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BIOEQUIVALENCY OF TWO BRANDS OF CEPHALOTHIN SODIUM

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ABSTRACT

In order to assess the bioequivalency of two USA commercially available brands of **cephalothin sodium, neutral, USP**, a double-blind, single-dose, human crossover study was conducted. Serum and urinary samples were tested by HPLC assay, and pharmacokinetic parameters were determined by computer analysis. The results revealed that both products are bioequivalent, and support a submission to the FDA for a claim of "aqueous bioequivalency" of the new Seffin™ (Glaxo) brand vs. the standard.

Hospital cost-containment programs, such as the recent Diagnostic Related Group (DRG) legislation, necessitates that

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Pharmacy & Therapeutic Committees evaluate competitive brands of identical drugs in order to realize cost savings but without sacrificing quality. Where generic equivalents are concerned, the major basis of comparison rests on clinical pharmacokinetic studies.

Cephalothin sodium for injection, USP (Neutral) has been available in the USA since 1975, but only as a single source product (**Keflin®**/ Lilly). An equivalent produced by Glaxo (**Seffin®**) has been marketed in 19 countries for over a decade. The Glaxo product is now available for marketing in the U.S.A. by Glaxo Inc. under the same tradename '**Seffin™**'.

The purpose of this double-blind, single-dose, human crossover study was to compare the pharmacokinetic characteristics and bioequivalency of both cephalothin products.

METHODS:

Eight normal male adult volunteers each received a single dose of either 1 g neutral cephalothin sodium manufactured by Glaxo[a] (Seffin™ ; Lot# GCR2309/A) or Lilly[b] (Keflin® ; Lot# 4GE42A) in part one of the randomized crossover study. Four days late, they each received a single intravenous dose of the other cephalothin product. Fluid and food intake was controlled during the trial periods. Each 1 g vial was reconstituted with 10 ml of **Sterile Water for Injection** (per manufacturer's label instructions) and administered manually as a direct intravenous bolus over a three-minute period.

Blood samples (10 ml per withdrawal) were obtained through a heparin lock prior to drug administration and at 5, 10, 15, 30, 45, 60

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and 90 minutes, and at 2, 4, and 6 hours after completion of the infusion. Blood samples were allowed to clot in their plastic tube, and serum was then removed for assay. Urine voids were collected just prior to drug administration and collection was repeated at intervals of 0-2 hours, -4 hours and 4-6 hours.

After each dose, serum and urinary concentrations of cephalothin were measured by a new high-pressure liquid chromatography (HPLC) assay[c] having a reproducibility of the calibration curve within 4%. The desacetyl metabolite of cephalothin does not interfere with concentrations reported by this new assay technique.

For each treatment, the serum concentrations of each subject from five minutes to two hours after each dose were fitted to a bi-exponential curve by log-linear regression[1]. The exponents and coeffients were then used as the starting values for the NONLIN computer program[2] to derive pharmacokinetic parameters from a two-compartment intravenous model. Assessed parameters from the intravenous model were area under curve, half-life, volume of distribution, and renal and plasma clearance values. The statistical analysis by Student 't' test appropriate for two treatment crossover trials was used to compare the pharmacokinetics of the drugs and dosing days[3]. A difference was not regarded as statistically significant unless it had a probability of less than 0.05 ($P < 0.05$).

RESULTS:

Results are displayed in the accompanying tables (see Tables I thru IV) and figure. There was a slightly higher mean urinary

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c -- Ayrton J: GDM/83/011 -- The HPLC assay of cephalothin in serum and urine from Human Volunteer Study GMH.83.001. Drug Metabolism Department, Glaxo Group Research Ltd.

Table I.

Urinary Recoveries of Cephalothin after 1 g. Intravenous Doses of Neutral Cephalothin sodium for injection, USP, Produced by Glaxo (Seffin™) and Lilly (Keflin®) in Seven Male Volunteers.‡

	Mean[e] Percentage Urinary Recovery During Period After Dose:			
Product	0-2h	2-4h	4-6h	Total (0-6h)*
Seffin™	54.0 ±0.9	1.2 ±0.1	0.1 ±0	55.3 ±0.9
Keflin®	51.7 ±0.9	1.0 ±0.1	0.2 ±0	52.9 ±1.0

‡ - Data from one subject omitted because of an incomplete collection.

• - indicates statistically significant difference ($P < 0.05$)

e - Mean ± S.E.M.

recovery (see Table I) of cephalothin after the Glaxo preparation (55.3% vs. 52.9%, $P < 0.05$), which resulted in a higher mean renal clearance value (0.223 l/h/kg vs. 0.197 l/h/kg, $P < 0.05$). However, there were no statistically significant differences in urine or serum concentrations (see Tables II and III).

The remaining derived pharmacokinetic parameters were not

Table II.

Urine Concentrations of Cephalothin Following i.v. Administration of 1.0 g of Neutral Cephalothin sodium for injection, USP, Produced by Glaxo (Seffin™) and Lilly (Keflin®) in Seven Male Volunteers.[#]

	Mean[f] Urine Concentrations (mcg/ml) During the Time Period after Administration		
PREPARATION	0-2h	2-4h	4-6h
Seffin™	3916 ±897	105 ±22	12 ±2
Keflin®	4274 ±877	92 ±20	15 ±3

[#] - All urine samples data from one volunteer were excluded due to collection error.

f - Mean ± S.E.M.

