Comparison of the in Vitro and in Vivo Release of Digoxin from Four Different Soft Gelatin Capsule Formulations

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Received August 10, 1978—Final October 17, 1978

A blinded, four-treatment crossover study in 16 normal adult male volunteers compared plasma concentrations and urinary excretion of digoxin, measured by radioimmunoassay, after oral administration of soft gelatin capsule formulations of digoxin. Four 0.4-mg formulations with different in vitro "burst times" and dissolution rates were administered, with 2-week intervals between treatments. The two capsules with lowest in vitro burst times (2.9 and 16 min) gave comparable in vivo results. The other two capsules, with in vitro burst times of 62 and 229 min, produced significant delays in digoxin absorption. In vitro—in vivo correlations were obtained by comparing the logarithm of the in vitro burst time with time to peak plasma level and the time to the first measurable plasma level (> 0.05 ng/ml). Also, the mean time to peak plasma level correlated with the logarithm of the time required to release either 50% or 85% of the digoxin in vitro. No significant changes were found in the amount of digoxin absorbed from each capsule as determined by urinary excretion or AUC₀⁻∞.

KEY WORDS: digoxin bioavailability; in vitro—in vivo correlations; digoxin radioimmunoassay; plasma concentrations and urinary excretion of digoxin; gelatin capsule formulations.

This work was supported by Arnar-Stone Laboratories, Inc., McGraw Park, Illinois.
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INTRODUCTION

Previous investigators (1–5) have reported that soft gelatin capsules containing digoxin in solution have enhanced bioavailability associated with reduced between-subject variability in digoxin plasma concentrations compared with digoxin tablets. Stoll et al. (6) reported that digoxin soft gelatin capsules, prepared by Arnar-Stone, Inc., showed considerably less within-subject variability than digoxin tablets when both capsules and tablets were administered twice to each subject of the panel. It should be noted that treatments B₁ and B₂ in the study of Stoll et al. (6) employed the same digoxin soft gelatin capsule as treatment A in the study reported in this article. The purpose of this investigation was to establish in vitro quality control limits for the digoxin soft elastic gelatin capsules by evaluating the in vivo absorption of capsules with varying in vitro release rates.

EXPERIMENTAL

Human Study

Sixteen adult male volunteers with no known disease who weighed between 61 and 92 kg and were between 21 and 34 years of age were selected. Before each subject could be included in the study, a complete physical examination, routine blood analysis and urinalysis, and electrocardiogram were carried out. As a screening procedure, values for the tests were required to be in the normal range. Informed consent was obtained from each subject.

A recent drug history was taken for each prospective subject. All subjects participating in the study received no barbituates or other enzyme-inducing agents for a period of 30 days preceding initiation of the study and none concurrent with it. They received no other medication or alcoholic beverages for a period of 7 days before initiation of the study and none during the study.

At 9 p.m. each night before dosing with digoxin, the subjects ate a late snack. From 10 p.m. the night before dosing to 4 hr after dosing, the subjects fasted. On the days of dosing they ate standard lunches and dinners which were not high in fat or protein content. Subjects drank lemonade and received no tea or coffee on the day of dosing or throughout the period of blood and urine collection.

The human study was performed "double blind." Arnar-Stone Laboratories, Inc., sent to The University of Michigan four bottles of capsules simply labeled A, B, C, and D. These were administered to the subjects as indicated by the study plan shown in Table I. The first day of one