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Three Generations of Cyclosporine A Formulations: An In Vitro Comparison

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ABSTRACT When the microemulsion formulation of the critical dose drug cyclosporine A (CsA) (Sandimmun Optoral®) was introduced in the mid-1990s, it became clear that this new formulation improves the oral bioavailability of CsA and has a positive influence on its pharmacokinetic variability. Previous studies with the original CsA formulation (Sandimmun®) showed that the size of the emulsion droplets and concomitant food intake has an effect on the absorption of CsA from the small intestine when orally administered. It was suggested that these effects might have an influence on the drugs' pharmacokinetic parameters.

In this study, we focused on the two above-mentioned aspects and compared the first and second generations of CsA products (Sandimmun, Sandimmun Optoral) to generic CsA formulations by analyzing the contents of cyclosporine A gel capsules with respect to their emulsion droplet and micelle sizes using photon correlation spectroscopy (PCS). We tried to discern any differences in droplet size between different generations of CsA formulations, primarily the second and third generation, through simple physical tests. Because a high fat content food may influence the absorption of CsA, we also determined the distribution of CsA between hydrophilic and lipophilic phases using high-performance liquid chromatography analysis.

It became clear that when compared under simple physical conditions, established cyclosporine formulations and new generic products show significant differences in droplet size and distribution between an aqueous phase and a high fat content food. Whether these differences are of clinical relevance remains to be investigated.

KEYWORDS Cyclosporine A, high fat content food, droplet size, bioavailability

INTRODUCTION

Cyclosporine A (CsA) is an immunosuppressant used to prevent organ rejection following solid organ transplantation and to treat selected autoimmune diseases or immunoregulatory disorders (Faulds et al., 1993). It is a critical dose drug that displays a narrow therapeutic index.

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Therefore, therapy is complicated by inter- and intra-individual variability in pharmacokinetic parameters caused by the drugs' unpredictable bioavailability (Lemaire et al., 1990).

Parameters that influence CsA absorption from the upper small intestine are the rate of bile flow, motility of the GI tract, the duration of the therapy, and concomitant food intake (Lemaire et al., 1990; Shah et al., 1998). It has been shown that meals containing large amounts of fat have a particularly pronounced effect on CsA absorption (Mueller et al., 1994a). A fluctuating bioavailability after oral administration of CsA can result from these parameters. This has contributed to the idea of creating a new superior formulation to Sandimmun that can use the full range of the absorption window for CsA and is independent of bile salts food intake, and the state of the GI tract (Müller & Hildebrand, 1998).

The first generation of orally administered therapeutics containing CsA consisted of an olive oil-based solution encapsulated in corn oil-based soft gelatine (Sandimmun) (Amante et al., 2001; Mueller, 1994). These formulations demonstrated a large degree of variability in CsA bioavailability and pharmacokinetics (Mueller, 1994). After oral administration, the oily solutions are emulsified by bile salts forming mixed micelles in the gastrointestinal fluid; absorption depends on the emulsion droplet size and triglyceride digestion by pancreatic lipase (Penaud et al., 1996; Senel et al., 1997; Tarr & Yalkowsky, 1989). In accordance with this, meals rich in fat that lead to an increased bile flow can enhance bioavailability significantly. To reduce the effect of food and related problems, cyclosporine A was reformulated in the mid-1990s. An orally administered microemulsion delivery system was created, representing the second generation of CsA preparations (Ritschel, 2001). It emerged that an improved oral absorption of CsA has a positive influence on its pharmacokinetic variability (Kovarik et al., 1994). Microemulsions are fine dispersion systems composed of two immiscible fluids such as oil and water, a surfactant or surfactant mixture, and a cosurfactant (Ritschel, 2001). They are distinctly different from conventional emulsions because they exhibit some of the typical characteristics of both emulsions and solutions. Medications, for example, have a saturation solubility in microemulsions rather than the partition coefficient expected for common emulsions. Microemulsions are furthermore thermodynamically stabile and have a smaller droplet size (micelles <0.15 μm) than regular emulsions (Muller & Hildebrand, 1998; Pfüller, 1985; Ritschel, 2001).

