PAPERS AND ORIGINALS

Comparative Study of the Absorption, Plasma Levels, and Urinary Excretion of the "New" and the "Old" Lanoxin

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British Medical Journal, 1973, 1, 695-697

Summary

A comparative study was performed of the absorption, the plasma level at equilibrium, and the urinary excretion of digoxin using two types of Lanoxin tablets, those produced before and after the 1972 alteration of the tablet manufacture.

After a single dose the absorption rate of the new tablets was about twice as great as the old, both in young subjects and in the elderly patients. There were no significant differences in the plasma levels of digoxin for the two tablets 15 hours after the last administration in patients on an equal maintenance dose. The urinary excretion of digoxin increased about 40% when the "old" Lanoxin was replaced by the "new." In elderly patients a daily dose of 0.125 mg twice daily of the new tablets should be sufficient to reach the therapeutic range. Young people need a higher dosage. If the kidney function is reduced by as much as 50% the dose should be reduced.

Introduction

In May 1972 Burroughs Wellcome & Co. altered the production process for their digoxin tablets (Lanoxin). The absorption of the new tablets has been presented by the manufacturer as being about twice that of the tablets produced before May 1972. In this study a comparison has been made of the absorption, the plasma levels at equilibrium, and urinary excretion of Lanoxin manufactured before, L 1 (batch No. 0383 0, 0042 0), and after, L 2 (batch No. 1546 X), the alteration of the tablets.

Subjects

Four groups of subjects were studied.

Group 1.—Twelve healthy fasting subjects (mean age 28 years, range 24-36) were given 0.5 mg of L 1 by mouth. The fast continued for two hours. Blood samples were taken before the dose, every 15 minutes during the next two hours, and thereafter at intervals of 30, 60, and 60 minutes. Four or five days later the procedure was repeated with 0.5 mg of L 2.

Group 2.—Four healthy fasting subjects (mean age 37 years, range 28-52) were given 1 mg of L 1 by mouth. Blood samples were taken before the dose and at intervals during 24 hours. Four days later the same procedure was repeated with 0.5 mg of L 2.

Group 3.—Fourteen patients (mean age 72 years, range 65-82), all suffering from congestive heart failure, had been treated with 0.125 mg of L 1 twice daily (8.30 a.m. and 5 p.m.) for at least eight days before the study started. On the first day of the study the concentration of digoxin in plasma and creatinine in serum was determined at 8 a.m. At 8.30 a.m. each of seven of the patients were, in a fasting state, given an oral dose of 0.25 mg L 1. Thereafter the plasma levels of digoxin were determined at the same intervals as in group 1. The urinary excretion of digoxin was determined concurrently in a 24-hour urine collection. From day two L 1 was replaced by L 2 given in a dose of 0.125 mg twice daily for all the patients. On day 10 the same procedure as on day 1 was repeated with L 2 for the seven patients mentioned above.

Group 4.—Eleven healthy subjects (mean age 35 years, range 21-53) were all given 0.75 mg of L 2 by mouth on the first day, and later 0.125 mg twice daily at 8.30 a.m. and 5 p.m. Digoxin in plasma was determined at 8 a.m. on the ninth day of the study. Urinary excretion of digoxin was determined in a 24-hour urine collection, started at 8 a.m. on the same day in eight of the subjects.

Methods

Digoxin in plasma and urine was determined by radioimmunoassay (Falch, 1973a, 1973b). In order to evaluate the quantity of digoxin absorbed, the areas beneath the curve for

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plasma concentration throughout the time period was cut out from a paper and weighed. Creatinine was measured using a Technicon AutoAnalyzer (method N 11).

Results

The consecutive plasma concentrations of digoxin for group 1 are shown in fig. 1. The peak value for L 1 (1.04 ng/ml) was found 60 minutes after the dose, and for L 2 (2.15 ng/ml) 75 minutes after the dose. The disappearance rate for L 2 was greater than for L 1 (plasma half-life for L 2 135 minutes, for L 1 270 minutes). The mean ratio of the areas under the absorption curves was 2.5:1 (range 1:1 5.2:1). Nausea was observed in five of the subjects 75 minutes after the dose of L 2. The digoxin levels of these subjects when nausea occurred were not higher than those for the other seven (mean 2.43 ng/ml compared with mean 2.40 ng/ml).

