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Clinical Significance of Bioequivalence and Interchangeability of Narrow Therapeutic Range Drugs: Focus on Warfarins

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INTRODUCTION

A Canadian Society for Pharmaceutical Sciences (CSPS) discussion group met on August 23, 1997 in Edmonton and December 13, 1997 in Winnipeg to discuss issues surrounding the bioequivalence and interchangeability of narrow therapeutic range drugs. Participants in the discussion presented topics on the variability of subject response, biostatistics in bioequivalence, the variability in drug manufacturing as well as the clinical relevance of bioequivalence and interchangeability of narrow therapeutic range drugs (1). This paper will discuss one of those debated topics, namely, the clinical significance of bioequivalence and interchangeability of narrow therapeutic range drugs, focusing on warfarin.

METHODS

An attempt was made to obtain the available published data regarding the clinical significance of bioequivalence and interchangeability of the narrow therapeutic range drug, warfarin. Specifically, the published literature describing negative clinical consequences (lack of efficacy or significant toxicity) resulting from the administration of generic warfarin to patients previously stabilized on brand name warfarin, or switching between generic and brand name warfarin were reviewed. Medline was searched from 1970-present and references of relevant papers were reviewed.

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RESULTS

Five prospective studies were identified in the literature. The first paper published by Wagner *et al.* (2), assessed the *in vivo* bioavailability of three different manufacturers of warfarin and compared them in a cross over study in 12 normal subjects after a 10mg dose. A comparison of the average peak plasma concentrations (Cp_{max}) of all 12 patients demonstrated no significant difference between the three different warfarin preparations. In addition, neither the average time to peak plasma concentration (T_{max}), nor the average area under the curve (AUC) varied significantly between the three formulations. However, assessment of the individual pharmacokinetics of the 12 patients, showed significant differences (>25%) in plasma concentrations at 4, 8, 12 and 24 hours post-dose in 6 of 12 (50%) patients. The clinical significance of this intra-patient variability between these different formulations was not discussed.

The second abstracted report described by Ruedy *et al.* (3), evaluated the bioavailability of four warfarin products (Coumadin® by Endo, Warfilone® by Frosst, Warnerin® by Warner/Chilcott, and Athrombin-K® from Purdue Fredrick). The precise methodology used in this study was unclear in terms of the number of patients studied and exactly how the study was performed. The results showed that the AUC for the products ranged from 87-101% compared with the reference product which was assigned a value of 100%. There were considerable differences in the observed Cp_{max} (78-100% of that of the reference product) and also in the T_{max} (1.8-3.7 hours). The clinical significance of these differences were not discussed. However, the Health Protection Branch Advisory Committee on Drug Bioavailability, which performed the study, recommended that except in emergencies it would be unwise, if not unsafe, to

substitute or interchange one warfarin product for another without taking all the precautions ordinarily taken when oral anticoagulant therapy is first begun.

The third study performed by McGilveray *et al.* (4) assessed the relative bioavailability of four warfarin products in eight healthy males using a cross-over design, administering 20mg and following plasma levels over 96 hours. Except during the first two hours, the mean arithmetic plasma concentrations of the four warfarin preparations did not show significant differences at any time point. Significant differences (>25%) could not be found when the average AUC, or the average Cp_{max} were compared between the different formulations. However, significant differences were noted in the T_{max} between the four preparations. Although the different products produced significant variability in absorption rate indices, the Health Protection Branch Advisory Committee on Drug Bioavailability which performed the studies, considered all the products to have satisfactory, though different, bioavailability characteristics. However, the committee recommended that substitution or interchange of one product for another without due precautions should not be undertaken.

