DIGOXIN AND JEJUNOILEAL BYPASS/Marcus et al.

previous clinical studies, our experience indicates that it is a useful agent and its effectiveness might be enhanced by the simultaneous use of a diuretic. Under the conditions of this study in which a diuretic was not used, no adverse effect on renal function and no change in peripheral renin activity was noted.

References

The Effect of Jejunoileal Bypass
on the Pharmacokinetics of Digoxin in Man

FRANK I. MARCUS, M.D., EDWARD J. QUINN, M.D., HERSCHELLA HORTON, R.N., SHANNON JACOB, R.N., SUSAN PIPPIN, M.S., MARVIN STAFFORD, M.S., AND CHARLES ZUKOSKI, M.D.

SUMMARY Seven subjects who underwent jejunoileal bypass surgery for massive obesity participated in a study to examine the relative bioavailability of digoxin before and one to two months after surgery. They were given a loading dose of 1 mg digoxin in divided oral doses followed by oral maintenance doses of 0.5 mg daily. There were no significant differences in the area under the serum concentration time curve, steady state serum levels or 24 hour steady state excretion of digoxin before and after surgery. We conclude that the bioavailability of digoxin from the Lanoxin tablets employed is not impaired in these patients, although urinary d-xylose and 24 hour fecal fat excretion indicated moderate to severe malabsorption after surgery.

THE EFFECT OF MALABSORPTION STATES on the absorption of digoxin continues to be a controversial subject. Hall et al. found no impairment of digoxin absorption when it was administered as tritiated digoxin in patients with malabsorption states caused by bacterial overgrowth, small bowel disease, pancreatic insufficiency or rapid intestinal transit time. Beermann et al. also found minimal, if any, malabsorption when tritiated digoxin in solution was given orally to five patients with partial gastrectomy, one patient with vagotomy and plastic reconstruction of the pylorus, and one with jejunal colostomy. In contrast, Heizer and co-workers found diminished absorption of digoxin from tablets in eleven patients with various causes for malabsorption including sprue, radiation enteritis, partial resection of the small intestine, pancreatic insufficiency and hypermotility due to excessive laxative ingestion. Their data suggested a positive correlation between digoxin levels and d-xylose absorption. The mean steady state serum digoxin level for the nine patients with other causes of malabsorption was significantly less than that of the control group. The two patients with pancreatic insufficiency had serum digoxin levels that were not different from the controls.

Jejunoileal bypass, performed for morbid obesity, provided us with an opportunity to study the bioavailability of digoxin in the same patients before and after a well defined malabsorption state.

From the Departments of Medicine and Surgery, University of Arizona College of Medicine, Tucson, Arizona. Supported in part by grant-in-aid #74-1085 from the American Heart Association, Grants HLJ 5265-03 and IMO1RR00714 from the National Heart and Lung Institute, and by the The Flinn Foundation, Phoenix, Arizona.

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Subjects and Operative Procedure

Five female and two male patients who were about to have jejunoileal bypass surgery for morbid obesity, consented to participate in the study. The patients’ ages and weights before surgery, weight loss after surgery and time from operation to the second study, are listed in table 1. Six of the seven patients were restudied within 2½ months after surgery. One patient, C.P., was studied in the reverse sequence. Prior to the operation, he weighed 154 kilograms. He lost 73 kilograms after operation, but became weak and had albuminemia, at which time he was first studied. The second investigation was done after reanastomosis when he had gained 22 kilograms. To avoid confusion, the data relating to this patient are listed in the tables to conform with the usual sequence of study, i.e., before indicates that his jejunum and ileum have been reanastomosed. Patients K.W. and B.C. had second postoperative studies 12 months after surgery.

One surgeon performed all the operations which consisted of joining the proximal twelve inches of jejunum, end-to-end, to the ileum six inches from the ileoceleal valve. In patient C.P. the jejunum was anastomosed directly to the cecum because the distal stump of the ileum became ischemic after transection. The distal end of the jejunum was closed and the proximal end of the ileum was anastomosed end-to-side to the ascending colon.

