COMPARATIVE BIOAVAILABILITY STUDY OF THREE ORAL PREPARATIONS OF GLICLAZIDE TABLETS

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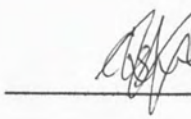

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ABSTRACT

The bioavailability of a generic preparation of gliclazide (Glimicron® 80 mg) was compared with the innovator products, Diamicron® 80 mg and a modified release tablet, Diamicron® MR 30 mg. Six healthy adult male volunteers participated in the study conducted according to a randomized, three-way crossover design and the plasma concentrations obtained were analyzed according to a validated liquid chromatography-tandem mass spectrometry method. The bioavailability was compared using the parameters total area under the plasma level-time curve ($AUC_{0-\infty}$), peak plasma concentration (C_{max}), and time to reach peak plasma concentration (t_{max}). No statistically significant difference was observed between the $AUC_{0-\infty}$ value of Glimicron® 80 mg and normalized $AUC_{0-\infty}$ value for Diamicron® MR 30 mg. However, there was a statistically significant difference in the C_{max} and t_{max} values for all the three pairs of the three preparation combinations. Meanwhile, after normalizing for dose difference, the 90% confidence intervals of the $AUC_{0-\infty}$ and C_{max} values of Glimicron® 80 mg over those of Diamicron® MR 30 mg were found to lie between 0.8-1.3 and 1.7-2.7 respectively. Similar to that observed with Glimicron® 80 mg, the Diamicron® MR 30 mg preparation also has a markedly higher extent of bioavailability over the conventional Diamicron® 80 mg preparation, being between 4.9 and 8.0 times higher. There was no statistically significant difference among the elimination rate constant (k_e) values of the three preparations and were similar to those reported in the literature. Based on these statistical inferences, it can be concluded that the extent of bioavailability of Glimicron® 80 mg was comparable to that of Diamicron® MR 30 mg with Diamicron® MR 30 mg exhibiting a sustained rate of absorption.

PERBANDINGAN KEPEROLEHAN-BIO ANTARA TIGA SEDIAAN ORAL TABLET GLICLAZIDE

ABSTRAK

Keperolehan-bio bagi suatu penyediaan gliclazide generik (Glimicron® 80 mg) telah dibandingkan dengan produk perintis, Diamicron® 80 mg dan suatu tablet pelepasan yang diubahsuai, Diamicron® MR 30 mg. Enam sukarelawan yang sihat telah terlibat dalam pelaksanaan kajian ini mengikut rekabentuk pindah silang tiga arah secara rawak dan kepekatan plasma darah yang diperoleh dianalisis dengan menggunakan suatu kaedah kromatografi cecair-spektroskopi jisim *tandem* yang telah disahkan. Keperolehan-bio tersebut dibandingkan dengan menggunakan parameter-parameter luas di bawah keluk kepekatan plasma darah melawan masa ($AUC_{0-\infty}$), kepekatan plasma puncak (C_{max}) dan masa untuk mencapai kepekatan plasma puncak (t_{max}). Tiada perbezaan yang signifikan secara statistik diperhatikan antara nilai $AUC_{0-\infty}$ Glimicron® 80 mg dan nilai $AUC_{0-\infty}$ Diamicron® MR 30 mg yang dinormalkan. Namun, terdapat perbezaan yang signifikan secara statistik bagi nilai C_{max} dan t_{max} bagi ketiga-tiga kombinasi penyediaan tersebut. Sementara itu, selepas perbezaan dos dinormalkan, selang keyakinan 90% untuk nilai $AUC_{0-\infty}$ dan C_{max} Glimicron® 80 mg kepada Diamicron® MR 30 mg adalah dalam julat 0.8-1.3 dan 1.7-2.7 masing-masing. Seiring dengan permerhatian Glimicron® 80 mg, penyediaan Diamicron® MR 30 mg juga mempunyai keperolehan-bio yang ketara berbanding dengan penyediaan Diamicron® 80 mg yang adalah di antara julat 4.9 dan 8.0 kali lebih tinggi. Tiada perbezaan yang signifikan secara statistik bagi nilai pemalar kadar penyingkiran (k_e) untuk ketiga-tiga penyediaan tersebut dan adalah serupa dengan yang telah dilaporkan dalam kajian lepas. Berdasarkan analisis statistik ini, dapat disimpulkan bahawa keperolehan-bio Glimicron® 80 mg adalah setara dengan Diamicron® MR 30 mg di mana ia menunjukkan kadar penyerapan yang berkekalan.