New oral CsA formulations that have been described as a "microemulsion preconcentrate with self-emulsifying properties" disperse immediately when coming into contact with aqueous fluids of the gastrointestinal tract and form a transparent microemulsion, which enables CsA to be more rapidly dispersed in the intestines (Ritschel, 2001). A more predictable absorption of the drug has been reported for these newer formulations, making the intestinal uptake independent of food intake and bile secretion (Amante et al., 2001; Kovarik et al., 1993). Improved oral bioavailability and dose linearity were shown in several studies (Frei et al., 1998). These advantages facilitate a more accurate dosage adjustment in clinical settings (Barone et al., 2001; Kovarik et al., 2001; Mueller, 1994).

More recently, two generic CsA formulations were approved by drug regulation authorities. Because the composition of these two products differ from the Optoral formulation, we decided to group the products under the generic term "third generation of CsA products." The term "generation" is used as a chronological term to describe the products in order of their appearance on the market.

In this study, the two generic CsA formulations were compared with formulations in the first and second generation.

In more recent years, it has become clear that different galenic formulations have a major impact on the pharmacokinetics of cyclosporine (Kahan, 1999). The aim of this study was to show that different formulations of the same critical dose drug CsA that were proven to be bioequivalent with standard bioequivalence criteria (as far as the microemulsion formulation and the new generic formulations are concerned) do not necessarily behave identically when compared in physical tests.

Because smaller emulsion droplet sizes enhance the absorption of CsA from the small intestine, we first analyzed the droplet sizes incorporated into the various CsA gel capsules using photon correlation spectroscopy (PCS). We tried to determine if differences in droplet size exist when different generations of CsA formulations, mainly from the second and

TABLE 1 Pharmaceutical Excipients and Composition of Examined CsA Products Taken from Hässner 2004

Product	Sandimmun	Sandimmun optoral	Generic formulation 1	Generic formulation 2
Solvents	Ethanol Glycerol Corn oil	Ethanol Glycerol Propylenglycol	Ethanol Glycerol Macrogol 400	Ethanol Glycerol Polyethylenglycol 400
Emulation	Macrogolglycerol-tri(oleat,linolat)	Polyoxyl-40-hydrogenated castor oil Corn oil glycerides	Polyoxyl-40-hydrogenated castor oil	Polyoxyl-40-hydrogenated castor oil
Preservation	Sorbitan-sorbitol mixture	α-Tocopherol	Tocofersolan	α-Tocopheryl polyethylenglycol 1000 succinate
			Sorbitol solution 70%	Sorbitol
Other	Colors Gelatine	Colors Gelatine	Ferrum(III)oxide Gelatine	Gelatine

third generation, are compared. A second aspect that we found necessary to consider was the influence that fat may have on the absorption of CsA when different formulations are orally administered. We therefore compared the three generations of CsA preparations concerning their behavior toward different lipids with the help of high-performance liquid chromatography (HPLC) analysis. To test the effect of food, we prepared samples that contained oils and a standardized high fat content food as a lipophilic phase and determined the distribution of CsA between the aqueous and the different lipid phases. Our goal was to demonstrate any differences in the behavior of the formulations in the presence of lipids. The question concerning whether this is of clinical relevance remains open.

MATERIALS

Drugs

We investigated capsules only and chose Sandimmun (100-mg capsules, Lot: 349, Novartis Pharma GmbH, Nürnberg, Germany) to represent the first generation of CsA preparations and Sandimmun Optoral (Sand. Opt.) (100-mg capsules, Lot: F33, from Sandoz Novartis Pharma GmbH, Nürnberg, Germany) as a representative of the second generation. Two further generic CsA formulations (100-mg capsules) were tested as examples of the third generation of CsA formulations. The pharmaceutical excipients of all examined products are shown in Table 1. Data that reveal the exact amounts of ingredients are not available.

Chemicals and Consumables

CsA powder was obtained from Novartis Pharma (Wehr, Germany). Acetonitrile and methanol (both HPLC grade) were purchased from Mallinckrodt Baker (Deventer, Holland) and hydrochloric acid (0.1 M) was bought from Carl Roth GmbH (Karlsruhe, Germany). If not indicated otherwise, all chemicals were analytical grade and purchased from Merck (Darmstadt, Germany).

