

# An elderly man with atrial fibrillation and exacerbated diabetes

A man in his late seventies who had had well-regulated diabetes mellitus type 2 for the previous seven years suddenly developed a sharp increase in blood glucose and haemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) levels. A probable cause was at length discovered. After action had been taken, the values rapidly fell back to normal levels.

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Digitoxin is regarded as a good choice for an elderly man with exacerbated heart failure, presumably conditioned by atrial fibrillation with an ensuing more rapid ventricular rhythm, and who has been using verapamil 120 mg daily for some time. This choice is consistent with the guidelines of the European Society of Cardiology (1). However, cardiac rhythm should be monitored closely because of the increased risk of bradyarrhythmia caused by the combination of digitoxin and verapamil (2). It is also important to titrate doses cautiously and to monitor the serum concentration of digitoxin, since concurrent treatment with verapamil increases the digitoxin level by an average of 30–40% (2).

At his next check-up ten weeks later, the patient had subjectively adequate heart function. He no longer became breathless with exertion and his activity level was normalised. A clinical examination revealed that he no longer showed signs of heart failure, and an ECG showed that his ventricular rhythm was back to an adequate level. Serum concentration of digitoxin taken in the meantime was 20 nmol/l (the reference range at that time was 15–33 nmol/l). Routine measurement of the HbA<sub>1c</sub> level showed that the value had risen from 6.2% the day of the start of digitoxin treatment to 10.1% at the time of the check-up. During the same period, fasting glucose had risen from 8.6 mmol/l to 14.6 mmol/l (Fig. 1).

His heart rhythm and heart failure had responded well to the treatment that had been initiated. But what could be the reason for the sharp rise in the levels of fasting glucose and HbA<sub>1c</sub>? Could it be incorrect readings? Had the patient's diet been more poorly regulated recently? Had his glucose metabolism changed – and, if so, why?

The patient stated that his diet was unchanged. His level of physical activity was higher as a result of the heart failure treatment,

and he had lost a couple of kilograms. The doctor and the patient initially agreed to continue without a change in his medication, but made an appointment for a further check-up some weeks later.

At the check-up after four weeks, his HbA<sub>1c</sub> level was 10.0%, i.e. approximately the same as the previous reading. This time fasting glucose was measured as 18.3 mmol/l (Fig. 1). The patient had still not made any dietary changes, and had maintained his physical activity. The serum concentration of digitoxin was 19 nmol/l.

The fact that the HbA<sub>1c</sub> value was at the same level as in the previous analysis, and that the values for glucose and HbA<sub>1c</sub> paralleled one another, made incorrect measurement very unlikely. Although there are several methods for analysing HbA<sub>1c</sub>, and these yield somewhat different results (3), these factors cannot explain such a sharp increase. The same laboratory was used for all tests for the patient in question. Nor were there any reasons for believing that the cause of the increase was changes in eating habits or in physical activity, since his body weight was stable. The only factor that could be seen to have been changed was that treatment with digitoxin had started.

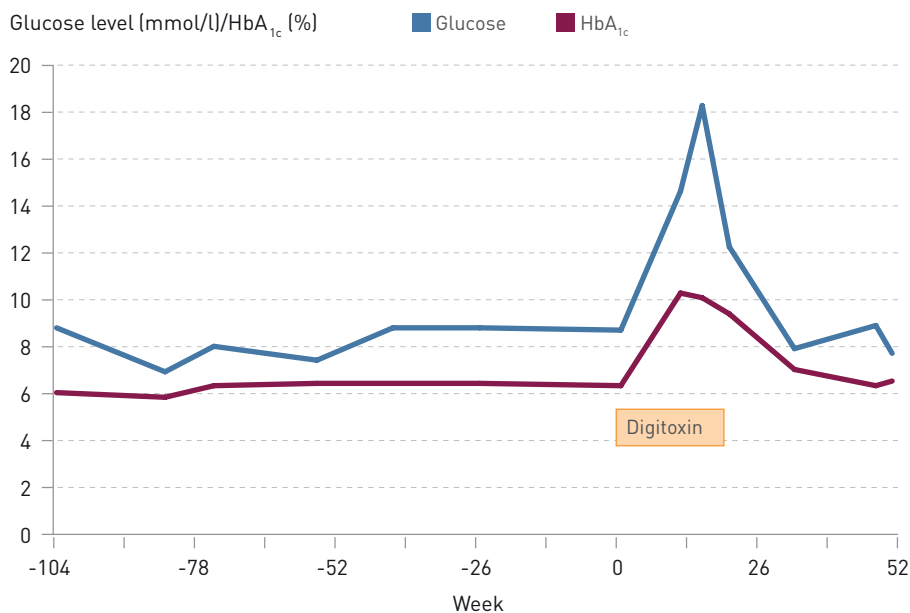
After discussion with the patient, it was decided at the next consultation to terminate digitoxin, 20 weeks after commencement of therapy and nine weeks after the rise in fasting glucose and HbA<sub>1c</sub> had been seen. In the course of a few months, the values of both fell to the same levels as before start-up with digitoxin (Fig. 1). At the 12-week check-up after termination, the level of fasting glucose was 7.8 mmol/l and that of HbA<sub>1c</sub> 6.9%. HbA<sub>1c</sub> levels six and eight months after termination of digitoxin were 6.2% and 6.4%. The patient did not want to undergo any further attempt at treatment with digitoxin. The event was reported to the RELIS Pharmacovigilance Centre as a possible adverse reaction. Despite the fact that digitoxin was terminated, the patient's ventricular rhythm did not show any noteworthy increase, nor were there any clinical signs of heart failure.