The only medications permitted during the studies were sleeping medications (chloral hydrate, flurazepam hydrochloride) and anti-inflammatory drugs (indomethacin, aspirin, acetaminophen). One patient, H.R., took codeine for relief of arthritic pain during her first study.

Study Protocol

The patients received 1.0 mg of digoxin on the first day (four tablets of digoxin, 0.25 mg). Thereafter, they took 0.5 mg of digoxin (two tablets in the morning) daily for the next eight days. Digoxin was given as Lanoxin tablets (Lot no. 772B). In vitro tests performed by the Burroughs Wellcome Company demonstrated that 69% of digoxin was in solution within one hour. The patients were admitted to the hospital the evening of the seventh day of each study. Twenty-four hour urine collections were obtained on day 9 in order to determine total urinary creatinine and digoxin excretion as well as creatinine and digoxin clearance. Blood samples for steady state serum digoxin levels were drawn 24 hours after the previously administered dose on days 7, 8, and 9. On day 9, blood was also drawn at the following times: ½, 1, 1½, 2, 3, 6, 8, 12 and 24 hours following administration of the 0.5 mg oral dose (fig. 1). The 24 hour area under the serum concentration time curve (AUC) was measured by the trapezoidal rule, and the renal clearance determined by dividing the total amount of digoxin eliminated in the urine during the 24 hours by the AUC for the same time interval. Blood was drawn each morning for five consecutive days after the last dose of digoxin was administered in order to calculate the biologic half-life of digoxin.

Tests of malabsorption included serum carotene, total protein and serum albumin. Two consecutive 24-hour collections of stool were analyzed for fecal fat. The dietary intake of fat was not controlled. A d-xylose tolerance test was performed on day 10. Urine was collected and analyzed for d-xylose after administration of 5 g of d-xylose dissolved in 250 ml of water. The serum concentration of d-xylose was measured 1, 2, 5, and 8 hours after d-xylose was given. Serum drawn on day 8 was analyzed for blood urea nitrogen, creatinine, glucose, sodium, potassium, CO₂, chloride, SGOT, thyroxine and prothrombin time. A complete blood count and urinalysis were also obtained. The same protocol was repeated after surgery.

Methods

Details of the tritium radioimmunoassay for digoxin in plasma have been described previously. The standard solutions were prepared in human pooled plasma in a concentration of 0–4 ng/ml. Digoxin concentration in urine was assayed as follows. One ml of urine was diluted with 19 ml of plasma. This solution was assayed in triplicate using 0.5 ml aliquots. An equal amount of blank urine was added to each plasma standard. The digoxin radioimmunoassay involved incubation of the sample with digoxin specific antiserum and 3H-digoxin. Dextran-coated charcoal was used to separate unbound isotope from that bound to antiserum. The supernatant containing the antibody-3H-digoxin complex was counted in a liquid scintillation spectrometer. The standard curve for each assay was a straight line obtained by plotting the reciprocal of the disintegrations per minute versus digoxin concentration at each standard point. The digoxin concentrations for the patient serum or urine samples were calculated after the slope and the intercept of the standard curve were obtained.

Total serum protein was determined by the biuret method; serum albumin by electrophoresis; serum carotene, serum d-xylose and urine d-xylose by spectrophotometric analysis. Normal values for serum carotene are 60–200 µg/dl. Normal subjects excrete one or more grams of d-xylose in urine within five hours of the oral dose. The normal values for fecal fat are between 5 and 10 g.

The data were statistically analyzed using the Student’s paired t-test.