The artificial gastric juice was prepared according to Ph.Eur.3.0 (1997): 2.0 g sodium chloride, 3.2 g pepsin (from porcine gastric mucosa), and 80 mL of 0.1 M hydrochloric acid were diluted with water to a final volume of 1000 mL.

Fifteen-milliliters centrifuge tubes and 40-mL centrifuge tubes made of polypropylene and purchased from Corning, Incorporated (Corning, NY, USA) were used for centrifuging sample and reference solutions.

Triglycerides were chosen to be representative of oils used in nutrition and oils used in pharmaceutical preparations, such as olive oil (Ph.Eur.3.0) and corn oil (Ph.Eur.3.0, Supplement 2001).

The olive oil was of pharmaceutical quality and was purchased from Henry Lamotte GmbH (Bremen, Germany). The vegetable oil was purchased from Bökelmann+Co (Hamm, Germany), and the corn oil was obtained from Bestfoods GmbH (Heilbronn, Germany).

"Food"

A combination of standardized meals was purchased from McDonald's Deutschland, Inc. (München, Germany) and served as a high fat content food. The meal contained a hamburger sandwich with an average weight of 100.6 g and a fat content of 8.65 g, a small portion of french fries (average weight: 106.05 g, average fat: 16.76 g), and small cup of Coca-Cola (average weight: 365.12 g, no details on fat). The average weight and fat content of the components were taken from McDonald's food nutrition breakdown.

METHODS

Determination of Droplet Size

The contents of a 100-mg soft gelatine capsule were dissolved in 50 mL artificial gastric juice, and the empty gelatine capsule was removed from the solution. The droplet sizes in artificial gastric juice were measured at 25°C. To avoid significant measurement errors due to convection or interference of correlation functions, all samples were prepared according to the same procedure. All measurements were commenced 15 min after placing the cuvette in the cell holder, allowing the sample to reach the stable measurement temperature. All experiments were carried out at 25°C. As the determined droplet size is subject to a small day-to-day variation, all measurements were made in 1 day.

Micelles and droplets were characterized by light scattering using PCS, a method that is based on light scattering caused by the Brownian motion of particles in the sample (Washington, 1992). The size measurement was performed with a Zetasizer 3000HSA purchased from Malvern Instruments Ltd. (Malvern, UK). Cuvettes measuring $10 \times 10 \times 48$ mm (No./Ref 67754) were purchased from Sarstedt (Nümbrecht, Germany) and were filled with 3.5 mL of a sample solution. All measurements were made at an angle of 90° with a laser wavelength of 633 nm. All results are given as mean droplet sizes from five experiments±-standard deviation ($n = 5$).

HPLC Analysis

CsA samples were investigated by HPLC analysis, using an HPLC system with an HPLC pump type ERC-64A, a UV detector ERC-7210, a degasser ERC CIM 3312 (Erma Cr, Inc.), an Autochrom M 300 Benchtop HPLC gradient controller, and an Autochrom Dynamic mixing chamber M300 from ERC (Alteglofsheim b. Regensburg, Germany), as well as a Basic-Marathon autosampler from Spark (Holland), an oven Shimadzu CTO-2A, and the software Shimadzu Class-VP, version 5.01, for data analysis from the Shimadzu Corporation (Shimadzu Deutschland GmbH, Duisburg, Germany). A C-18 reversed-phase analytical column for CsA was purchased from ClinRep (Recipe Chemicals+Instruments, Munich, Germany; Lot Nos. 53037 and 53043).

Samples of 100 μL were injected via an automatic autosampler and injector. The mobile phase consisted of 220 parts acetonitrile, 80 parts methanol, and 120 parts water. An oven temperature of 75°C was needed for analysis, and a flow rate of 1.0 mL/min resulted in retention time of 6 min for CsA. The absorbance was measured at 205 nm. External standards were used to convert the measured peak areas into concentration units.

Stock Solution

A stock solution was prepared by dispersing a 100 mg soft gelatine capsule in 400 mL of artificial gastric juice. After the capsule contents were released, the solution was separated from the gelatine capsule, and the empty capsule was washed with a few milliliters of gastric juice. This was performed to prevent the shell material from effecting the HPLC analysis. The solution was diluted to a final volume of 1,000 mL.