## Discussion

This patient's levels of fasting glucose and HbA<sub>1c</sub> rose sharply after he started on digitoxin, and fell correspondingly after termination. Another factor that might possibly explain this effect is the heart failure itself. A

The patient was a man in his late seventies who had had diabetes type 2 for seven years. The disease had been treated by dietary means and with physical activity. Despite the fact that he had lost weight, he was still to be regarded as overweight. In addition he had atrial fibrillation which was treated with verapamil (Istoipin Retard) 120 mg daily without the development of heart failure and with adequate ventricular rhythm. The patient had been unwilling to undergo treatment with warfarin, but throughout these years had taken acetyl salicylic acid (Albyl-E) 75 mg daily instead. The disease had been well regulated during the entire period, with HbA<sub>1c</sub> values between 5.7% and 6.3% (reference range 4.3–5.6%) for the previous four years (Fig. 1).

At a routine check-up, the patient complained of impaired physical function – he became breathless and tired from walking up even slight hills. His symptoms and a clinical examination indicated incipient heart failure, probably due to a more rapid ventricular frequency. This was verified by an ECG. After discussion with the patient it was decided to start treatment with digitoxin, initially with 0.1 mg daily five days a week, with subsequent dose adjustments following checks of the serum concentration.



**Figure 1** The patient's fasting glucose and HbA<sub>1c</sub> values. The coloured box shows the time period of digitoxin treatment (Week 0 – Week 20). Both glucose and HbA<sub>1c</sub> values were completely stable for a long time before this period and stabilised at the same low level after termination of digitoxin.

number of studies have shown that there is a connection between increasing heart failure and the development of diabetes (4, 5), but in our patient the heart failure had commenced a good while before the rise in glucose and HbA<sub>1c</sub> had started. Moreover, the heart failure had already subsided when the levels of glucose and HbA<sub>1c</sub> were highest, and long before they fell after the termination of digitoxin. According to the Naranjo algorithm for assessing suspected adverse drug reactions (6), the causality between the exacerbation of the patient's diabetes and the treatment with digitoxin is classified as «probable».

In the Norwegian summary of product characteristics for digitoxin (7), none of the factors elevated blood glucose level, increased HbA<sub>1c</sub> level, exacerbated diabetes nor other, related factors, are listed as adverse effects of digitoxin. However, an article has been published that describes three similar case histories where digoxin is suspected of being the cause (8). In the two cases where HbA<sub>1c</sub> values were available, these were 5–6% without use of digoxin and 7–8% during digoxin treatment. In the third patient, who also used glibenclamide, the level of fasting blood glucose was 8–10 mmol/l during treatment, whereas it decreased to hypoglycaemic levels when digoxin was terminated. A similar rise in the blood glucose level was seen in this patient when he started taking digoxin again.

In a study on rabbits, it was found that digitalis glycosides can have an unfavourable effect on glucose homeostasis (9). The author of this article urges caution and thorough follow-up when digoxin is used in diabetics. One possible explanation may be that digitalis glycosides and insulin have opposite effects at cellular level: insulin increases the

activity of Na<sup>+</sup>/K<sup>+</sup>-ATPase, which leads to both enhanced metabolism of glucose and increased transport of Na<sup>+</sup> out of cells and glucose into cells. Digitalis glycosides inhibit Na<sup>+</sup>/K<sup>+</sup>-ATPase, which reduces active transport of Na<sup>+</sup> out of the cells. It is conceivable that this may lead to both reduced glucose metabolism and reduced transport of glucose into the cells. It has been demonstrated in experimental studies that endogenously produced digitalis-like substances may modulate the effect of insulin via other mechanisms and may possibly be involved in the pathogenesis of diabetes mellitus, but the results are uncertain (10, 11).