Results

Jejunooileal bypass in our patients caused definite malabsorption as evidenced by a significant decrease in urine
Table 1. *Patient Information and Absorption Studies*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Weight before (kg)</th>
<th>Weight change (kg)</th>
<th>Time from ileal bypass</th>
<th>Serum albumin (g/100ml)</th>
<th>Fecal fat (g/24hr)</th>
<th>Serum carotene (µg/100ml)</th>
<th>Urine d-xylene excretion (g/hr)</th>
<th>Serum d-xylene peak conc. (mg/100ml)</th>
<th>AUC (0-24 hr) (mg x hr/100ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K.W.</td>
<td>30</td>
<td>152.3</td>
<td>6.0</td>
<td>1 mo after</td>
<td>3.9</td>
<td>6.2</td>
<td>168</td>
<td>2.9</td>
<td>6.0</td>
<td>32.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12 mo after*</td>
<td>7.1</td>
<td>4.4</td>
<td>25.0</td>
<td>0.6</td>
<td>5.5</td>
<td>16.8</td>
</tr>
<tr>
<td>S.R.</td>
<td>37</td>
<td>171.2</td>
<td>12.5</td>
<td>1 mo after</td>
<td>7.1</td>
<td>3.4</td>
<td>28.0</td>
<td>2.2</td>
<td>27.0</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12 mo after*</td>
<td>7.1</td>
<td>3.4</td>
<td>28.0</td>
<td>2.2</td>
<td>27.0</td>
<td>—</td>
</tr>
<tr>
<td>H.R.</td>
<td>55</td>
<td>127.9</td>
<td>8.5</td>
<td>Before</td>
<td>5.3</td>
<td>3.0</td>
<td>4.9</td>
<td>93</td>
<td>18.0</td>
<td>64.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 mo after</td>
<td>5.2</td>
<td>2.7</td>
<td>52.0</td>
<td>60</td>
<td>10.5</td>
<td>56.0</td>
</tr>
<tr>
<td>B.C.</td>
<td>32</td>
<td>133.7</td>
<td>19.2</td>
<td>Before</td>
<td>6.3</td>
<td>3.3</td>
<td>2.2</td>
<td>110</td>
<td>2.2</td>
<td>24.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2½ mo after</td>
<td>5.8</td>
<td>3.0</td>
<td>8.0</td>
<td>16</td>
<td>0.5</td>
<td>6.0</td>
</tr>
<tr>
<td>S.R.</td>
<td>30</td>
<td>173.6</td>
<td>16.9</td>
<td>Before</td>
<td>6.9</td>
<td>3.5</td>
<td>33.0</td>
<td>14</td>
<td>0.8</td>
<td>10.0</td>
</tr>
<tr>
<td>G.F.</td>
<td>39</td>
<td>172.5</td>
<td>24.2</td>
<td>Before</td>
<td>7.7</td>
<td>4.1</td>
<td>12.0</td>
<td>64</td>
<td>2.2</td>
<td>15.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 mo after</td>
<td>7.4</td>
<td>3.8</td>
<td>56.0</td>
<td>68</td>
<td>0.9</td>
<td>5.5</td>
</tr>
<tr>
<td>C.P.</td>
<td>50</td>
<td>103.0</td>
<td>22.0</td>
<td>Before</td>
<td>7.4</td>
<td>3.8</td>
<td>19.0</td>
<td>122</td>
<td>1.6</td>
<td>9.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1½ mo after</td>
<td>4.6</td>
<td>2.6</td>
<td>110.0</td>
<td>12</td>
<td>0.4</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**Mean values**

Before: 39 145.0 15.0 6.9 3.6 10.5 92 2.2 16.6 48.1

After: 64 3.4 41.7 37.3 0.7 6.3 25.5

Statistical significance

*Data obtained 12 months after ileal bypass were not included in the calculations of the mean and were not used for statistical analysis.