Distribution of Cyclosporine A Between an Aqueous Phase and Different Oils

Four milliliter of the stock solution were diluted with 6.0 mL of artificial gastric juice and used as a reference solution containing 40 μg/mL of CsA. A sample solution was prepared in the same way by adding 1 g of oil to the aqueous solution. To achieve a homogenous emulsion, the sample solution was vortexed on a Heidolph Reax 2000 for 25 s. Afterward, the emulsion was again separated in a GS-15R centrifuge bought from Beckman at 5500 rpm for 30 min at room temperature. The clear gastric juice phase was separated immediately from the lipid phase to avoid further distribution of CsA between the phases. One

hundred microliter of the aqueous phase were diluted with 90 μL methanol 70% and used for HPLC injection. All results are given as means of 10 independent experiments ± standard deviation ($n = 10$).

Distribution of Cyclosporine A Between a Hydrophilic Phase and a Fat-Rich Meal

To perform the experiment under realistic conditions that prevail during a therapy with CsA, a small calculation was made to approximate the average dose of CsA for an average patient. Maintenance therapy for renal transplant recipients amounts to a dose of 2 to 6 mg/kg/day of CsA. The daily dose of CsA should always be given in two divided doses. If an average patient weights 70 kg and receives two 100-mg capsules per day, his total intake of CsA lies within the range of the maintenance therapy dosage.

For sample preparation, one capsule (representing a single dose) of CsA was dissolved in 200 g of artificial gastric juice and mixed with standardized meal after removing the soft gelatine capsule from the solution. After diluting the mixture to a total of 1000 g with artificial gastric juice, the sample was incubated for 60 min in a water bath at 37°C, with stirring consistently every 10 min. Forty milliliter of the prepared solution were centrifuged for 30 min at 5500 rpm at room temperature using a GS-15R centrifuge from Beckmann. To avoid further distribution of CsA between the phases, the clear gastric juice phase in the middle of the receptacle was separated immediately from the remains. Five hundred microliter of the aqueous phase were diluted with 4.5 mL methanol 70%. For the following HPLC analysis, 100 μL of the methanol solution were again diluted with 900 μL methanol 70% and used for HPLC injection.

An incubated standard meal without any added CsA and a 100-mg CsA capsule dissolved in 1000 g artificial gastric juice served as reference solutions. Reference solutions and sample solutions were diluted in the same way prior to HPLC injection. All results are given as means ± standard deviation of three independent experiments ($n = 3$).

Statistical Analysis

All statistical tests were carried out using SPSS for Windows, version 10.0. It was further assumed that all results were normally distributed.

We refrained from statistically comparing the data taken from the droplet-size measurements because a small underlying variation is inherent in the results, depending on the measurement method rather than on actual changes in particle sizes. Calculations could indicate statistical differences between PCS test results that would lead to a wrong overall impression of the results.

In the following experiments, we concentrated on showing differences between the Sandimmun Optoral formulation and the generic products. We, therefore, focused the statistical comparison on the results obtained from the generic formulations and the established Optoral product, in particular, on the distribution of CsA in the aqueous phase and the lipophilic phase. The experimental data were evaluated by one-way analysis of variance (ANOVA) ($\alpha = 0.05$) in conjunction with Tukey's post hoc range test. The resulting p values designate the level of significance. All results are expressed as arithmetic means ± standard deviation.

RESULTS

Determination of Droplet Size

Tarr and Yalkoswsky suggested that the bioavailability of CsA administered as an olive oil emulsion could possibly be increased by enhancing its rate of absorption through the reduction of emulsion droplet size. Because pancreatic lipase only acts at the interface of oil droplets, a small emulsion droplet size enhances the breakdown of triglycerides that carry the drug, and therefore, facilitates a rapid drug release from the vehicle (Tarr & Yalkowsky, 1989).

Because different emulsion droplet sizes and different galenic formulations have an effect on drug absorption, we compared the contents of the gelatine capsules using PCS to show differences or common features between the formulations concerning micelle and emulsion droplet sizes. All samples were measured using the Zetasizer 3000HS_A, except the Sandimmun samples, because Sandimmun forms a coarse oil-in-water emulsion, which cannot be characterized using PCS (Humberstone & Charman, 2001).

A comparison of droplet and micelle sizes is given in Fig. 1, showing differences in droplet sizes between second- and third-generation products after dispersion in artificial gastric juice.

