COMPARING GENERIC AND INNOVATOR DRUGS: A REVIEW OF COMPARISON OF BIOEQUIVALENCE DATA OF HYDROCORTISONE CONVENTIONAL TABLET AND HYDROCORTISONE MODIFIED RELEASE TABLET

Manish Mudaliar* Dr Dilip Maheshwari

ABSTRACT
In patients taking Plenadren (Hydrocortisone Modified Release) the cortisol levels achieved were considered to be satisfactory for patients with adrenal insufficiency. The overall amount of cortisol absorbed into the blood was around 20% lower in patients taking Plenadren compared with patients taking conventional hydrocortisone treatment. Moreover generic drug of Plenadren is cost effective treatment and serve as a gold standard therapy. Most nations require generic drug manufacturers to prove that their formulation exhibits bioequivalence to the innovator product. A generic product is considered to be bioequivalent to the pioneer product if the 90% confidence interval (CI) of the mean AUC and the relative mean \( C_{\text{max}} \) is 80% to 125%. This criterion is the same standard used for testing the bioequivalence of branded products with reformulation or manufacturing changes.

Keywords: Generic drug, q.d or o.d (once in day), t.i.d (thrice in day), Plenadren (Modified Release Dosage form)

Generic Drugs
According to the FDA, a generic drug is a product that compares to the pioneer, or reference, drug product (usually a branded drug) in dosage form, route of administration, strength, quality, safety, and performance characteristics. The generic drug must have the same intended use as the pioneer product that serves as its prototype. The generic drug industry has been awash in controversy since the establishment of the pharmacy and medical
communities in the U.S. In 1888, the American Pharmaceutical Association (APhA) published the National Formulary to help prevent counterfeiting of branded products. \[2, 3\] Congress came on board in 1906 with the passage of the Federal Food and Drugs Act. This law, signed by President Theodore Roosevelt, was the first to require product labeling in an effort to prevent misbranding and adulteration, and it enabled the government to take action if a product caused substantial injury or death. This was the beginning of pharmaceutical regulation by what was soon to become the FDA. \[4, 5\]

Concern arose in 1928 regarding the substitution of generic drugs for brand-name products. A well-accepted pharmacy magazine published articles commenting on the appropriateness of this practice and voiced its concern that generic substitution might be deceptive. This came at a time when many mainstream drugs were beginning to enter the market. \[2, 3\] Then, in 1938—in response to the 1937 Elixir Sulfanilamide incident, which killed 107 people—Congress passed the Federal Food, Drug, and Cosmetic Act (FDCA). \[6\] The FDCA designated products introduced after 1938 as new drugs and required them to be proven safe through manufacturer testing and FDA clearance before they could be marketed. While the FDCA was an important step in improving the drug-regulation system, guidelines were not always followed when an identical or similar product was introduced after a patent on a pioneer drug expired. Because the drug was not always considered to be a new drug by the FDA, the same rigorous testing for safety and efficacy was not performed, resulting in a variety of original and derivative products of varying integrity. \[7\]

The Durham-Humphrey Amendment of 1951 established two distinct categories of drugs: those that are unsafe to use without medical supervision and must be prescribed, and those that can be sold without a prescription \[8\]. Despite the differentiation, multiple products continued to appear on the market, which potentiated difficulties with inventory and drug counterfeiting. This led to efforts by the APhA to pass ant substitution resolutions and state legislation requiring pharmacists to dispense either the branded drug prescribed or a generic drug from a specific manufacturer unless only a generic name was provided. \[9, 10\] While these laws helped prevent substitution of low-quality products, it limited opportunities for the manufacture of generic products of sufficient quality. \[5\]

In 1962, the Kefauver-Harris Drug Amendments were mandated. These amendments were the first to require drug manufacturers to prove a product’s safety and efficacy to the FDA prior to marketing it. \[7\] Also at that time, all products on the market that had been released
between 1938 and 1962 were declared once again to be new drugs, and pioneer products had to submit efficacy data for evaluation by active ingredient. If a product was found to be ineffective, all related products, in addition to the pioneer product, were removed from the market. [8]

