Atrial Flutter as a Manifestation of Digitalis Toxicity

By Jay D. Coffman, M.D., and Gerald H. Whipple, M.D.

Although digitalis overdosage is known to produce a variety of atrial, junctional, and ventricular arrhythmias, atrial flutter due to digitalis intoxication has been rarely reported. The present paper reviews the literature and reports what appears to be the sixteenth case. The available information on the accepted cases of atrial flutter due to digitalis toxicity has been analyzed for clues as to when digitalis can be considered the cause of the flutter.

Digitalis is usually administered in the treatment of atrial flutter, but in the exceptional patient it may cause the arrhythmia, and more of the drug could lead to disastrous results. This paper emphasizes the rarity of atrial flutter due to digitalis intoxication, presents criteria to help determine whether digitalis is the cause of a given episode of atrial flutter, and adds what appears to be the sixteenth case to the literature.

CASE REPORT

A 79-year-old man had congestive heart failure for 19 months due to arteriosclerotic heart disease. An electrocardiogram at the onset of his symptoms revealed sinus rhythm at a rate of 106 with a P-R interval of 0.19 second, low QRS voltage, and ST-T abnormalities. He was digitalized and maintained on 0.2 mg of digitalis leaf per day and intermittent diuretic therapy. Four weeks prior to admission, following a "cold," all symptoms of congestive failure increased and he was hospitalized.

Physical examination revealed a disoriented man with Cheyne-Stokes respiration. Funduscopic examination showed narrowed, tortuous arterioles with arteriovenous nicking. There was distention of the neck veins. Coarse, moist rales were heard over both lower lung fields posteriorly. The heart was moderately enlarged to percussion. The cardiac rhythm was regular with occasional premature beats; the aortic component of the basal second sound was louder than the pulmonic; a grade III, coarse, blowing systolic murmur was best heard at the apex and was transmitted to the axilla. The liver was enlarged but nontender. There was 1+ pretibial pitting edema. The blood pressure was 152/80.

The urine showed 1+ protein and rare hyaline and granular casts. The hematocrit level was 46 per cent and the corrected sedimentation rate (Wintroub) was 32 mm per hour; the white blood cell count was 12,700. The blood urea nitrogen was 21 mg., the creatinine 1.5 mg., the total protein 7.1 Gm., the albumin 3.4 Gm., and the globulin 3.7 Gm. per 100 ml. The serum sodium was 137 mEq., the potassium 5.9 mEq., the chloride 95 mEq., and the carbon dioxide 27.3 mEq. per liter.

An electrocardiogram showed sinus rhythm at a rate of 110 with a P-R interval of 0.22 second, occasional ventricular premature beats, low QRS voltage, and ST-T abnormalities. A chest film revealed the heart to be generally enlarged, with a cardiothoracic transverse diameter ratio of 17:30, an elongated tortuous calcific norta, and congested lung fields.

The patient was given two 0.2-mg. doses of lanatoside C intravenously over a 2-hour period. This caused a slight increase in rate and in the number of ventricular premature beats. Consequently, no further digitalis was given for 3 days. Treatment consisted of bed rest, aminophylline suppositories, and a low-sodium diet. No diuretics were given. The patient's disorientation and Cheyne-Stokes respiration became worse. The urine output remained low (about 500 ml. per day) while the blood urea nitrogen rose gradually.

Because of persistent tachycardia and heart failure, digoxin was begun on the fourth hospital day; table 1 shows the dosage of digoxin each day. By the sixth hospital day the patient was much improved. He had lost 4 pounds, was able to lie flat without dyspnea, and his ankle edema had disappeared. However, Cheyne-Stokes respiration and disorientation continued. An electrocardiogram at this time showed a sinus rhythm at a rate of 118 with a P-R interval of 0.22 second and disappearance of the ventricular premature beats.

On the twelfth hospital day, after a total of 7.25 mg. of digoxin in 9 days and a weight loss of 10 pounds, the heart rate suddenly slowed. The electrocardiogram (fig. 1) revealed atrial flutter with an atrial rate of 240, an average ventricular rate of 80, and a shifting atrioventricular block.