FIG. 1—Concentration of digoxin from 12 healthy subjects after ingestion of Lanoxin tablets. Open columns indicate concentration of digoxin after a dose of 0.50 mg of "new," and dark columns the concentrations after a dose of 0.50 mg of "old" Lanoxin. S.E. of mean is indicated by vertical lines.

The consecutive plasma concentrations of digoxin for group 2 are shown in fig. 2. The peak level for L 2 is higher than for L 1, but after the equilibrium plateau is obtained the curves are almost parallel. The mean ratio of the areas under the curves was 1.06:1 (range 0.84:1 — 1.38:1) in the favour of L 2.

FIG. 2—Plasma levels of digoxin from four healthy subjects (mean values) after ingestion of 1.0 mg of "old" Lanoxin (broken line) and four days later 0.50 mg of "new" Lanoxin (unbroken line).

The difference in absorption in the patients on a constant maintenance dose (group 3) is shown in fig. 3. There was little difference in their plasma levels before the dose was

FIG. 3—Dark columns show plasma concentration of digoxin after ingestion of 0.25 mg of "old" Lanoxin in seven patients treated with maintenance dose of 0.125 mg twice daily of same drug. Open columns show plasma concentration of digoxin after ingestion of 0.25 mg of "new" Lanoxin in same patients after one week's treatment with 0.125 mg twice daily of "new" drug.

given. Peak value for L 1 (1.14 ng/ml) was obtained 90 minutes after the dose, and for L 2 (1.90 ng/ml) 60 minutes after the dose. A second peak was observed 150 minutes after the dose of L 2 in all the patients. They had taken their breakfast 30 minutes before the second peak was observed. When the areas of the absorption curves over the fasting level were compared a mean ratio of 2.01:1 (range 0.86:1—3.14:1) was found.

The plasma levels of groups 3 and 4, observed after the equilibrium plateau was obtained, are given in table I.

TABLE I—Plasma Levels of Digoxin for Group 3 Patients, Treated with the New and the Old Lanoxin, and Group 4 Subjects, Given the New Lanoxin

Maintenance dose:	Old Lanoxin	New Lanoxin	
	0.125 mg b.i.d.	0.125 mg b.i.d.	
Group (No. in group)	3 (14)	3 (14)	4 (11)
Digoxin in plasma (ng/ml):			
Mean (S.E. of mean)	0.94 (0.12)	1.03 (0.13)	0.47 (0.04)
Time since last dose (hr)	15	15	15
Creatinine in serum (mg/100 ml):			
Mean (S.D.)	1.0 (0.3)		
Mean age (years)	72	72	35

The urinary excretion of digoxin of the different groups is shown in table II.

TABLE II—Urinary Excretion of Digoxin for Group 3 Patients, Treated with the New and the Old Lanoxin, and Group 4 Subjects, Given the New Lanoxin for 8-10 Days

Maintenance dose:	Old Lanoxin	New Lanoxin	
	0.125 mg b.i.d.	0.125 mg b.i.d.	
Group (No. in group)	3 (7)	3 (6)	4 (8)
Digoxin excreted (μg/24 hr):			
Mean (S.E. of mean)	81.3 (3.7)	115.3 (13.9)	115.7 (3.3)
Digoxin excreted as percentage of daily dose	33.2	46.0	46.3

Discussion

Several workers have reported that the absorption of digoxin varies with the brand of tablet given (Lindenbaum *et al.*, 1971; Manninen *et al.*, 1971; Shaw *et al.*, 1972). The rate of excretion and metabolism has, however, not been studied.

It is evident from the observations presented that the rate of absorption of the "new" Lanoxin in normal subjects, as well as in patients on a constant maintenance dose, is about twice that of the "old" (figs. 1-3).

The second peak of the absorption curves observed in the group 3 patients (fig. 3) is probably explained by "biliary recycling." This observation was unexpected and therefore not studied under ideally controlled circumstances with standardized meals and at standardized time after digoxin administration. But the evidence is striking all the same. It may indicate that the drug is excreted in the bile and reabsorbed when food is given. Another explanation is that the bile enhances the absorption of the drug present in the bowel. White *et al.* (1971) found that the absorption of digoxin was reduced when the drug was given after food. It is therefore unlikely that the food by itself increased the absorption and gave the second peak observed.

