Generic substitution — comparing the clinical efficacy of a generic substitute for fluphenazine decanoate with the original product

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Long-acting neuroleptics have become the mainstay of the long-term treatment of schizophrenia, improving compliance and thus preventing relapse. Since schizophrenia is a common condition and treatment is usually long-term, this has important financial implications.

Objective. Generic substitution is an important cost-saving measure and generic psychopharmacological agents are also currently available in South Africa. There have been concerns about the quality of these products, but these often arise from anecdotal reports. This study was undertaken to compare the clinical efficacy of a generic substitute of fluphenazine decanoate with the original product.

Design and setting. The study was a double-blind randomised trial involving two parallel groups — generic substitution v. original product. Chronic schizophrenics, aged between 18 and 65 years, who had been on a constant dose of fluphenazine decanoate for at least 3 months preceding the trial, all treated as outpatients in the community, were studied.

The Positive and Negative Syndrome Scale (PANSS) (positive scale) was used as measuring scale and patients were evaluated at inclusion and then every 2 weeks for the next 12 weeks.

Results. Both groups had a median change of zero in PANSS scores over the 12-week period. No clinically significant differences between the change in PANSS score were found in respect of the two products.

Conclusions. Generic substitution could play an important role in containing the costs of health care in South Africa. Concerns about the quality and efficacy of these drugs should be investigated. In this study, no significant differences in the efficacy of the two products were found.

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The maintenance treatment of chronic schizophrenics with long-acting neuroleptics remains an integral part of the management of this condition, especially in rural areas and in cases where compliance is a problem. The prevention of relapse by these products has been proved in a number of trials. These patients also have a more rapid recovery rate than patients prescribed oral neuroleptics in cases of exacerbation.[1]

Fluphenazine decanoate is a widely used long-acting neuroleptic and has proved to be at least as effective as other available products.[1] The generic pharmaceutical industry has expanded rapidly during the last 2 decades.[2] The need to contain the spiralling costs of health care has largely been responsible for this. Generic prescribing is perceived as providing cost-effective alternatives where and when available.[3-5] Unfortunately, doubts have been expressed about the quality control of these products.[5-7] There are currently numerous generic psychopharmacological agents available in South Africa, among them two generic substitutes for fluphenazine decanoate.[8] These products are both cheaper than the innovator product.

Substitution of a generic drug product for an innovator product requires that the products be not only pharmaceutically equivalent, but also bio-equivalent. This implies that any difference in the rate and extent of absorption must be judged to be clinically insignificant. Much more attention has been given to the development of requirements for immediate-release oral products than of controlled-release products.[2]

Bio-equivalence testing is intended to establish that the rate and extent of absorption are similar and that there are therefore not likely to be any differences in safety and efficacy between a generic and an innovator product, i.e. that there is therapeutic equivalence. While it seems reasonable to assume that if products are bio-equivalent based on pharmacokinetic measurements, they will also be therapeutically equivalent, the validity of this assumption has not been examined systematically. In the past there was also no universally accepted standard for requirements and guidelines for bio-equivalence testing. This implied that data indicative of bio-equivalence in one country did not necessarily support such a conclusion in another country.[2] This is changing and there are international attempts to standardise procedures and regulations.

The Medicines Control Council (MCC) is responsible for regulating the availability of generic products in South Africa. Guidelines on the data required as evidence of efficacy are provided (MCC Circular 14/95) and also pertain to generic products. Data submitted must be comparative and, in the case of a generic, the product must be compared with a well-established innovator product (reference product), the choice of which must be justified by the applicant. In the case of a product like fluphenazine decanoate, proof of

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efficacy is required. This is assessed on the basis of bio-availability or any other method an applicant wishes to submit, provided the rationale for the particular method is included. Proof of clinical efficacy is not required.

The generic fluphenazine decanoate has been used locally and there have been anecdotal reports by nursing personnel of inferior therapeutic efficacy. The use of the generic product is relevant, since it costs less than the original, and doubts about its efficacy should be addressed. It was therefore decided to compare the efficacy of the generic product with that of the original in a randomised trial.

The Positive and Negative Syndrome Scale (PANSS) for schizophrenia is a valid instrument for rating symptoms in this condition.[9-11] It has high inter-rater reliability and describes symptoms well.[10] It is based on two established psychiatric rating systems and was conceived as an operationalised, drug-sensitive instrument that provides balanced representation of positive and negative symptoms. It constitutes four scales measuring positive and negative syndromes, their differential, and general severity of illness.