It is striking that so few cases of increased blood glucose levels have been described earlier, not least because digitalis products are commonly used in patients with diabetes. In the DIG study, which included 6 800 patients with heart failure who were randomised to either digoxin or a placebo, 28% had diabetes at the time of inclusion (12). The patients were followed for four years, but no differences have been reported in the risk of onset of or exacerbated diabetes between the digoxin group and the placebo group (12, 13). Nor is a possible connection discussed in a more recent review article (14).

One explanation may be that in most cases the changes in the blood glucose level are of a magnitude not causing any suspicions of a connection with the use of the digitalis product, and that it is only in persons who for some reason are particularly sensitive that the effects are as pronounced as in our patient. The effect may also develop more slowly and gradually than in our patient, which also reduces the probability of a connection being made with commencement of the digitalis product. On the

other hand, in a study of the effect of candesartan in patients with heart failure, a significantly increased risk was detected that patients who were being treated with digoxin at the time of inclusion would develop diabetes (odds ratio 1.65; 95% CI 1.08–2.54;  $p = 0.22$ ) (15). The authors of this paper suggest further studies to clarify these relationships (15). We propose prospective systematic studies designed especially for the purpose. Until such studies are available, we recommend that patients with known diabetes be monitored closely, with blood glucose and HbA<sub>1c</sub> measurements after they start on digitoxin/digoxin. If digitalis is terminated, there may be a need to reduce the diabetes medication.

While waiting for studies that may resolve this and similar issues, we recommend that clinicians be on the watch for suspected side effects and report them.

*The patient has consented to the publication of the article.*

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## Comment

### Digitalis and diabetes

Digitalis has been used for over 200 years, and there is extensive literature on the subject. A search in PubMed on 27 February 2012 with the search word «digitalis» turned up more than 12 000 citations. Despite the long tradition, many questions concerning digitalis had not been resolved until fairly recently. It has two important areas of use: heart failure and atrial fibrillation. It was not until the large DIG study of 1997 (Digitalis Investigation Group (1) that it was determined that digitalis (digoxin) really did have a beneficial effect in connection with heart failure. One thing that was learned from this study was that the serum concentration should be lower than had been usual earlier (2). The reference intervals for digitoxin and digoxin were reduced.

In the present case report, the authors show that a patient's levels of HbA<sub>1c</sub> and glucose rose significantly after commencement of digitalis (digitoxin) therapy. In the past, there have been a few reports of diabetes being exacerbated by digoxin (3). If there really is a connection between digitalis and exacerbated diabetes, it is very strange that this was not discovered earlier, a point the authors also make. Possible explanations are that the effects in most patients are less pronounced than in the present case, or that diabetes is so common among persons who take digitalis that exacerbation or a few extra cases are not noticed. We will probably never have a definite answer. It would be very difficult to find funding for a prospective trial to study diabetes in patients who are taking digitalis. Perhaps more could be learned from looking

at patients from the major blood pressure and heart failure studies who were given digitalis. In order to do this, access to original data will probably be necessary.

The authors recommend that the HbA<sub>1c</sub> and glucose levels of patients with known diabetes be closely monitored after they start taking digitalis. I do not think the basis for such a recommendation is strong enough, and believe patients can manage with ordinary diabetes follow-up.

In Norway, pharmacies dispensed digitoxin to some 24 000 persons and digoxin to over 1 000 in 2010. The use of digitoxin is a Norwegian tradition; most other countries use digoxin. Digitoxin has a number of advantages, and I am tempted to assert that Norway is right and the rest of the world is wrong. Unfortunately, this will not help now that digitoxin has been taken off the market in this country, and we have to switch all patients digoxin in the course of 2012 and 2013. The Norwegian Medicines Agency has drawn up guidelines for the transition in collaboration with cardiologists and clinical pharmacologists (4). Unfortunately, one death as a result of overdosing of digoxin in connection with a change of medication has already been reported. Digitoxin and digoxin are both drugs with a narrow therapeutic window and regular checking of the serum concentration is necessary to avoid both overdosing and underdosing.

Observant clinicians who describe unusual incidents in case reports can call attention to the problem and draw other researchers into the debate. The most famous

case report in medical history is probably the description of abnormalities in the babies of mothers who had used thalidomide (5).

Perhaps Norwegian clinicians can contribute to solving the riddle: does one get diabetes from digitalis?

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