Table 2. *Digoxin Relative Bioavailability Data*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Time from ileal bypass</th>
<th>Serum albumin (g/100ml)</th>
<th>Serum carotene (µg/100ml)</th>
<th>Urine d-xylene excretion (g/hr)</th>
<th>Serum d-xylene peak conc. (mg/100ml)</th>
<th>AUC (0-24 hr) (mg x hr/100ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K.W.</td>
<td>Before</td>
<td>7.1</td>
<td>68</td>
<td>2.9</td>
<td>6.0</td>
<td>32.0</td>
</tr>
<tr>
<td></td>
<td>1 mo after</td>
<td>7.2</td>
<td>35</td>
<td>0.6</td>
<td>5.5</td>
<td>16.8</td>
</tr>
<tr>
<td>S.R.</td>
<td>Before</td>
<td>7.1</td>
<td>96</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>12 mo after*</td>
<td>7.1</td>
<td>96</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>H.R.</td>
<td>Before</td>
<td>5.3</td>
<td>93</td>
<td>2.3</td>
<td>18.0</td>
<td>64.5</td>
</tr>
<tr>
<td></td>
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<td>20</td>
<td>0.6</td>
<td>10.0</td>
<td>56.0</td>
</tr>
<tr>
<td>B.C.</td>
<td>Before</td>
<td>6.3</td>
<td>110</td>
<td>2.2</td>
<td>24.0</td>
<td>81.5</td>
</tr>
<tr>
<td></td>
<td>2½ mo after</td>
<td>5.8</td>
<td>16</td>
<td>0.5</td>
<td>6.0</td>
<td>28.8</td>
</tr>
<tr>
<td>S.R.</td>
<td>Before</td>
<td>6.9</td>
<td>14</td>
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<td>1.0</td>
<td>4.0</td>
</tr>
</tbody>
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After: 64 3.4 41.7 37.3 0.7 6.3 25.5

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*Data obtained 12 months after ileal bypass were not included in the calculations of the mean and were not used for statistical analysis.

**Corrected for differences in body weight before and after surgery.**

***Corrected for differences in body weight before and after surgery.***

d-xylene excretion and by a significant increase in fecal fat (table 1). There was a trend toward a decrease in serum carotene concentration after surgery but no apparent decrease in the mean concentrations of total serum protein or serum albumin after the jejunal bypass.

The digoxin data are summarized in table 2. Steady state digoxin serum concentrations did not differ significantly before and after surgery. The ratio of these values indicates that the average digoxin bioavailability in these patients after surgery is 87% of that prior to surgery. Another way of evaluating bioavailability is to compare the AUCs during a dosing interval at steady-state. As seen in table 2, the average ratio of the AUCs indicates a 9% decrease in bioavailability after surgery which is similar to the decrease observed in the steady-state digoxin serum concentrations.

When steady-state digoxin serum concentrations and AUCs are adjusted for differences in body weight before and after surgery, the apparent differences in bioavailability are reduced and the average ratio of these respective parameters approaches 1.0. In addition, these adjusted ratios agree closely with the ratios of urinary digoxin recovery before and after surgery. The urine data are based upon the results...
in four subjects since there was incomplete urine collection in three patients.

There was no statistical difference in the mean serum half-life after surgery (P < 0.1). The mean values were 1.18 ± 0.22 days before and 1.36 ± 0.21 days after bypass in the five patients with adequate data for analysis.

Discussion

These results indicate that there is no apparent impairment of absorption of digoxin from the tablets employed in this study after removal of the distal jejunum and proximal ileum even though definite evidence of malabsorption was documented in all our patients. When assessing bioavailability from serum concentration data one usually assumes drug clearance from the body in a given patient to be constant. However, the influence of jejunileal bypass surgery on the disposition kinetics of digoxin or drugs in general is not known. As a result any changes which surgery of this type may produce in digoxin clearance could influence the interpretation of these data. No apparent change was observed in the biologic half-life of digoxin in patients after surgery. It is difficult from the data obtained to determine whether or not there were any changes in the apparent volume of distribution and hence any changes in digoxin clearance. Since digoxin is cleared primarily by the kidney, and since no apparent changes in the half-life and renal clearance of digoxin were observed, it would appear that the apparent volume of distribution of digoxin was unchanged. If the loss in weight after surgery was due to a loss in adipose tissue only, no adjustments in plasma levels and AUCs would be required, since there is insignificant distribution of digoxin into adipose tissue and the same dose per kg lean body weight would have been administered. However, it is possible that the loss in weight after jejunileal bypass surgery may be a consequence of a loss in both adipose and muscle tissue, and steady-state serum concentrations and AUCs should be normalized for changes in body weight. This has been done in table 2 and results in a slight but insignificant increase in the ratios of steady-state plasma concentrations and AUCs.