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VENTRICULAR PREMATURE BEATS HAD REAPPEARED, SOMETIMES IN RUNS OF 2. NO GASTROINTESTINAL SYMPTOMS WERE PRESENT. DIGOXIN WAS STOPPED.

THE FOLLOWING DAY THE SERUM POTASSIUM WAS 4.9 mEq. PER LITER. AN ELECTROCARDIOGRAM ON THE FOURTEENTH HOSPITAL DAY SHOWED COARSE ATRIAL FIBRILLATION WITH A VENTRICULAR RATE OF 85; VENTRICULAR PREMATURE BEATS HAD DISAPPEARED. THE NEXT DAY AN ELECTROCARDIOGRAM DISCLOSED REVERSION TO SINO-RHYTHM AT A RATE OF 100 WITH A P-R INTERVAL OF 0.24 SECOND. DIGOXIN WAS RESUMED 2 DAYS LATER WITHOUT FURTHER ATRIAL ARRHYTHMIA.

DURING THIS PERIOD, THE PATIENT CONTINUED TO BE DISORIENTED. DESPITE A MARKED IMPROVEMENT IN THE SIGNS OF CONGESTIVE FAILURE, CHEYNE-STOKES RESPIRATION WAS STILL PRESENT. DEHYDRATION AND A URINARY TRACT INFECTION WERE TREATED BUT THE PATIENT WENT INTO A COMA AND DIED QUIETLY ON THE TWENTY-FIFTH HOSPITAL DAY.


DISCUSSION

A NUMBER OF AUTHORS" 5 HAVE HEMPHAZED THE RARITY OF ATRIAL FLUTTER DUE TO DIGOXIN INTOXICATION. OTHERS" 7 HAVE MERELY REMARKED THAT ANY ARRHYTHMIA MAY BE THE RESULT OF TOO MUCH DIGOXIN AND HAVE USUALLY REFERRED TO KATZ 8 AS THE BASIS FOR THIS STATEMENT. RECENT REVIEWS" 11 OF DIGOXIN TOXICITY FAIL TO MENTION ATRIAL FLUTTER IN THIS REGARD.

AUTHENTIC CASES OF ARRHYTHMIAS DUE TO DIGOXIN INTOXICATION SHOULD MEET 3 CRITERIA: THE PATIENT SHOULD DEVELOP THE ARRHYTHMIA WHILE TAKING DIGOXIN; HE SHOULD NOT BE TAKING ANY OTHER DRUGS KNOWN TO CAUSE CARDIAC ARRHYTHMIAS; AND THE ABNORMAL RHYTHM SHOULD DISAPPEAR WHEN THE DIGOXIN IS DISCONTINUED.

ATRIAL FLUTTER DUE TO DIGOXIN INTOXICATION MUST BE CAREFULLY DIFFERENTIATED FROM PAROXYSMAL ATRIAL TACHYCARDIA WITH ATRIOVENTRICAL BLOCK, WHICH IS A MUCH MORE COMMON MANIFESTATION OF DIGOXIN INTOXICATION. THE ABSENCE IN ALL LEADS OF THE CONTINUOUS BASE LINE UNDULATION SO CHARACTERISTIC OF FLUTTER AND THE SLOWER AVERAGE ATRIAL RATE ARE THE MOST IMPORTANT ELECTROCARDIOGRAPHIC FEATURES THAT DISTINGUISH PAROXYSMAL ATRIAL TACHYCARDIA WITH BLOCK. 12 13 THE LATTER IS ORDINARILY A DISTINCTIVE CLINICAL ENTITY WHICH MAY USUALLY BE DIFFERENTIATED FROM ATRIAL FLUTTER NOT DUE TO DIGOXIN. 13