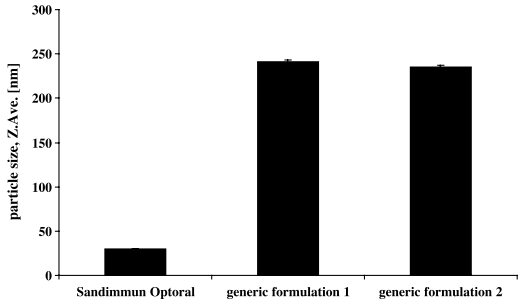

FIGURE 1 **Mean Droplet Size Detected in Artificial Gastric Juice (n = 5 ± SD).**

Distribution of Cyclosporine A Between Different Lipophilic Phases

In the past, it has been shown that food can have an effect on the absorption of the highly lipophilic molecule CsA after oral administration (Kovarik et al., 1993). Changes in the absorption of CsA can result either in underimmunosuppresion or in CsA-related toxicity in patients. To reduce the variability in CsA absorption, patients were required to administer CsA within a consistent schedule with regard to food intake. The food effect seemed to depend on the fat content of the meal and the composition of lipids in the food (Tan et al., 1995). It soon became clear that high fat content food increased the bioavailability of CsA when given as an emulsion (Sandimmun) compared with microemulsion formulations (Gupta & Benet, 1990; Mueller et al., 1994a,b; Tan et al., 1995). Apparently, the behavior of CsA toward lipids and high fat content food is formulation dependent. Taking these aspects into consideration, we focused on the question concerning probable differences that might appear in CsA partitioning from the examined formulations in different oils because CsA absorption depends on amount and composition of the lipids present. We compared the formulations with respect to their distribution and partitioning in oils that are used as pharmaceutical excipients and in nutrition.

We chose olive oil, corn oil, and vegetable oil for our tests. The major triglyceride component of corn oil is linoleic acid. Olive oil, in contrast, primarily contains triglycerides consisting of oleic acid and palmitic acid. This experiment may give information about the susceptibility of CsA from the formulations toward different lipids.

We expected to see differences between the Sandimmun and the Optoral formulations in this test, but we were furthermore interested in how the generic products behave in the presence of different lipids compared with the first and second generation of CsA preparations.

In the subsequent experiments, we compared the distribution of CsA from pharmaceutical formulations between the artificial gastric juice phase and the different oils. Figure 2 shows the CsA contents of the gastric juice phases after overlayering and homogenizing the different formulations with 1 g of the various oils.

In Fig. 2, the statistically significant differences in the behavior of a generic CsA formulation and Sandimmun toward the different oils are marked. The second generic formulation behaves substantially different on contact with olive oil compared with corn oil ($p = .045$). Further significant differences were

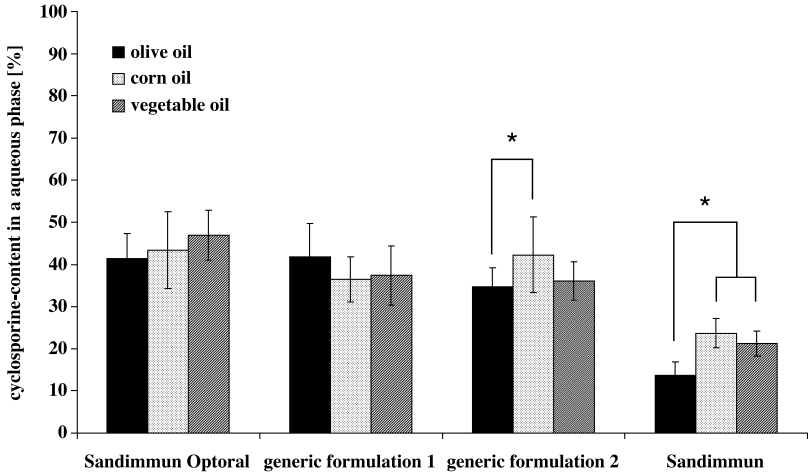

FIGURE 2 **Mean Cyclosporine A Content in the Gastric Juice Phase. Statistically Significant Differences are Marked with * (p = .045); (n = 10 ± SD).**