It has been suggested that measurement of urinary excretion of digoxin is less variable and perhaps a more valid measure of digoxin bioavailability than serum concentrations or AUCs. In the present study urine and serum data agree very well. However, the urine data only represent the results of four subjects and hence this comparison is incomplete. In those subjects where digoxin excretion was determined, approximately 50% of the oral dose was recovered in the urine prior to surgery (range 36–61%) and 44% after surgery (range 33–59%). These mean urinary recoveries of digoxin are consistent with the reports of other investigators using digoxin elixir or tablet formulations that had rapid dissolution. In the data in the present study are consistent with the findings of Hall et al. and Beerman et al. that various malabsorption states do not interfere with the absorption of digoxin. Beerman et al. found that 40–60% of the tritiated digoxin was absorbed in normal subjects by the time the test solution reached the proximal part of the small intestines (110–200 cm from the nose). Most of the absorption occurred in the duodenum and upper jejunum and only 10% of the tritium label was absorbed in the stomach. These investigators documented that digoxin could also be absorbed in the jejunum since intrajejunal administration resulted in the same 14 day urinary excretion as intragastric drug administration. Absorption of digoxin from the colon has recently been found. It appears, therefore, that the diminished absorption of digoxin in various states of malabsorption reported by Heizer et al. may be due to a diminished bioavailability of their digoxin tablets. Evidence to support this hypothesis is provided by Jusko et al. who found that patients with radiation induced malabsorption had no measurable amounts of digoxin in their serum after being given Lanoxin tablets, but had measurable levels after being given the elixir. Data regarding the dissolution rate of the digoxin tablets in the study were not given. Greenblatt and coworkers found that there was a diminished bioavailability of digoxin tablets that have less than 65% dissolution in one hour compared with the bioavailability of the elixir when given to normal subjects. However, when greater than 65% of the tablets went into solution within one hour they could find no difference in bioavailability between the tablets and the elixir. Since 1974 the Food and Drug Administration has specified that digoxin tablets must meet the dissolution rate requirements established by the United States Pharmacopeia in 1973. These requirements stipulate that at least 65% of digoxin must be dissolved within one hour. If diminished bioavailability of digoxin tablets was responsible for the decreased absorption of digoxin in malabsorption states reported by Heizer et al., then absorption of digoxin that meets the current USP dissolution rate requirements should not be decreased in patients with malabsorption. This does not negate the possibility that isolated cases of decreased absorption of digoxin may occur in patients with malabsorption or in patients receiving a digoxin preparation with a slower rate of dissolution. Serum levels of digoxin will verify diminished absorption of digoxin when this problem is suspected.

Acknowledgment

We wish to acknowledge the secretarial assistance of Mrs. Edith Makler and Miss Ann Vallefuoco. We also wish to thank Drs. Philip Walson, Murray Katz and David Alberts of the University of Arizona College of Medicine and Dr. James Blanchard, College of Pharmacy, University of Arizona, for critical review of the manuscript. We are especially indebted to Dr. Michael Mayersohn and Dr. Donald Perrier of the College of Pharmacy for their assistance in data analysis and assistance in revising the manuscript.

References


Experience with Bretylium Tosylate By a Hospital Cardiac Arrest Team

DOUGLAS A. HOLDER, M.D., ALLAN D. SNIDERMAN, M.D., GEORGE FRASER, M.D.,
AND ERNEST L. FALLEN, M.D.