The Kefauver-Harris Drug Amendments also required all manufacturers of related products to submit an Abbreviated New Drug Application (ANDA) for products manufactured between 1938 and 1962. ANDAs contained information similar to that found in a pioneer drug application, with the exception of safety and efficacy. After 1962, the FDA established a new mechanism of proving safety and efficacy by allowing the "literature-based" New Drug Application. This meant that submission of published data regarding a branded product's safety and efficacy by a generic products manufacturer was permitted. [8] Over the next several years, the Kefauver-Harris Drug Amendments were challenged, most notably in Upjohn v. Finch in 1970, in which the courts upheld the amendments by ruling that evidence of drug safety and efficacy cannot be substantiated by commercial success alone. [7]

The Medicaid and Medicare amendments to the Social Security Act (enacted in 1965) and additional legislation passed in 1967 helped move generic drug products into the forefront. After a cost-effectiveness analysis of drug products conducted by Congress, the use of generic products by federal health and welfare programs was strongly encouraged to safeguard against inflated pricing arising from lack of competition. [5]

Legislation to expedite the availability of generic drug products was passed in 1984. [4,5,7] The Drug Price Competition and Patent Term Restoration Act, more commonly known as the Hatch-Waxman Act, allowed the FDA to approve applications to market generic versions of brand-name drugs released after 1962 without repeating efficacy and safety research. This legislation also allowed brand-name manufacturers to extend their patent protection for up to 5 years for new products. This meant that these manufacturers could make up for time lost while their products were going through the FDA approval process. [7] Despite the increase in patent protection, the Hatch-Waxman Act is considered to be one of the most pivotal legislative moves on behalf of the generic drug industry. In 1994, through the passage of the Uruguay Rounds Agreements Act, the patent term of drugs manufactured in the U.S. was extended from 17 to 20 years after original filing. [7]
In the last 30 years, several controversies have arisen surrounding legislation involving generic drugs. In particular, the approval process, issues of bioequivalence and corruption have been at the forefront of the disputes. In 1987, an investigation into the FDA Office of Generic Drugs (OGD) was conducted after a complaint from Mylan Laboratories that several of its ANDAs had been purposely delayed. The investigation revealed that some government officials had taken kickbacks to accelerate the ANDA approval process for some manufacturers. Additionally, evidence was discovered linking some manufacturers to the submission of false ANDA information in order to decrease their products' time to market. The FDA conducted its own internal review of the OGD, after which it changed the procedure for processing ANDAs, intensified ANDA requirements, and regulated other OGD procedures. A scientific advisory team on generic drugs was created, and investigations into generic drug practices were performed by an independent panel so as to limit fraud. [5]

In response to this corruption, the Generic Drug Enforcement Act of 1992 imposed penalties for illegal acts related to abbreviated drug applications and required generic drug manufacturers to include more scientific data concerning quality and bioequivalence. Fortunately, this legislation brought needed change and credibility to the generic drug industry and was a timely move toward restoring the integrity of the industry in a time of greatly rising health care costs. [5, 7]

The Approval Process
Unlike the approval process for new chemical entities, that for generic drugs allows use of the ANDA, which does not require the submission of clinical data regarding safety and efficacy since this information was already provided for the pioneer product. Since the original active ingredient was already proven safe and effective, the manufacturer must now prove bioequivalence for the pharmaceutically equivalent generic drug product.

In order to receive approval for marketing, a generic drug must meet the same batch requirements for identity, strength, purity, and quality and be therapeutically equivalent to the branded product. Additionally, the drug must be manufactured according to the same Good Manufacturing Practice regulations required by the FDA. [4] For the generic drug to be therapeutically equivalent, two clinical characteristics must apply: It must be pharmaceutically equivalent as well as bioequivalent. Pharmaceutical equivalence means that the active ingredient(s), dose form, route of administration, and strength are the same for both
the branded product and the generic product. Bioequivalence is when both products have comparable bioavailability when studied under similar conditions.\textsuperscript{[10-14]}