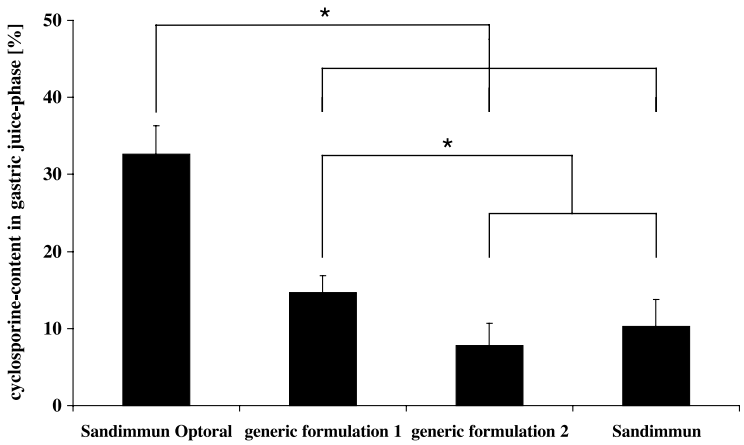

FIGURE 3 **Mean Cyclosporine A (CsA) Content of Gastric Juice Phase After Mixing CsA Capsule with a High Fat Content Food. Statistically Significant Differences are Marked with * ($p < .01$); ($n = 3 \pm SD$).**

shown for the innovator product Sandimmun when olive oil samples were compared with corn oil and vegetable oil samples ($p < .001$). No differences were found on comparing Sandimmun Optoral and the generic CsA formulation 1 concerning their behavior and distribution in the different oils. There are only slight or no differences between the behavior and susceptibility of the CsA formulations toward the oils. Furthermore, it can be seen that the average cyclosporine content in the aqueous phase is about 25% for the Sandimmun formulation and about 35–45% for the preparations of the second- and third-generation products.

In another experiment, we were examining the postulation that high fat content foods have an influence on CsA absorption when the Sandimmun formulation is administered, but that the adsorption from the Sandimmun Optoral formulation is independent of concomitant food intake. Studies in healthy volunteers showed a higher CsA absorption profile when generic CsA formulations were administered with a concomitant food intake than under fasting conditions, as well as differences in CsA absorption from the second-generation formulation (Johnston et al., 2004).

Therefore, we determined the distribution of CsA between an aqueous phase and a high fat content food using simple test conditions that approach the prevalent conditions in the gastrointestinal tract when food is digested.

Figure 3 shows the CsA concentration in the artificial gastric juice phase after mixing CsA preparations with a high fat content food. Sandimmun Optoral has the highest CsA content (32.62%) in the aqueous phase in relation to the other three products. When comparing the results, significant differences in partitioning can be found between Sandimmun Optoral and the generic formulations, as well as between Sandimmun Optoral and the corn oil-based formulation Sandimmun ($p < .001$). Further significant differences were found between the two generic CsA formulations and Sandimmun ($p < .01$). In contrast, no differences were found between generic product 2 and the preparation from the first generation of CsA formulations. The results show that differences between the generations of formulations with respect to the distribution of CsA in the presence of high fat content food exist.

DISCUSSION

By looking at the development and use of new therapeutic CsA formulations over the past several years, one can see that several problems have arisen that were caused by the drugs' narrow therapeutic index, the unpredictable inter- and intraindividual variability, and erratic drug absorption profiles (Holt et al., 1994; Kahan et al., 1996; Mueller, 1994; Olyaei et al., 1997).

For example, several studies showed that when a conversion from preparations of the first generation to the microemulsion formulation representing the second generation of CsA formulations was performed at a 1:1 dose ratio, a significant increase in CsA exposure was produced, which, in the long run, exposes patients (especially CsA low absorbers) to an increased risk of side effects, particularly nephrotoxicity (Frei et al., 1998; Gaspari et al., 1998; Neumayer,

1996; Neumayer et al., 1994). Although the microemulsion formulation improved therapy, a simple changeover in allograft patients from traditional Sandimmun to the new formulation was not without consequences (Neumayer et al., 1994).

Further problems arose when it came to developing generic formulations. Generic drug products are usually encouraged by health authorities for economic reasons and, because transplant recipients require lifelong treatment, which is expensive, generic CsA formulations are of great interest.