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LIST OF SYMBOLS AND ABBREVIATIONS

C_{max}	maximum plasma concentration
t_{max}	time to reach maximum plasma concentration
AUC_{0-t}	area under the plasma concentration-time curve from time zero to the last measurable concentration
$AUC_{0-\infty}$	total area under the plasma concentration-time curve
k_e	elimination rate constant
$t_{1/2}$	elimination half-life
CV	coefficient of variation
SD	standard deviation
SEM	standard error of the mean
ANOVA	analysis of variance

CHAPTER 1

INTRODUCTION

1.1 COMPARATIVE BIOAVAILABILITY

The concept of bioavailability was introduced in 1945 by Oser *et al.* (Wagner, 1975). According to Shargel and Yu (1999), bioavailability indicates a measurement of the rate and extent or amount of therapeutically active drug that reaches the systemic circulation and is available at the site of action. Bioequivalence is a comparison of the bioavailability of ≥ 2 drug products; thus, 2 products or formulations containing the same active ingredient are bioequivalence if their rates and extents of adsorption are the same (Borgherini, 2003). Chow and Liu (2000) refer a comparative bioavailability study as the comparison of bioavailability of different formulations of the same drug or different drug products.

Drug regulation in Malaysia was first introduced through the promulgation of the Regulation for the Control of Drugs and Cosmetics in 1984 and the establishment of the Drug Control Authority. In line with the Ministry of Health's objectives, the Drug Control Authority is responsible for ensuring the quality, efficacy, effectiveness and safety of all marketed medicinal products to safeguard the Malaysian public (Abida, 2003).

Due to the expiration of the patent granted to brand-name drug innovator, other manufacturers may market the drug under its chemical or generic name usually at a considerably lower price (Westlake, 1979). The manufacturing of generic drugs do not require large and extensive clinical trials in patients for claimed indications, nor does it involve safety studies in animal models because they are already conducted by the brand-name drug innovator. Therefore, the lower cost of research and development as well as the competition in the market place has lead to cheaper price in generic drugs (Dighe, 1999).

With the increasing availability of generic products in the Malaysian market (Abida, 2003), it is imperative that a mechanism be introduced to further ensure that generic products available are therapeutically equivalent to the innovator's products and are clinically interchangeable (http://www.bpfk.gov.my). In practice, demonstration of bioequivalence is generally the most appropriate method of substantiating therapeutic equivalence between medicinal products because for a generic product to be considered bioequivalent to a pioneer drug product, it must be shown to have the same rate and extent of absorption as the pioneer drug product when administered at the same molar dose of the active therapeutic moiety under similar experimental conditions (Welling *et al.*, 1991). Unfortunately, the pharmaceutical industry in Malaysia is still very much focused on marketing and little emphasis has been placed on safety monitoring (Abida, 2003).

Bioavailability studies are of clinical, academic and regulatory interest. In approving a drug for marketing, when a new formulation of a drug product is developed, the Food and Drug Administration (FDA) requires that a bioavailability

study be conducted to assess its bioequivalence to the standard (or reference) marketed formulation of the drug product (Chow and Liu, 2000; Welling *et al.*, 1991) to ensure that the drug products is safe and effective for its labeled indications for use (Shargel and Yu, 1999).

Furthermore, the purpose of bioavailability studies is to determine the bioavailability and to characterize the essential pharmacokinetics parameters including the rate and extent of systemic absorption, elimination half-life and rates of excretion and metabolism of the new formulation, new dosage form or new salt or ester relative to a reference formulation. Data from these in vivo bioavailability studies are important to establish recommended dosage regimens, instruction for use and to support drug labeling (Shargel and Yu, 1999).

1.2 OBJECTIVES

As most drugs are developed in the west, until recently, most data available were based on the Caucasian population. Little information is available on genetic effects involving Asians and particularly Malaysian population (Abida, 2003). This comparative bioavailability study will be a pilot study comparing the bioavailability of three oral preparations of gliclazide tablets in Malaysia. The objectives of this research are:

a) To compare the bioavailability of a generic gliclazide 80 mg tablet, Glimicron®, manufactured by Hovid Bhd., Ipoh, Malaysia, with the innovator products, Diamicron® (80 mg gliclazide) and a modified release tablet of

gliclazide 30 mg, Diamicron® MR. Both Diamicron® products were manufactured by Les Laboratories Servier Industrie, Gidy, France.

b) To analyze, using an analysis of variance (ANOVA) procedure which distinguishes effects due to subjects, periods, and treatment, the values of the maximum plasma concentration (C_{max}), the area under the plasma concentration-time curve from time zero to the last measurable concentration (AUC_{0-t}), total area under the plasma concentration-time curve ($AUC_{0-\infty}$) and the elimination rate constant (k_e) obtained from the three preparations.