Method

Thirty patients with schizophrenia aged between 18 and 65 years, who were treated with fluphenazine decanoate in the community and from whom informed consent had been obtained, were included in the trial. To be eligible for the trial, the patients had to have been on unchanged dosages of fluphenazine for at least 3 months before the trial. Patients who were receiving other antipsychotics in addition to fluphenazine were not included.

This was a double-blind study with patients randomised to two parallel groups — one group receiving the original product (group 1) and the other the generic substitute (group 2), with dosages unchanged during the preceding 3 months. The medication was supplied to the main investigator in syringes marked only by the patient's identification number and by the dosage of fluphenazine. The two products were indistinguishable in respect of colour and consistency.

The positive scale of the PANSS was used as rating scale and was completed by the same investigator for each patient at admission and every 2 weeks thereafter for 12 weeks. This scale consists of seven positive symptom items (Table I) and each item is rated from 1 to 7, according to the absence or degree of presence of the symptom. A maximum score of 49 and a minimum score of 7 could therefore be obtained at each visit. Changes in PANSS scores from baseline to each visit were calculated, and 95% confidence intervals were calculated for the median difference of these changes between groups 1 and 2. Complaints and side-effects were also noted at each visit.

Table I. PANSS positive scale

Delusions
Conceptual disorganisation
Hallucinatory behaviour
Excitement
Grandiosity
Suspiciousness/persecution
Hostility

Results

Thirty patients were initially included in the trial, but only 27 completed the trial. One patient withdrew consent and 2 were lost to follow-up.

The median age of the group receiving the original product was 48 years and that of the group receiving the generic product was 44 years. The minimum and maximum ages in the respective groups were also similar, and there was a preponderance of male patients in both groups (Table II).

Table II. Demographic characteristics of patients

	Original (N = 13)	Generic (N = 14)
Age		
Median	48 years	44 years
Minimum	29 years	24 years
Maximum	56 years	56 years
Sex		
Male/female	8:5 (62% male)	12:2 (86% male)

The median PANSS score in both groups was the same at visit 1 (Table III) and remained unchanged throughout the 12 weeks of the trial (see Table IV). The 95% confidence intervals for the median difference between group 1 and group 2 in respect of the changes were all 0 - 1, indicating that there is either no difference between the two groups or that, contrary to expectation, group 1 would increase by at most 1 point more than group 2 on the PANSS positive scale. Since the maximum score is 49, a difference of 1 point is not considered clinically significant.

Table III. Baseline visits (PANSS scores)

	Group 1 (original product)	Group 2 (generic product)
Minimum	7	7
Median	7	7
Maximum	10	17

Table IV. Changes in PANSS scores

	Visit					
	1 to 2	1 to 3	1 to 4	1 to 5	1 to 6	1 to 7
Group 1 (original product)						
Minimum	–3	–3	–3	–3	–3	–3
Median	0	0	0	0	0	0
Maximum	1	4	1	2	1	2
Group 2 (generic product)						
Minimum	–6	–6	–10	–10	–10	–10
Median	0	0	0	0	0	0
Maximum	0	1	0	1	0	0

A number of complaints were noted during the various visits (Table V), but since these applied only to the visit in question they were not statistically analysed. The authors' clinical global impression was that the side-effect profile of the two products did not differ notably.

Table V. Side-effects reported by patients on entry and during the trial period

	Visit						
	1	2	3	4	5	6	7
Group 1 (original product)							
Headache		2					
Diarrhoea				1			
Tremor	1				1	1	1
Muscle rigidity						1	1
Orthostatic hypotension							
Dermatological problems							
Hypersomnia							
Myalgia	1						
Tiredness	1	1	1	2	1		
Arthralgia					1		
Dizziness							
Insomnia							
Group 2 (generic product)							
Headache	1	1					
Diarrhoea							
Tremor							
Muscle rigidity							
Orthostatic hypotension		1					
Dermatological problems			2				
Hypersomnia	1	1		1			
Myalgia							
Tiredness							
Athralgia							
Dizziness		1	1				
Insomnia	1	1					

Discussion

On the basis of this study it would seem that there are no significant differences in the clinical efficacy of the two products studied. The low PANSS (positive scale) scores indicated that patients were stable at inclusion and remained stable throughout the trial. It has to be kept in mind that the duration of the study was only 12 weeks and, when evaluating relapse in schizophrenia, studies of longer duration would have even more predictive value.

Nevertheless, this study could be used to allay concerns that the generic product is inferior to the original product. It would also appear as if there is no difference in the side-effect profile of the two products.

Recruitment of patients for the study was reasonably easy once the rationale and the absence of placebo control were explained to the patients. The simple design and minimal financial expenditure suggest that similar studies could easily be undertaken and could aid in answering queries about the efficacy of a number of generic products.

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