The fourth pharmacokinetic study was performed by Muller *et al.* (5) and assessed the bioavailability of four different warfarin preparations (Marevan® by Allen and Hanburys, Warfarin® by Petersen, Coumadin® by Boots and Warfarin® by Lennon). All of the products were administered as a single 10mg oral dose and bioavailability was compared in a single-blind cross-over study in 12 healthy adult male volunteers. When the authors compared the mean AUC and the Cp_{max}, no significant differences were noted between the different preparations. Significant (>25%) differences were found in the T_{max}. However, upon analysis of individual pharmacokinetic data 6 of 12 (50%) patients demonstrated significant (>25%) differences in the Cpmax of warfarin obtained between the different products, 12 of 12 patients (100%) demonstrated significant (>25%) differences in Tmax and 1 of 12 (8%) patients demonstrated significant (>25%) differences in the AUC. These authors concluded that the products differed by less than 20% from the reference products, suggesting that all four products could be used interchangeably without risk of compromising safety and efficacy. As shown, however, intra-patient variability was significant when switching between products.

The first study to assess the clinical consequences of interchanging brand and generic warfarin was published by Richton-Hewett *et al.* (6). In 1980 a Boston City Hospital pharmacy made a bulk purchase of amorphous warfarin sodium, Panwarfarin® (Abbott Laboratories) to replace the crystalline warfarin sodium (Coumadin®) which was previously stocked by the pharmacy. The pharmacy began dispensing Panwarfarin® to patients requiring prescription refills instead of Coumadin® which had previously been filled. The majority of these outpatients at Boston City Hospital were followed in a specialized anticoagulation clinic which was managed by a clinical nurse specialist and a physician who were not notified when the anticoagulant brand substitution was made. When wide fluctuations in prothrombin time (PT) values were noted in several patients, the authors performed the following retrospective study.

Hospital records for all available patients of the 104 patients followed in the anticoagulant clinic were reviewed. After exclusion of patients for a variety of reasons, including a duration of Coumadin® therapy of less than 2 months, active alcohol abuse, non compliance, death, etc. 55 patient charts remained to be retrospectively reviewed. Group 1 (n=15) consisted of patients who were maintained on Coumadin® and were subsequently switched to Panwarfarin®. Group 2 (n=40) consisted of patients who had continued on Coumadin® and did not switch to Panwarfarin®. The 15 patients that received generic warfarin were significantly ($p<0.001$) more likely to have a PT out of the therapeutic range. They were also significantly ($p<0.05$) more likely to require a dosage change. One patient presented to the emergency room with a very elevated PT (32/13 sec) and had epistaxis another patient was hospitalized with a very high PT (63/13 sec) and required six days for stabilization. These investigators concluded that a

significant increase in morbidity as well as overall health care costs resulted from an attempt to change from brand name warfarin to generic warfarin (6).

DISCUSSION

Presently, bioequivalence testing compares products based on averages obtained in the AUC and Cp_{max} (7). However, the true purpose of bioequivalence testing should be to assure switchability of a patient's medication (7,8). The limited amount of published data involving warfarin suggests that we do not have enough data to make a decision at this time whether generic warfarin and Coumadin® products allow for switchability in individual patients. What we have are a series of bioavailability studies performed in young healthy volunteers suggesting that the average AUC and Cpmax are not different between various generic and innovator warfarin products. However, when individual patients are analyzed, significant variability is reported in Cp_{max}, AUC and T_{max}. The overriding question is what is the clinical relevance of these observations (9). The only clinical data provided are by Richton-Hewett *et al.* (6) suggests that significant clinical and also economic consequences can result from switching a patient from a brand name to a generic preparation of warfarin. Although these clinical data are disturbing, it is difficult to make an across-the-board decision not to substitute narrow therapeutic range drugs such as warfarin with generic products based on the results of one clinical study. An argument could be made that generic products could be used as long as patients are initiated and maintained on one brand. However, this is unlikely to be practical if patients get medications from different pharmacies, or a different brand is used upon hospital admissions.

CONCLUSION

Limited data in the literature addressed the issue of whether generic warfarin can be substituted for brand name warfarin without a poor clinical outcome. Although several bioavailability studies are available in healthy volunteers suggesting that average AUC and average T_{max} are not different between generic and innovator warfarin products, it is clear that significant differences occur when individual patients are analyzed. Therefore, switchability between products cannot be assured. Only one clinical study is available describing adverse clinical and economic consequences of switching between brand name and generic warfarin. Before an across-the-board decision is made not to substitute brand name and generic warfarin products, more prospective clinical studies are needed.

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