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The mission of the journal is to serve the need of the internist to practice up-to-date medicine and to keep track with important issues in health care. With this purpose we publish editorials, original articles, reviews, controversies, consensus reports, papers on specialty training and medical education, book reviews and correspondence.

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ABSTRACT
A careful evaluation and interpretation of the symptoms of the patient with atrial fibrillation should be the first step in selecting a treatment modality. Arrhythmia burden is not equal to symptoms. Some patients will have and continue to have symptoms not related to the occurrence of arrhythmias. Recognition of these patients is important in the treatment of atrial fibrillation.

KEYWORDS
Arrhythmia, atrial fibrillation, thromboembolic symptoms

The success of treatment in a patient with atrial fibrillation depends on a subtle balance between the evaluation and interpretation of the symptoms due to atrial fibrillation in that specific patient and the prevention of thromboembolic complications.

Prevention of thromboembolic complications has recently become quite simple. An indication for oral anticoagulation is present if a patient has a high-risk profile: age above 75 years, or age <75 years with left ventricular hypertrophy and hypertension, a previous transient ischaemic attack or cerebrovascular accident and/or diabetes mellitus. Once the criteria for anticoagulation are met, the patient will have a lifelong need for treatment, irrespective of the rhythm (sinus or paroxysmal, persistent or permanent atrial fibrillation). It can be said: once atrial fibrillation, always atrial fibrillation. The patient with lone atrial fibrillation (no structural heart disease) below the age of 65 should either have no preventive treatment or low-dose aspirin since the risk of thromboembolic complications is very low.1

Evaluation of the symptoms of atrial fibrillation should be done systematically. Is the patient having palpitations: are they fast or mainly irregular or does the patient feel both? When does he/she have these palpitations? Is there a relation with exercise or body position (lying, sitting or standing)? Is chest pain or chest discomfort present and when is this feeling most prominent. Is there dizziness or (near) syncope? Is polyuria present when the patient has palpitations? Is there a feeling of fatigue after the atrial fibrillation has stopped and how long does this feeling remain present? Sometimes to your surprise the patient with atrial fibrillation has none of the above-mentioned symptoms at all and the discovery of atrial fibrillation is coincidental. This especially occurs in the elderly patient on routine check-up.

The most invalidating symptom of atrial fibrillation is a decrease in exercise tolerance. This may vary from a diminished peak exercise (during sport/bicycling) to intolerance for slight exercise (walking a flight of stairs or even just walking). Generally, the younger the patient, the more prominent the decrease in exercise tolerance will be.

Whether the treatment of atrial fibrillation will be successful depends on an appropriate interpretation of the patient’s symptoms. Why is this so complicated? Patients with clear symptoms of atrial fibrillation do not only have symptomatic episodes of atrial fibrillation but will also have many asymptomatic episodes of atrial fibrillation. This may

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even amount to up to 70% of the total burden of atrial fibrillation! In general it might be the case that there is no clear correlation between the number of attacks of atrial fibrillation and the patient’s symptoms. Some have recurrent attacks of atrial fibrillation but hardly notice them, or at least are not limited in their daily functioning by these attacks. Others have one or two short-lasting episodes of atrial fibrillation and cannot function in their work or in their social environment! Is this related to the type of personality?

In this issue Van den Berg et al. report on whether traits of the personality may be helpful in evaluating the success of treatment of atrial fibrillation. They investigated whether neuroticism is more frequently present in patients with atrial fibrillation in comparison with age-matched controls. A high score on the neuroticism scale indicates persons who are anxious and may have vague complaints about their health. In the present study patients were included with paroxysmal atrial fibrillation with ‘lone atrial fibrillation’ or atrial fibrillation in the setting of hypertension. Nearly 70% were males.

Interestingly, they found no differences in the degree of neuroticism in the study group as a whole in comparison with the age- and sex-matched control group. So patients with paroxysmal atrial fibrillation have, on average, a ‘normal’ degree of neuroticism. However, in those persons with a high level of neuroticism, social functioning and mental health scored low. This caused a clear negative impact on the quality of life. This negative impact even seemed to be independent of the presence or absence of atrial fibrillation! In other words: if the arrhythmia burden in patients can be diminished this may not necessarily lead to improvement of quality of life in a patient with a high degree of neuroticism. Evaluation of any intervention for the social functioning and mental health in these patients will be difficult if it is possible at all.