SUMMARY The effect of bretylium tosylate (BT) was determined in 27 consecutive cases of resistant ventricular fibrillation (VF) encountered by a hospital cardiac arrest team. The VF was sustained and completely resistant to multiple injections of lidocaine, sequential DC shocks at 400 watt-sec and one or a combination of intravenous propranolol, diphenhydantoin or procainamide. Following 30 min of sustained cardiac massage, BT (5 mg/kg i.v.) was administered. In 20 patients, VF was terminated within 9-12 min after DC shock. Eight of these patients failed to recover while 12 (44%) of all patients resuscitated survived to be discharged from hospital. Eleven out of 20 (55%) of all patients who had a cardiac arrest outside the CCU were survivors; only one out of seven in the CCU was successfully resuscitated. While receiving maintenance BT post-resuscitation (5 mg/kg i.m. q 8-12 hrs X 48 hrs), half the patients developed hypotension and three required vasopressors and/or fluid replacement.

The data indicate that BT is a useful agent in patients with sustained VF refractory to repeated lidocaine injections, some other antiarrhythmic agents, and multiple DC shocks.

THE WIDESPREAD USE OF ANTIARRHYTHMIC AGENTS in coronary care units has succeeded in decreasing the incidence of ventricular fibrillation (VF) as a primary electrical disorder. It is estimated, however, that 30-50% of in-hospital deaths from ischemic heart disease occur suddenly either during the postcoronary care unit phase or on arrival in the emergency room. An effective in-hospital mobile cardiac arrest team can serve as an extended CCU for these patients, and in fact, our experience since 1962 revealed that a significantly higher survival rate from resuscitation, presumably after primary VF developed, occurred in patients arresting outside the CCU compared to those within. A decade's experience from our hospital also revealed that an increased survival rate from resuscitation occurred suddenly in 1966-67 and was sustained thereafter. This was the period during which lidocaine was introduced as a routine antiarrhythmic agent in resuscitative measures for resistant VF. Although a causal relationship between the use of lidocaine and the increased survival rate cannot be established with certainty, it raises the tantalizing suggestion that cases of primary VF that remain resistant to lidocaine therapy may respond to a different antiarrhythmic agent.

Since 1966, a number of clinical studies have demonstrated that bretylium tosylate is an effective drug against recurrent ventricular arrhythmias complicating myocardial infarction. The aim of this study was to evaluate the efficacy of bretylium tosylate on VF resistant to multiple DC shocks, lidocaine, and a variety of antiarrhythmic agents.

Methods

The Royal Victoria Hospital is a 1,100 bed University Teaching Hospital where an average of 154 calls for cardiac arrests are handled by a single mobile resuscitation team each year. This study deals with the period from July 1970 to January 1973 where out of a total of 330 cardiac arrests, 27 consecutive cases were encountered in whom VF was sustained and completely resistant to the conventional forms of electrical and pharmacological resuscitative therapy over a 30-minute period. These 27 cases form the basis of this report. Twenty-one of these patients had ischemic heart disease, two patients were recovering from aortic valve replacement, and one each had subacute bacterial endocarditis, renal failure, digitalis toxicity, and trauma.

The composition and operation of the mobile cardiac arrest team has been described in a previous report. Briefly, the four-member team was gathered in the CCU and consisted of a senior and junior house officer attached to the acute care cardiorespiratory service, a specially trained nurse and an inhalation therapist. All cardiac resuscitations in hospital were carried out by this team, and following initial recovery, the same team continued to care for the patient in the CCU. Seven resuscitations were performed within the CCU and 20 occurred in other areas of the hospital including the medical and surgical wards, emergency room, and postoperative recovery areas.

From the Cardiovascular Division, Royal Victoria Hospital and McGill University, Montreal, Quebec. Address for reprints: Dr. E. L. Fallen, McMaster University Medical Center, 1200 Main Street West, Hamilton, Ontario, L8S 4J9, Canada. Received June 1, 1976; revision accepted October 25, 1976.
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