While pharmaceutical equivalence is relatively easy to comprehend, the concept of bioequivalence is more difficult to grasp. Bioequivalence is determined by evaluation of the AUC and the maximum concentration of drug (C\text{\text{max}}). A generic product is considered to be bioequivalent to the pioneer product if the 90% confidence interval (CI) of the mean AUC and the relative mean C\text{\text{max}} is 80% to 125%. This criterion is the same standard used for testing the bioequivalence of branded products with reformulation or manufacturing changes. Bioequivalence is determined by conducting crossover studies of at least 12 patients in which half of the patients receive the generic drug first and then the pioneer drug, with a washout period in between. The remaining patients receive the pioneer drug first, followed by a washout period and then the generic drug. The C\text{\text{max}}, time to reach C\text{\text{max}}, and AUC are determined by taking multiple blood samples from individual patients. Based on the 90% CI, if drug levels vary by more than 10%, failure to reach FDA criteria disqualifies a drug for a bioequivalence rating. According to data for bioequivalence testing performed on 224 drugs after 1962, the mean variation in bioavailability between branded and generic drug products was approximately 3.5%.\textsuperscript{[14-21]}

Despite determinations of statistical bioequivalence, some health care providers still have concerns about interchange ability between narrow-therapeutic-index (NTI) branded and generic drugs. Currently, however, no data suggest that the bioequivalence criteria for NTI drugs should be more rigorous. Opponents of generic substitution have raised questions about changes in efficacy and toxicity in drugs such as antiepileptic and have voiced concerns about receiving consistent product with routine refills. In addition, it has been difficult to determine bioequivalence in products with timed-release properties.\textsuperscript{[19]}

A common misconception in the evaluation of generic substitution relates to therapeutic equivalence. While a generic drug may be AB-rated to a branded drug, there is no testing to determine whether generic products are bioequivalent to each other, although it is expected that their efficacy would not differ significantly.\textsuperscript{[11]}
MATERIALS AND METHOD

Comparisons between the conventional tablets and Plenadren. [23, 24]

Treatment groups
1. Plenadren (oral modified-release hydrocortisone tablet administered o.d.)
2. Conventional hydrocortisone replacement therapy administered t.i.d.

The concentration-time profile of Plenadren q.d. and conventional hydrocortisone t.i.d. was compared in study in patients with adrenal insufficiency. The study was of sequential crossover design where patients were treated with total daily hydrocortisone tablet doses of 20, 25, 30 or 40 mg, doses being individually titrated based on clinical response. The total daily dose was divided and given (t.i.d. separated by 4 hours) as follows: 20 mg (10+5+5), 25 mg (15+5+5), 30 mg (15+10+5) or 40 mg (20+10+10). The patients were then switched to the same daily dose as Plenadren. As there is little accumulation of cortisol during multiple-dose administration, the pharmacokinetic data obtained may be seen as comparative to single dose data for Plenadren. Frequent blood samples were collected over 24 h. The results are presented below (Fig 1) exemplifies the plasma concentration time courses, (Table 1) presents the results irrespective of daily dose). When all dose levels were analysed together, the AUC0-24h was about 20% lower (ratio 0.806 [95%CI: 0.753; 0.862]) after administration of prolonged release tablets than after conventional tablets.

Figure 1 Mean (+-SD) plasma concentration versus time after dosing of o.d. and t.i.d. after single+multiple dosage of 30 mg.jpg
Table 1 Descriptive statistics and test for the primary PK variable, o.d. vs. t.i.d., at multiple dosage population with both o.d. and t.i.d

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD) Median (Min; Max)</th>
<th>p-value within group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliance during o.d.</td>
<td>104.8 (7.5) 102.4 (94.7; 138.9) n=58</td>
<td>0.0420</td>
</tr>
<tr>
<td>Compliance during t.i.d.</td>
<td>103.1 (13.2) 100.9 (61.2; 168.2) n=58</td>
<td></td>
</tr>
<tr>
<td>Difference in compliance o.d.-t.i.d.</td>
<td>1.28 (15.08) 2.26 (-63.47; 43.04) n=56</td>
<td></td>
</tr>
</tbody>
</table>

The blood samples of this study were analysed by an immunoassay (Centaur) for which the validation data is sparse and mainly derived from the manufacturer's documentation. However, if assuming that during the analysis of these samples, the potential errors will have affected the analysis results in a similar way for the two treatments, the comparison of treatments is considered sufficiently reliable for comparison of the shape of concentration time profile and relative PK parameters for Plenadren q.d. vs Conventional t.i.d.