WEDD, 14 IN 1924, WAS APPARENTLY THE FIRST TO REPORT A CASE OF ATRIAL FLUTTER DUE TO DIGOXIN INTOXICATION. EIGHT YEARS LATER, Mc Millan AND Bell E 15 REPORTED 2 MORE CASES. IMELIO AND TALTAVULL 16 IN 1940 AND ZUBILLAGE 14 IN 1942, EACH ADDED 1 CASE TO THE LITERATURE. COLE 5 IN 1950, WHILE EMphasizing diarrhea as a toxic effect of digoxin, presented a patient who developed atrial flutter after an overdose of the drug. BICKEL AND ASSOCIATES 17 REPORTED A TRANSIENT EPISODE OF ATRIAL FLUTTER IN A YOUNG

<table>
<thead>
<tr>
<th>Hospital day</th>
<th>Digitalis preparation</th>
<th>Digitalis dosage (mg)</th>
<th>Cardiac rhythm</th>
<th>Serum potassium (mEq/L)</th>
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<tr>
<td>1st</td>
<td>Lanatoside C</td>
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<tr>
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<td>Normal sinus rhythm</td>
<td>4.9</td>
</tr>
<tr>
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<tr>
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<td>Digoxin</td>
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<td>1.65 mg</td>
<td>Atrial flutter</td>
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<td>Normal sinus rhythm</td>
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The table shows the digitalis dosage, cardiac rhythm, and serum potassium levels during hospitalization.
woman who tried unsuccessfully to commit suicide with 50 mg. of digitoxin. Hejtmancik, Herrmann, and Bradfield\textsuperscript{18} mentioned 5 cases of atrial flutter produced by digitalis intoxication and found that the arrhythmias reverted to normal sinus rhythm after withdrawal of the digitalis. Unfortunately, these 5 cases are the only ones of the 15 in the literature in which electrocardiograms were not illustrated. The comment in the text that one of the cases showed several shifts from paroxysmal atrial tachycardia to flutter and back, strongly suggests that this may really have been a typical example of the several phases of paroxysmal atrial tachycardia with block due to digitalis intoxication. Lown and Levine\textsuperscript{18} have recently commented on 3 cases of atrial flutter which they thought were unequivocally due to digitalis overdosage. Two of these cases were different from the other cases reviewed here in that both were known to have had atrial fibrillation as their basic rhythm before the flutter appeared. The presence of prior atrial irritability weakens the evidence for digitalis as the cause of flutter in these 2 cases; in the absence of digitalis intoxication, atrial fibrillation may often shift in and out of flutter.\textsuperscript{3} Other clinical evidence in these 2 cases points to digitalis as a likely cause of the flutter, however.

The present case was an elderly man with arteriosclerotic heart disease and severe heart failure who developed atrial flutter with ventricular premature beats after a total dose of

**Fig. 1.** Electrocardiogram showing atrial flutter with varying atrioventricular block and ventricular premature beats.
7.25 mg. of digoxin during a 9-day period. This was probably an excessive amount if the average digitalizing dose of digoxin is considered to be 3.75 mg.\textsuperscript{19} or even less\textsuperscript{20} and the maintenance dose 0.25 to 0.75 mg.,\textsuperscript{21} in view of the following coexisting factors, which lower digitalis tolerance: (1) the patient having taken digitalis leaf 0.2 Gm. per day up to 3 days previously, and this preparation possibly not having been fully excreted for 3 weeks,\textsuperscript{12} (2) advanced age\textsuperscript{22, 23} (3) severe congestive heart failure,\textsuperscript{22, 23} (4) renal disease,\textsuperscript{22} and (5) a diuresis of 9 pounds with a probably significant potassium loss. Although serum levels do not necessarily indicate the magnitude of potassium shifts, it is noteworthy that the patient's serum potassium fell 1.1 mEq. per liter during the period of digoxin administration. Supplementary potassium was not given because of a rising blood urea nitrogen.