When the same maintenance dose of L 1 and L 2 was given, there was a little difference in the plasma levels of digoxin 15 hours after the dose (table I). This indicates that the excretion rate or metabolism of digoxin was greater for L 2 than for L 1. Since the urinary excretion was increased only about 40% when L 1 was replaced by L 2 (table II), an increase in metabolism or intestinal excretion is suggested. If the "second peak" observed (fig. 3) represents biliary recycling this indicates that the amount of digoxin excreted in the bile when L 2 was given is important. Because of the rapid absorption of L 2 the level of digoxin in the portal vein and in the liver is higher for L 2 than for L 1 during the first hours after the administration of the drug. The biliary excretion of digoxin must, therefore, be expected to be greater for L 2 than for L 1 as digoxin is eliminated on first order kinetics. A greater biliary excretion of digoxin from the systemic circulation should also be expected for L 2 because of higher plasma levels.

The absorption curves after the dose of 1.0 mg of L 1 and 0.5 mg of L 2 are almost parallel after constant plasma levels were obtained (fig. 2). This suggests that digoxin in plasma from L 1 and L 2 is handled in the same manner. The difference in metabolism and excretion therefore seems to be a matter of plasma concentration.

The constant plasma levels obtained after ingestion of 1.0 mg L 1 ought to be higher than after a dose of 0.5 mg L 2. The equal plasma levels 15 hours after administration of 0.5 mg of L 2 and 1.0 mg of L 1 (group 2, fig. 2) seems to con-

flict with the equal levels 15 hours after the same maintenance dose of L 1 and L 2 given to the patients of group 3 (table I). This might be explained by characteristics of the digoxin assay, since the concentrations after equilibrium in group 2 are at the lowermost end of the range of sensitivity for the radioimmunoassay. A difference in metabolic clearance rate between digoxin given in a single dose and on a constant maintenance dose is, however, possible.

The shape of the absorption curves for L 1 and L 2 is influenced by a difference in absorption rates. Before the equilibrium the new drug shows a faster rate of fall than the old (fig. 2). This might be partly explained by a more rapid excretion of L 2 because of higher concentration. In addition, the slow absorption of L 1 may continue for several hours and thereby influence the curve for its disappearance rate.

The relation of nausea to peak blood levels observed in five of the subjects in group 1, and the more rapid fall off of the new digoxin should be emphasized. This means that L 2 is more toxic than L 1 for only a few hours after the dose is given. It can therefore be recommended that the daily dose be subdivided in order to avoid too high peak levels shortly after the administration.

Our observations do not indicate that the new digoxin should be given in half the dosage of the old, as has previously been recommended. A dose of 0.125 mg twice daily of L 2 given to elderly patients is usually sufficient to reach a plasma level within the recommended therapeutic range between 1 and 2 ng/ml. Young people need a higher dosage. If the kidney function is reduced at least 50% (glomerular filtration rate, renal plasma flow) (Falch, 1973b) the dosage has to be reduced according to the reduction in the kidney function.

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Bubble Stability Test Compared with Lecithin Assay in Prediction of Respiratory Distress Syndrome

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British Medical Journal, 1973, 1, 697-700

Summary

A simple test for surfactant, utilizing bubble stability in ethanol, was performed in 106 samples of amniotic fluid obtained from 94 patients. Of these patients 80

delivered within 48 hours of the collection of the sample. The results were compared with the lecithin concentration in the same amniotic fluid samples and with the quality of respiration in the neonate. The test was "positive," indicating fetal pulmonary maturity, in 37 cases and none of these infants developed respiratory distress syndrome (R.D.S.). In only one of these cases, however, was gestation less than 37 weeks. The test was "intermediate" or "negative" in 43 cases but in 35 of these infants respiration at birth was perfectly normal.

Performed by the method described by its originators, this simple test gives too many false negative results to be of value in routine clinical practice, although a positive result is helpful. The concept of the test is ingenious, however, and further developments may be expected.

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