed diplopia initially. Pedersen and Dam[30] pointed out that the particle size in the 'Karbamazepin-DAK' formulation was smaller than in 'Tegretol' and argued that this resulted in both an earlier peak concentration and greater fluctuations in carbamazepine concentrations.

Welty et al.[31] described 2 cases, a 15-year-old boy and a 21-year-old woman, in whom seizure control was lost in association with substitution of a generic product for 'Tegretol'. The increase in seizure frequency was associated with a 27 to 45% decrease in the carbamazepine concentration. The second of these cases was complicated by pregnancy and other drug changes, notably discontinuation of phenobarbital. It was suggested that seizure control might be difficult to regain, once lost through switching formulations. In the first of their 2 cases there had been generic substitution even though the physician had signed the 'do not substitute' line in the prescription.

Meyer et al.[32] tested 3 lots of generic carbamazepine made by the same manufacturer which had been withdrawn from the market against 'Tegretol' in 20 healthy volunteers. They found a wide range of bioavailability.

Gilman et al.[33] described two 6-year-old children who had signs of carbamazepine toxicity when the proprietary 'Tegretol' they had been taking was replaced with a generic brand, 'Epitol'. However, when Oles et al.[34] performed a randomised double-blind crossover study comparing 'Epitol' with 'Tegretol' in 40 patients with epilepsy they concluded that the 2 formulations performed equally well in clinical efficacy and bioequivalence.

Silpakit et al.[35] compared the bioavailability of 3 generic brands of carbamazepine tablets with a proprietary brand. This was a double-blind, randomised, 3-phase, crossover study involving 18 adult patients who had taken carbamazepine for at least 5 months. They found that there were no statistically significant differences in the AUC, C_{max} or T_{max} between the 4 different brands of carbamazepine.

In a further study, Meyer at al.[36] compared 3 generic carbamazepine formulations with the proprietary preparation. Although the generic products were more rapidly absorbed, they concluded that steady state concentrations would be similar and that it was unlikely that there would be any significant clinical effect.

Aldenkamp et al.[37] intended to assess both the pharmacokinetic and adverse cognitive effects of

switching between generic and branded formulations of carbamazepine, using 3 different formulations in monotherapy: branded 'Tegretol', carbamazepine Pharmachemie and carbamazepine Pharbita. They were unable to test changes based on pharmacokinetic differences because the 3 formulations did not differ in terms of pharmacokinetic profile. Although no differences were found, they stated that their conclusions could not be extended to other formulations of carbamazepine, higher doses or polytherapy.

4.3 Valproic Acid (Sodium Valproate)

Vadney and Kraushaar[38] carried out an open, randomised, 8-week substitution study involving 64 patients, who were switched between the proprietary preparation of valproic acid 'Depakene' and a generic valproic acid, manufactured by Solvay. Each patient was switched to the other medication after 4 weeks. They found no statistically significant differences between seizure occurrence or serum concentrations when the 2 treatment regimes were compared. The pointed out that the generic drug cost less than one-tenth the price of the proprietary drug.

Sherwood Brown at al.[39] reported gastrointestinal adverse effects after switching to generic valproic acid in a single case. MacDonald[22] commented on a breakthrough seizure following substitution of the proprietary 'Depakene' with the generic preparation. It should be noted that valproic acid is available in generic forms but the formulation of enteric-coated valproate semisodium (divalproex sodium), which is associated with reduced gastrointestinal toxicity, is only available as a proprietary preparation.

Variability in serum concentration over the course of the day does not appear to be related to transient adverse effects with valproic acid as it does with carbamazepine. This suggests that bioavailability might be less of an issue with this agent.

4.4 Primidone

The available published data on comparisons between proprietary and generic primidone are sparse.

Meyer and Straughn[40] stated that the bioequivalence of generic primidone was contested in an adolescent girl who appeared to experience more frequent seizures with a generic product than with a proprietary formulation. Wyllie et al.[41] reported increased seizure frequency with generic primidone.

It is difficult to draw any firm conclusions from such limited data and in the absence of any well conducted blinded, comparative trials.

5. Discussion and Conclusions

There is a strongly held view that generic prescribing is undesirable because it may result in drug toxicity or loss of seizure control. Although this argument is plausible, most of the reports supporting it are anecdotal or subjective. Because consistency of anticonvulsant treatment is so important, it would seem wise to avoid frequent changes of formulation, either from proprietary to generic preparations or, indeed, between generic preparations.

Firm control of the quality of generic products would, in any case, seem strongly advisable. In countries where such control cannot be enforced, problems with generic anticonvulsant drugs are much more likely to occur. However, there may be even greater problems in such countries. For example, a lack of consistent supplies of anticonvulsant drugs may result in more difficulties than changes in bioavailability between different preparations.

Another way of examining the question is to consider the requirements of the various interested parties. What do patients, doctors, managers and a drug companies want? The patient might reasonably expect consistency in the effects of the drugs that he or she takes. In the current financial climate, doctors are also required to satisfy their managers that resources are being used to best advantage. Managers like to appear to be avoiding any unnecessary expense. It has been argued that short term savings from prescribing generic anticonvulsant drugs are not justifiable, because the overall expense is greater in the long term but is the case entirely convincing? Finally, the drug companies have to make a profit. However, established companies cannot afford to lose their credibility. Doctors writing prescriptions are aware of this and might feel more confident in prescribing a proprietary anticonvulsant drug as a

result. The irony of the situation is that as the proportion of generic prescribing increases, the price of the generic formulations may also increase. Perhaps we shall be left with all the disadvantages of generic prescribing and few of the advantages.

If there is doubt about consistent bioavailability of a drug and the effect of the drug on the patient depends critically on the serum concentration or dose, then the doctor might decide that it would be best to prescribe the proprietary formulation. However, if the doctor is reasonably confident that the requirements of the regulatory authorities and compliance with these requirements result in consistency in drug efficacy then there is a strong argument for generic prescribing. Because the doctor has to take responsibility, it is the doctor who should make the decision. Good decisions depend on good information. Regulatory authorities, drug companies and pharmacists play a key role in providing the necessary information and guidance.

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