Dose proportionality – between strengths and dose levels

As different doses and dose regimens will be used, the dose proportionality of the two strengths needs to be evaluated and a comparison of whether the dose-exposure relationship is similar for the different formulations supplies useful background information for changing from treatment with conventional tablets to Plenadren and compliance is shown in (Table 2).
There are two sets of dose proportionality information. The first is the proportionality of exposure between the two different Plenadren strengths. This has been investigated in a study in healthy volunteers with pharmacologically induced suppression of the endogenous cortisol production. In this study, single doses of 5 and 20 mg Plenadren were compared during fasting conditions. In this study it was shown, that instead of the expected 4-fold difference in exposure between strengths, the increase in exposure (AUC) when comparing 20 to 5 mg was 3-fold. Thus, the exposure is increased when increasing the strength, but is not completely dose-proportional. The reasons for this are unknown but as nonlinear pharmacokinetics of cortisol have been reported, potentially caused by saturable protein binding or dose dependent bioavailability due to incomplete dissolution; this may be a substance and not a formulation effect. LC-MS/MS was used for quantification of cortisol in plasma in this study. This method does not have interference but has not been validated in an optimal way. However, the results may be used to illustrate relationship in total cortisol exposure between the two strengths.

The second part of the dose-proportionality documentation is related to dose proportionality in the therapeutic dose range. As doses as high as 40 mg qd may be administered in patients in the normal treatment situation without intercurrent illness, it is adequate to show that the differences in drug release pattern between the conventional tablet and Plenadren does not give rise to any major differences in the dose-exposure relationship. In study DC06/02 where patients were transferred from conventional tablets tid to Plenadren qd, full concentration-time profiles are available for different daily doses. The mean (SD) AUC(0-24h) for conventional tablets t.i.d. was 4305 (1285), 5353 (1256), 4905 (1155) and 4770 (1140) nmol*h/l at the total daily dose levels 20 (n=8), 25 (n=4), 30 (n=36) and 40 mg (n=13), respectively. The corresponding values for Plenadren were 3250 (998), 4290 (278), 3757 (956) and 4357 (1179) nmol*h/l, respectively. For the different dose levels in the study the AUC-ratios [95%CI] q.d./t.i.d.were as follows: 0.737 [0.596; 0.912] N=8 for the 20 mg dose, 0.784[0.371;1.658] N=4 for 25mg dose, 0.762[0.710; 0.818] N=36 for the 30 mg dose and 0.911[0.821;1.011] N=13 for the 40 mg dose. Since the number of subjects on some dose levels was small, the precision in the estimates are poor and an approximate 20% difference may be concluded supporting the fact that the relationship between dose and AUC is similar for the two formulations. The AUC observed per dose level was not proportional to dose for any of the formulations, with AUCs of the same magnitude at the 25, 30 and 40 mg dose levels. There may be several contributing factors to this observation including a higher
clearance in patients with a higher dose requirement, reduced bioavailability at higher doses and possibly saturable protein binding. These data were obtained with a non-specific immunoassay method. However, under the assumption that the interference is similar for both products, inter formulation comparison of concentration-time profiles and by calculating the AUC ratio can be made.

In intercurrent illness, dosing bid or, if needed, tid, with Plenadren is recommended using 8-hour intervals between administrations. Since the same dose per occasion is given but in a higher frequency, the resulting exposure in the patient with intercurrent illness may be estimated by calculations using the superposition principle and is expected to increase in proportion to dose.

RESULTS AND DISCUSSION
The blood samples of this study were analysed by an immunoassay (Centaur). However, if assuming that during the analysis of these samples, the potential errors will have affected the analysis results in a similar way for the two treatments, the comparison of treatments is considered sufficiently reliable for comparison of the shape of concentration time profile and relative PK parameters for Plenadren q.d. vs conventional t.i.d.

CONCLUSION
The pharmacokinetic data are considered sufficiently reliable comparison of shape of concentration time profile and relative PK parameters for Plenadren q.d. vs IR t.i.d. Also when changing treatment from conventional tablets to the same total daily dose of Plenadren there will be an approximately 20% decrease in overall exposure (AUC) regardless of dose level. Based on the bioequivalence data, decision is rendered that generic drug are bioequivalent to that of innovator drug.

REFERENCE

5. Meyer GF. History and regulatory issues of generic drugs. Transplant Proc. 1999;31(suppl 3A):10S-12S.