In medical publications, concerns about the U.S. Food and Drug Administration's (FDA's) standards for bioequivalence of generic formulations of critical dose drugs, such as CsA, have been voiced and discussed in the past (Haug & Wimberly, 2000; Johnston & Holt, 1998, 2001; Johnston et al., 1997; Kahan, 1999). It became clear that the standard bioequivalence criteria usually used for approving generic products has major limitations when it comes to reviewing generic CsA products. In general, the evaluation of generic products in patient populations or in steady state is not required. This means, for example, that differences in CsA absorption between healthy volunteers and transplant recipients are not addressed (Johnston et al., 2004). The problems that can occur in developing a generic CsA formulation may be similar to the issues raised by the SangCya solution produced by Sangstat. The oral solution SangCya, a nanodispersion containing ethanol, propylenglycol, and polysorbate 80, proved to be equivalent to Sandimmun Neoral, was withdrawn from the market on a precautionary basis in July 2000, because of a reduction in bioavailability when administered with apple juice. This occurrence made it clear that concerns about the bioequivalence guidelines for CsA products were justified and that new generic formulations may behave contrary to expectations in clinical use.

This study demonstrated that formulations that have been proven to be bioequivalent using the standard criteria do not necessarily behave identically when compared in simple physical tests. In light of the aspects mentioned previously and the fact that the emulsion droplet size and high fat content food influence the absorption of CsA, more or less, depending on the formulation, we compared the contents of available cyclosporine A gel capsules with regard to their droplet and micelle size with the distribution between hydrophilic and lipophilic phases. It is remarkable that the generic products, which have identical ingredients and show equal droplet sizes, show a statistically different partitioning of CsA between the high fat content food and the aqueous gastric juice phase. Differences between Sandimmun Optoral and the generic products, however, might be attributable to the emulsifying properties of the additives in Sandimmun Optoral (corn oil mono-, di-, and triglycerides) or the use of different solvents, such as propylenglycol, instead of macrogol 400. Effects may be further influenced by the relative amounts of each pharmaceutical excipient. Still, the question as to whether these aspects are of any clinical relevance cannot be answered by the described experiments.

By using PCS, we compared the micelle and emulsion droplet sizes of the microemulsion formulation with the generic formulations. We discovered that the droplet sizes of the new generic products, which seem to form neither a microemulsion, such as the Sandimmun Optoral formulation, nor a coarse oil-in-water emulsion when dissolved in the artificial gastric juice, are approximately 10 times the size of the microemulsion particles from the Optoral formulation and considerably smaller than the emulsion droplets from the innovator product. The question concerning whether this result has any effect on CsA absorption from the generic formulations remains unanswered.

We further tested the distribution of CsA with the help of HPLC analysis between different lipids and aqueous phases, and found that differences between the formulations in their behavior toward different oils, as well as toward a high fat content-food, can be detected. The content of the microemulsion formulation itself proved to be the least affected with the high fat content food when compared with the generic formulations and the preparation from the first generation of CsA formulations. Although the test conditions that were used were chosen in view of prevalent physiological conditions, one must keep in mind that they cannot simulate the complexity and dynamics of the in vivo situation.

CONCLUSION

One of the major limitations of standard bioequivalence studies concerning CsA is the fact that no

evaluation of generic formulations in the patient population is required. Because the absorption of CsA differs between healthy volunteers and transplant recipients, data from patient populations should absolutely be provided. The little data currently available from in vivo studies comparing the second-generation product to new generic formulations indicates that generic formulations may not be therapeutically equivalent to the established Sandimmun Optoral formulation.

Still, further studies in transplant patients are necessary to evaluate the topic of CsA generic products. Until more data are available, it is recommended that any switching between or to CsA formulations of the second and third generation should be undertaken with supervision by the transplant physician only (Johnston & Holt, 2001, Pollard et al., 2003). Owing to the lack of comparative data concerning the transfer of patients to or between generic CsA formulations, it would be speculative to put the results obtained from this work into perspective to any bioequivalence studies. When compared under simple physical test conditions, the established CsA formulations and new generic products show significant differences. Whether the differences in micelle and emulsion droplet size and distribution between an aqueous phase and a high fat content food are of clinical relevance remains to be scrutinized.

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