Table III.

Mean[g] Serum Concentrations of Cephalothin Following Administration of 1.0 g i.v. of Neutral Cephalothin for injection, USP Produced by Glaxo (Seffin™) and Lilly (Keflin®) to Eight Male Volunteers.

Time(min)	Seffin™ (mcg/ml)	Keflin® (mcg/ml)
0	0	0
5	90.7 ±4.1	96.1 ±2.1
10	59.2 ±4.1	52.2 ±2.4
15	39.2 ±2.8	37.0 ±1.9
30	19.2 ±2.5	18.7 ±1.4
45	10.2 ±1.2	9.6 ±0.8
60	5.5 ±0.7	6.7 ±1.0
90	1.8 ±0.3	2.4 ±0.4
120	0.9 ±0.2	1.0 ±0.3

g -- Mean ± S.E.M.

Table IV

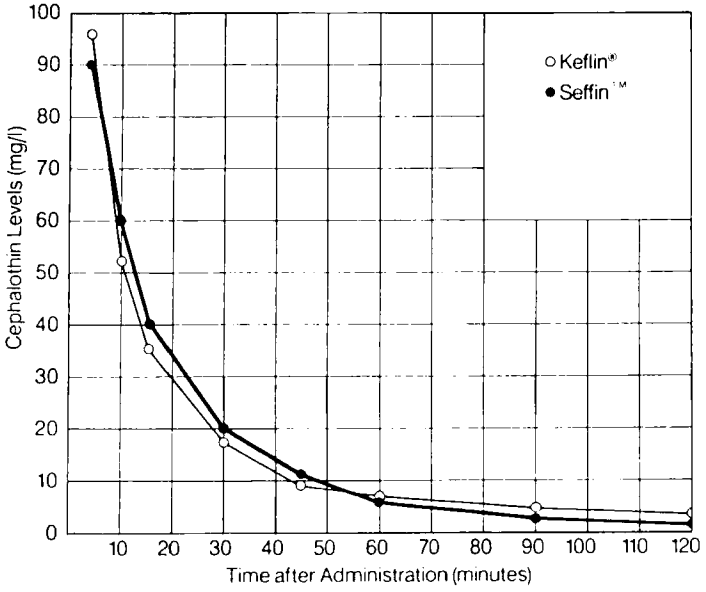
Mean[h] Pharmacokinetic Parameters Of Cephalothin After i.v. Administration of 1 g Of Neutral Cephalothin For Injection, USP Produced By Glaxo (Seffin™) And Lilly (Keflin®) To Eight Male Volunteers.

PRODUCT	Area under serum level/ time curve (mg/l·h)	Volume of distribution (l/kg)	Serum clearence (l/kg/h)	Renal* clearence (l/kg/h)	Elimination constant (h^{-1})	Terminal half-life (h)
SEFFIN™	35.0±1.8	0.134±0.007	0.398±0.014	0.223±0.009	4.75±0.35	0.309±0.020
KEFLIN®	37.0±1.1	0.126±0.007	0.377±.022	0.197±0.011	6.11±0.94	0.326±0.034

*-indicates statistically significant difference ($p<0.05$)

h-Mean ± SEM

Mean Cephalothin Serum Levels Following 1.0 g i.v. Neutral Cephalothin for Injection, USP (Seffin™/Glaxo and Keflin®/Lilly)



statistically different between the two cephalothin preparations (see Table IV). Statistically significant differences for several parameters did occur for dosing days, which could possibly be attributed to normal physiological variation over time[4,5]. A large proportion of cephalothin is hepatically converted to a desacetyl metabolite, which might explain the observed intra-individual variation.

The doses of both preparations were observed to be well tolerated without local or systemic adverse effects.

CONCLUSION & DISCUSSION:

The study revealed that it is justified to substitute Glaxo's brand of neutral cephalothin sodium (**Seffin™**) for Lilly's **Keflin®**.

The FDA has published a list entitled "**Approved Prescription Drug Products with Therapeutic Equivalence-4th Edition**", which most states use as a reference guide to permit generic substitution by dispensing pharmacists. The recent supplement to this FDA list cites **Seffin™** with an "**AP**" symbol, signifying an aqueous parenteral product that is "pharmaceutically equivalent" and for which no bioequivalency problem is thought to exist. With this FDA rating, it is legally permissable to allow generic substitution between the **Keflin®** and **Seffin™** brands of cephalothin sodium, USP., unless otherwise prohibited by certain local regulations.

Thus, this research study substantiates the "**AP**" rating for **Seffin™**, and additionally provides clinical bioequivalency data in human subjects.

Since Keflin® is one of the most widely prescribed brands of first-generation cephalosporins in USA hospitals today, with total sales exceeding $40 million in 1983[d], the availability of a quality alternative brand may offer the potential for significant cost-savings, and fulfill the objectives of DRG legislation.

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