

# Relative Bioavailability of Two Oral Dosage Forms of Cyclosporine A

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## Abstract

Bioequivalence of two oral dosage forms of cyclosporine A\* oral solution and soft gelatin capsules was evaluated in 18 healthy adult male volunteers. Both products were administered in single dose in a randomized crossover manner and serial venous blood sampling was performed at time 0 (before administration) and at 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8 and 12 hours after administration. Mean ( $\pm$ sd) Cmax, Tmax and AUC<sub>0-12</sub> were 858.06  $\pm$  230.02 ng/ml, 1.42  $\pm$  0.46 hours and 2995.78  $\pm$  591.08 ng.hr.ml<sup>-1</sup> respectively for the oral solution and 792.94  $\pm$  222.96 ng/ml, 2.09  $\pm$  0.32 hours and 3266.71  $\pm$  812.75 ng.hr.ml<sup>-1</sup> respectively for the soft gelatin capsules. Relative bioavailability for soft gelatin capsules was 109% with reference to oral solution.

## Introduction

Evaluated product is a galencial formulation of cyclosporine A\* available as oral solution of cyclosporine A USP-modified (solution of cyclosporine A in a pharmaceutically acceptable base consisting of solvents and emulsifiers which on dilution (*in-vivo*), keep the drug in solubilized form; hence differing in this aspect from normal solutions in which active form of cyclosporine A is unaltered), The solution contains hydrophilic and lipophilic solvents and co-solvents which allocate cyclosporine A in an optically clear pale yellow solution. The product has been comprehensively evaluated through numerous studies for its bioavailability performance in volunteers and pre/post renal transplant patients, and all studies indicate similar absorption with the widely marketed cyclosporine Neoral.

The current study was aimed at the assessment of relative bioavailability of cyclosporine A from the two manufactured dosage forms. Soft gelatin capsules was the test form compared with oral solution under appropriate fasting restrictions.

## Material and Methods

Eighteen healthy male volunteers, age 29.1  $\pm$  5.8 years (mean  $\pm$  sd) and weighing 57.3  $\pm$  8.2 kg (mean  $\pm$  sd) participated in the study. Written informed consent was obtained from all volunteers after educating them about the nature and details of the study. The subjects were evaluated for health on the basis of medical history, physical examination and the biochemical / hematologic tests.

## Study design

The study protocol was approved by the Institutional Ethical Review Committee. The study was a single dose, two way non-crossover design. Cyclosporine A oral solution and soft gelatin capsules were administered in two separate phases of the study and each phase was spaced with a washout period of eight weeks. Subjects were given an overnight fast and standard diet was given at 3 hours, 8 hours and 12 hours as breakfast, lunch and dinner respectively. 1.8 ml of oral solution equivalent to 180mg of cyclosporine A and 25x7 soft gelatin capsules equivalent to 175mg of cyclosporine A were administered with a glass of water. Following drug administration whole blood samples (3ml) were collected at time 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, and 12 hours after initial collection of the time '0' sample just before drug administration with the help of venous catheter cannulated in the cubital vein of the arm. All blood samples were collected in EDTA lined glass tubes.

**Table 1. Mean ( $\pm$ SD) calculated bioavailability parameters following administration of cyclosporine A.**

Product	Cmax (ng/ml)	Tmax (hours)	AUC <sub>0-12</sub> (ng.hr.ml <sup>-1</sup> )	T <sub>1/2<math>\beta</math></sub> (hours)
Oral solution	858.06 $\pm$ 230.02	1.42 $\pm$ 0.46	2995.78 $\pm$ 591.08	4.80 $\pm$ 1.58

Soft gelatin capsules	792.94 ±222.96 (P>0.05)	2.09 ±0.32 (P>0.05)	3266.71 ±812.75 (P>0.05)	4.87 ± 1.73
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Whole blood cyclosporine A samples were assayed using a radio immuno assay which was validated according to manufacturer's specifications (Incstar Corporation - USA).

Bioavailability parameters of C<sub>max</sub>, T<sub>max</sub> and AUC<sub>0-12</sub> were obtained from the blood concentration vs time data using standard methodology and trapezoidal rule.

All available data was subjected to student 't' test at 0.05 level of significance.