1.3 SCOPE

This is a single-dose, randomized, three-way crossover study to evaluate the relative bioavailability of one test formulation compared to an equivalent dose of a commercially available reference drug product and a reduced-dose of modified-release reference product, in 6 healthy male volunteers under fasted condition. The plasma concentrations of gliclazide obtained from the volunteers are analyzed according to a validated method using liquid chromatography-tandem mass spectrometry (LC-MS-MS).

CHAPTER 2

LITERATURE REVIEW

2.1 PROPERTIES OF GLICLAZIDE

2.1.1 Gliclazide

Gliclazide is a second generation oral hypoglycaemic sulphonylurea agent (Holmes *et al.*, 1984) which is widely used to reduce plasma glucose levels in Type 2 or non-insulin-dependent diabetes mellitus (NIDDM) patients (Palmer and Brogden, 1993; Glowka *et al.*, 1998). Parfitt (1999) defines diabetes mellitus as a group of disorders of carbohydrate metabolism in which the action of insulin is diminished or absent through altered secretion, decreased insulin activity, or a combination of both factors which is characterized by hyperglycaemia. In Type 2 diabetes mellitus, insulin secretion may appear normal or even excessive but it is insufficient to compensate for insulin resistance (Parfitt, 1999).

Gliclazide works in several different ways, but it acts mainly by stimulating insulin release from pancreatic β cells in which may result in the inhibition of hepatic glucose production and by increasing the sensitivity of peripheral tissues to insulin (Najib *et al.*, 2002). Besides that, gliclazide has also been shown to reduce platelet

adhesion and aggregation, increase fibrinolysis and scavenge free radicals (Palmer and Brogden, 1993). The chemical name of gliclazide is (1-(1-azabicyclo[3,3,0]oct-3-yl)-3-(ptoylsulphonyl) urea) and its molecular formula is $C_{15}H_{21}N_3O_3S$ with a molecular weight of 323.4 g/mol (Parfitt, 1999). Molecular structure of gliclazide is shown in Figure 2.1:

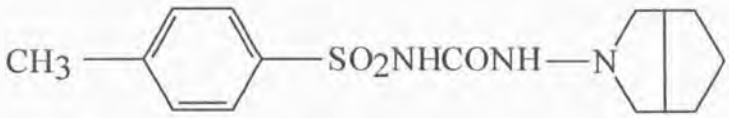

Figure 2.1 The structure of gliclazide.

Gliclazide is available in a white or almost white powder (Parfitt, 1999) and practically insoluble in acidic media but its solubility increases as the pH becomes more alkaline (Delrat *et al.*, 2002). The compound is a weak acid with a good lipophilicity and a pH dependent solubility having a pKa of 5.8.

2.1.2 Gliclazide Immediate Release (IR)

Gliclazide IR reduces blood glucose levels in healthy volunteers and NIDDM patients by correcting both defective insulin secretion and peripheral insulin resistance. Various studies carried out suggested that gliclazide IR is an effective agent for the treatment of the metabolic defects associated with NIDDM and may be useful in slowing the progression of diabetic retinopathy. Moreover, its good general tolerability and low incidence of hypoglycaemia have allowed gliclazide IR to be well placed within the array of oral hypoglycaemic agents available for the control of NIDDM (Palmer and Brogden, 1993).

a. Pharmacokinetic Profile

Palmer and Brogden (1993) stated oral absorption of gliclazide is similar in patients and healthy volunteers, although intersubject variation in time to reach peak plasma concentrations (t_{max}) and age-related differences in peak plasma concentrations (C_{max}) and t_{max} have been observed. According to Najib *et al.* (2002), when a single 80 mg oral dose was administered orally, C_{max} of 3 to 8 μg/ml are achieved within 2 to 4 hours whereas Palmer and Brogden (1993) reported C_{max} of 2.2 to 8 mg/L within 2 to 8 hours are obtained from a single-dose oral administration of gliclazide IR 40 to 120 mg.

The volume of distribution of gliclazide in healthy volunteers and patients is low (13 to 24L) which may be partially explained by extensive protein binding (85 to 97%) (Najib *et al.*, 2002; Glowka *et al.*, 1998; Palmer and Brogden, 1993). The reported elimination half-life ($t_{1/2}$) of gliclazide is 8.1 to 20.5 hours after single-dose and repeated oral administration of 40 to 120 mg to healthy volunteers and patients (Palmer and Brogden, 1993) and it tends to be longer in elderly patients (Najib *et al.*, 2002).