Sampson, Alberton, and Kondo\textsuperscript{24} were the first to point out that ectopic beats due to digitalis toxicity could be abolished by the administration of potassium even with normal serum levels. Numerous subsequent studies have confirmed this and have established that depletion of potassium sensitizes the heart to digitalis.\textsuperscript{25-29}

When atrial flutter developed, the patient was also receiving aminophylline suppositories, tetracycline, and methylphenidate hydrochloride (Ritalin); these drugs are not known to cause this arrhythmia. Two days after digitalis had been discontinued the atrial flutter changed to atrial fibrillation and in 3 days normal sinus rhythm was again present. Lown and Levine\textsuperscript{31} treated 2 patients with atrial flutter due to digitalis intoxication with intravenous potassium chloride, 35 and 40 mEq, respectively. They observed the same sequence, namely a period of atrial fibrillation before reversion to normal sinus rhythm in 10 and about 24 hours. Since it is well established that potassium loss causes atrial muscle to become refractory to vagal or other cholinergic influence, they presumed that while the administered potassium was counteracting the direct muscular effects of digitalis it was also restoring atrial responsiveness to the excitatory vagal effects with an interval of atrial fibrillation resulting. However, the same sequence took place in the present case without supplementary potassium administration. Further, such a sequence is of course common following digitalis treatment of ordinary atrial flutter.\textsuperscript{30} Since digitalis facilitates potassium loss from the cardiac muscle cell, the similar sequence from flutter through fibrillation to sinus rhythm under these 3 different circumstances may reflect the reentry of potassium into the cell, either as the digitalis effect recedes or as serum potassium levels are raised. Of greater practical significance was the observed prompt dissolution of digitalis-induced atrial flutter by means of potassium administration, because ordinary flutter may not respond even to toxic doses of potassium.\textsuperscript{31} This suggests that a therapeutic trial of potassium may be undertaken in instances of flutter in which digitalis intoxication may be implicated, provided no contraindications exist and proper safeguards are employed.

Several reports of atrial flutter associated with digitalis intoxication have not been included in this review as examples of flutter due to digitalis. Two papers concerning digitalis toxicity, one by Herrmann, Decherd, and McKinley\textsuperscript{31} and the other by Crouch, Herrmann, and Hejtmancek\textsuperscript{32} list 5 cases of atrial flutter occurring in patients who had digitalis toxicity but fail to mention whether these patients had arrhythmias before digitalization or if the arrhythmias disappeared on withdrawal of the digitalis. Moreover, these patients may be the same as those mentioned in the previously cited paper by this group.\textsuperscript{18} In a recent review Shrager\textsuperscript{22} enumerated 3 cases of atrial flutter among 40 selected cases of digitalis toxicity but pointed out that these arrhythmias were associated with, and not necessarily caused by, the intoxication. In this regard, one should note that digitalization to the point of toxicity is often employed in patients with atrial flutter because the margin between the toxic dose and that required to achieve the therapeutic goal may be very narrow in these cases.\textsuperscript{23} Two case reports\textsuperscript{33, 34} of atrial flutter due to digitalis toxicity fail to
meet the criterion that the arrhythmia should disappear when the drug is stopped. Both these patients were given more digitalis and finally reverted to normal sinus rhythm while still taking digitalis.

The available information on the accepted cases of atrial flutter due to digitalis toxicity has been analyzed for clues as to when digitalis intoxication could be considered the cause of the flutter. The ages of the patients varied from 32 to 85 years. Of 12 cases, only 3 were female but this incidence is presumably coincidental, or perhaps reflects the male preponderance that has been noted in ordinary atrial flutter.13, 18 The types of heart disease included syphilitic, rheumatic, and arteriosclerotic; 2 patients13, 17 had normal hearts. With the exception of these 2 cases, the patients were in moderate to severe congestive heart failure. The digitalis preparation or route of administration did not appear to be significant variables. Data concerning serum potassium were lacking in most of these reports but, as far as could be determined, the administration of diuretics was not a possible cause of potassium loss when atrial flutter was developing except in 2 cases of Lown and Levine.13

Although the ventricular rate ranged from 66 to 160, all but 3 of the cases had rates near the lower figure. The degree of atrioventricular block varied from 2:1 to 12:1, but was usually of the higher degrees. Ventricular premature beats were observed in our patient and in at least 3 others in the literature; adequate tracings were usually not available for analysis. In untreated flutter of the ordinary type the ventricular rate is rapid because the atrioventricular block is usually 2:1 and ventricular premature beats have been stated to be rare.12 The latter observation would be consistent with the fact that a rapid ventricular rate tends to suppress the intrusion of ventricular premature beats,35 including those due to digitalis.36 However, in one series of 40 patients with ordinary atrial flutter, 22 per cent showed ventricular premature beats.13 The discrepancy may have been due to the presence of congestive heart failure, which may in itself be associated with ventricular premature beats.37