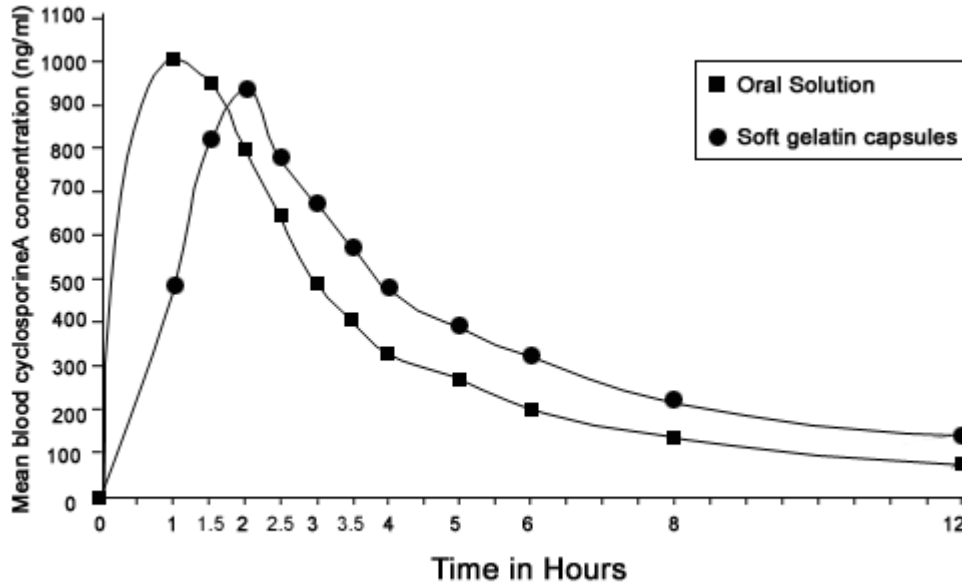


Fig 1: Mean whole blood CyclosporineA concentrations from soft gelatin capsules and oral solution in 18 healthy adult male volunteers

## Adverse drug reactions

Symptoms for adverse events included drowsiness, sedation, abnormal hypotension, ataxia, vertigo, headache, confusion, mental depression, dysarthria, changes in libido, tremors, visual disturbances, urinary retention, gastrointestinal disturbances, amnesia, changes in salivation, paradoxical excitation and disinhibition, hypersensitivity reaction, flushed face, palpitation, dry nose and any other observed.

## Results

Bioavailability parameters, viz C<sub>max</sub>, T<sub>max</sub> and AUC<sub>0-12</sub> for both formulations are shown in Table 1. The mean C<sub>max</sub> with oral solution was 858.06 ng/ml compared to 792 ng/ml achieved with soft gelatin capsules. The difference is not statistically significant.

The mean T<sub>max</sub> with oral solution was 1.42 hours compared to 2.09 hours with soft gelatin capsules. The difference barely misses statistical significance at 5% level. The mean AUC<sub>0-12</sub> with oral solution was 2995.78 ng.hr.ml<sup>-1</sup> compared to 3266.71 ng.hr.ml<sup>-1</sup> observed with soft gelatin capsules. The difference is again not statistically significant.

The results showed that both preparations are bioequivalent with relative bioavailability from soft gelatin capsules of 109%. The mean elimination half life was 4.80 hours and 4.87 hours for solution

and soft gelatin capsules respectively. No adverse effect was observed in any volunteer.

Fig. 1 shows the mean blood cyclosporine A concentration time curves for both preparations. It is apparent that cyclosporine A absorption from soft gelatin capsules is slower and more sustained compared to that from oral solution.

## Discussion

Cyclosporine A is vital life saving drug and is known to present bioavailability problems. It is therefore, necessary to establish bioequivalence of all marketed preparation. Bioequivalence of the tested formulation has already been demonstrated in comparison with the innovator product.

A new capsule formulation has been found to be more convenient and has achieved wide acceptance among patients. In this study bioequivalence of cyclosporine A from soft gelatin capsules with that from oral solution has been established. The doses administered were not exactly the same. Dose in capsules was 2.78% lower. In spite of this the relative bioavailability from capsules was 109%. The T<sub>max</sub> was delayed in the case of capsules and Fig I clearly shows that absorption from capsule form is delayed but more sustained. This may be a significant advantage and efficacy comparisons seem warranted. Both preparations were well tolerated and no adverse events were observed or reported.

In conclusion, the soft gelatin capsule formulation of cyclosporine A is bioequivalent to oral solution.

## References

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\*The evaluated Cyclosporine A product was Panimun Bioral® manufactured by Panacea