Najib *et al.* (2002) reported that the bioavailability is 80% while the effect of food is clinically insignificant but studies have shown that the administration of gliclazide with food reduces C_{max} and delays t_{max} (Palmer and Brogden, 1993). Gliclazide is extensively metabolized to 7 metabolites, majority of those being inactive. The most abundant urinary metabolite being the carboxylic acid derivative, which are predominantly excreted in the urine, 60 to 70% of the dose is excreted in

the urine and 10 to 20% in the faeces (Najib *et al.*, 2002; Glowka *et al.*, 1998; Palmer and Brogden, 1993).

b. Tolerability

Gliclazide is well tolerated by most patients. The most frequently reported side effect has been gastrointestinal upset such as abdominal pain, nausea, vomiting, dizziness, skin reactions and symptoms of hypoglycaemia. Generally, gliclazide is associated with a low incidence of hypoglycaemia (Palmer and Brogden, 1993; Holmes *et al.*, 1984).

2.1.3 Gliclazide Modified Release (MR)

Gliclazide MR is a new once-daily formulation of the sulfonylurea gliclazide incorporating the molecule in a hydrophilic matrix of hypromellose-based polymer that expands to form a gel when exposed to gastrointestinal fluid, which ensures a progressive release of gliclazide and reduces plasma glucose levels over a 24-hour period (Schernthaner, 2003; McGavin *et al.*, 2002).

Gliclazide MR was chosen to properly address morning hyperglycemia and to avoid excessive release during the night due to its release profile of more than 50% of the gliclazide being released within the first 4 to 6 hours. Furthermore, it is insensitive to pH, so that the plasma concentration is not affected by food or by treatment with drugs that modify gastrointestinal pH (Diamicron® MR Study Group and Drouin, 2000).

Besides that, it has shown similar efficacy to gliclazide IR in clinical trials, appears of particular benefit in patients previously untreated with oral antidiabetic drugs and is generally well tolerated (McGavin *et al.*, 2002).

a. Pharmacokinetic Profile

Studies on gliclazide MR shows predictable and reproducible release of gliclazide over a 24-hour period observed in untreated patients with type 2 diabetes mellitus (Schernthaner, 2003; McGavin *et al.*, 2002). Gliclazide MR shown to have a linear pharmacokinetics over the 15 to 120 mg dose range in patients with type 2 diabetes mellitus and the plasma gliclazide concentrations reach a plateau at 3 to 12 hours after a dose and decline thereafter (McGavin *et al.*, 2002).

Delrat *et al.* (2002) reported that C_{max} is reached at about 6 hours after administration (t_{max}) and the mean absolute bioavailability of gliclazide was 97% and ranged between 79 to 110% showing complete absorption after administration of a single oral dose of gliclazide MR 30 mg to 16 healthy volunteers.

Furthermore, the apparent clearance of gliclazide MR was 0.9L/h with an apparent volume of distribution of 19L. Plasma concentrations declined exponentially, with an elimination half-life ($t_{1/2}$) of approximately 16 hours. Gliclazide is highly bound to albumin (95%) and unchanged gliclazide accounts for <1% of compounds retrieved in the urine. Moreover, it is extensively metabolized to at least seven metabolites, with no circulating active metabolite (McGavin *et al.*, 2002).

According to Delrat *et al.* (2002), no significant effect of food on various pharmacokinetic parameters (t_{max}, $t_{1/2}$, C_{max} and AUC) was observed when gliclazide MR 30 mg was given prior to, or 10 minutes after starting breakfast. Similarly, age and mild to moderate renal impairment do not significantly influence the pharmacokinetic parameters of gliclazide MR (McGavin *et al.*, 2002).

b. Tolerability

Gliclazide MR showed similar tolerability to gliclazide IR after 10 months' treatment in the randomized trial. Adverse events were reported in 46.9 and 50.3% of patients who received gliclazide MR and gliclazide IR, respectively (Diamicron® MR Study Group and Drouin, 2000). The most commonly observed adverse events reported by Diamicron® MR Study Group and Drouin (2000) were arthralgia (3.4%), arthritis (2.8%), back pain (3.4%) and bronchitis (4.9%) and bodyweight remained stable. There were no episodes of nocturnal hypoglycaemia or hypoglycaemia requiring third party assistance were observed during treatment with gliclazide MR whereas episodes of symptomatic hypoglycaemia were infrequent, occurring in approximately 5% of patients (Schernthaner, 2003; McGavin *et al.*, 2002; Diamicron® MR Study Group and Drouin, 2000)

Table 2.1 Comparison of gliclazide IR and gliclazide MR.

Type of gliclazide	Pharmacokinetic Profile	Adverse events
Gliclazide IR	Bioavailability : 80% t_{max} : Within 2 - 8h $t_{1/2}$: 8.1 – 20.5h	Abdominal pain, nausea, vomiting, dizziness, skin reactions.
Gliclazide MR	Bioavailability: Approximely 97% t_{max} : Approximely 6h $t_{1/2}$: 16h	Arthralgia, arthritis, back pain and bronchitis (incidence <5% for each).

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