From these considerations digitalis intoxication may be suspected as the cause of atrial flutter when a patient with normal sinus rhythm develops atrial flutter with a slow ventricular rate after the administration of large amounts of digitalis. When the ventricular rate is rapid under such circumstances, the occurrence of ventricular premature beats also raises the possibility of digitalis overdosage, especially if congestive heart failure is not prominent. If there is reason to believe that the patient has recently lost potassium by diuresis or other means this may be another helpful clue. Finally, even if serum potassium levels are normal and there is no clear-cut evidence of potassium loss, the prompt dissolution of a well-established flutter after a therapeutic trial of potassium points strongly to digitalis intoxication as a possible cause of the flutter.

**SUMMARY**

Atrial flutter is a rare complication of digitalis toxicity. Only 15 fairly definite cases could be found in the literature.

A sixteenth case of atrial flutter due to digitalis toxicity is presented. The patient was an elderly man in severe congestive heart failure who received 7.25 mg. of digoxin during a 9-day period.

Digitalis as a cause of atrial flutter should be suspected when the arrhythmia is associated with ventricular premature beats, despite a rapid ventricular rate, if congestive heart failure is not marked. The same may be said of flutter that develops in the presence of a slow ventricular rate in a heavily digitalized patient with congestive failure. A therapeutic trial of potassium may be helpful in doubtful cases.

**SUMMARIO IN INTERLINGUA**

Flutter atrial es un complication rar de intoxication per digitalis. Solmente 15 casos definite poeta esse trovat in le litteratura.

Es presentate un dece-sixte caso de flutter atrial causate per toxicitate de digitalis. Le
ATRIAL FLUTTER AS A MANIFESTATION OF DIGITALIS TOXICITY

patiente esseva un masculo de etate avantiate qui esseva in sever disfallimento cardiac congestive e recepiva 7,25 mg de digoxina durante un periodo de 9 dies.

Digitalis como causa de flutter atrial debeera esser suspicite quando le arrhythmia es associate con prematur pulsos ventricular in respecto del accelerate frequenta ventricular, in casos in que le congestive disfallimento cardiac non es marcate. Le mesmo pote esser dicite con respecto a flutter que se disveloppa in le presenzia de un lente frequenta ventricular in patientes con congestive disfallimento qui es fortemente digitalisate. Un proba therapeutic con kalinium es a recommendar in casos de dubita.

REFERENCES


John Wesley
Physician and Apothecary

Wesley emphasized the use of simple remedies. “Experience shows that one thing (one medicine at a time) will cure most disorders. Why administer more? Only to swell the apothecaries’ bill? Nay, possibly on purpose: to prolong the distemper so that the doctor and apothecary may divide the spoil.” Indeed those appear to be harsh words and sentiments from a man of the cloth.

Wesley established his “visitors of the sick” organizations in all his “Societies” of Methodists throughout England. He set up regular outpatient clinics in Bristol and in London. But wherever he went (and he travelled more than five thousand miles a year on foot and by horse) he saw the sick and prescribed for them within his abilities. In his absence from his clinics (he eventually made his peace with organized medicine of that day) he states in 1780 that “a physician is in regular attendance at the Chapel House in West Street (London) twice a week for three hours.”

Wesley established his first clinic in 1746. One year later he decided the need for transmission of medical knowledge to the public had to be met. And he did so in his inimitable manner. He wrote a book “Primitive Physic” or “An Easy and Natural Method of Curing Most Diseases.”—Alfred A. Weinstein. John Wesley Physician and Apothecary. The Georgia Review 10: 3, 1956.
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Circulation. 1959;19:188-194
doi: 10.1161/01.CIR.19.2.188

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/19/2/188

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