Evaluation and interpretation of the symptoms of patients with atrial fibrillation should be done meticulously. Which symptoms have the greatest negative impact on the patient’s quality of life and what are the patient’s expectations? One should take time to make a proper evaluation. Only then the appropriate therapy can be selected and both physician and patient can be satisfied with the treatment option that has been selected.

REFERENCES

Hepatitis C virus and human immunodeficiency virus coinfection: where do we stand?

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ABSTRACT

Both human immunodeficiency virus (HIV) and hepatitis C (HCV) are globally infecting millions of people. Since these viruses are both transmitted through blood-blood contact the rate of coinfection is as high as 30% and among IV drug users in the Western world 70%. In the Netherlands, 8% of HCV-infected patients are coinfected with HIV. After the successful introduction of antiretroviral therapy (HAART) the survival of patients with HIV has increased considerably. Coinfection leads to accelerated progression of liver cirrhosis and liver failure but conflicting evidence exists about the effect of HCV on the natural course of HIV. Four randomised controlled trials have shown that treatment with pegylated interferon plus ribavirin leads to an overall sustained viral response (SVR) rate between 27 and 44%. Divided by genotype the SVR is between 14 and 38% in genotype 1 (and 4) while between 53 and 73% for genotype 2 and 3. These percentages are calculated based on an intention-to-treat analysis.

Although lower than in HCV-monoinfected patients this is much higher than achieved with conventional interferon. However, coinfected patients with genotypes 2 and 3 also need to be treated for 48 weeks in contrast to monoinfected patients. As the number and severity of side effects is low, coinfected patients now have a substantially better option for treatment.

KEYWORDS

Hepatitis C, human immunodeficiency virus, treatment, viral kinetics

INTRODUCTION

Hepatitis C virus (HCV) is a global health problem with an estimated 170 million people (3% of the total population) infected with this virus worldwide. In the United States nearly four million and in Europe more than five million people are infected with hepatitis C. At least 20% of these patients are expected to develop cirrhosis of the liver and approximately 25% of them will eventually die from hepatic failure or require liver transplantation. At the end of 2003 the human immunodeficiency virus (HIV) had infected an estimated 37.8 million people worldwide causing devastating economic, social and cultural problems. HIV (a retrovirus) and HCV (a flavivirus) are both RNA viruses. Both viruses are transmitted through blood-blood contact while transmission of HIV is much more effective through sexual intercourse than HCV. Coinfection among patients is as high as 30% both in Europe and the United States. The group of patients most at risk in the Western world is IV drug users, where the prevalence of coinfection is as high as 80 to 90%. Among 6000000 HIV positive patients in the Netherlands only 8% have HCV antibodies. Due to a widespread needle exchange and education programme the rate of coinfection is lower than in other parts of Europe.

Since the introduction of highly active antiretroviral therapy (HAART) in 1996, the survival of patients with HIV has increased considerably. The mortality caused by opportunistic infections has declined shifting the focus of treatment to cardiovascular and liver-related pathology. Coinfection of HCV and HIV is leading to long-term complications of liver disease such as cirrhosis, liver failure and hepatocellular carcinoma. In this subgroup of patients it is becoming a serious problem with a high morbidity...
and currently the leading cause of death among coinfected patients.\textsuperscript{41,42} In recent years, with the introduction of pegylated interferon, the treatment of hepatitis C has undergone major changes. The enhanced bioavailability leading to a prolonged serum half-life, allowing once-weekly administration, results in a higher sustained virological response (SVR) than with conventional interferon.\textsuperscript{33} An SVR is defined as an undetectable HCV-RNA (<50 U/ml) at 24 weeks of follow-up after 48 weeks of treatment.

In a recent publication by Vridal et al.\textsuperscript{44} in this journal, an excellent overview of the current treatment modalities for hepatitis C (non-coinfected) infected patients was given. Recently a few trials have been published on the treatment of hepatitis C in coinfected patients.\textsuperscript{45,46} The focus of this paper will be on the current available knowledge of virological interaction, viral kinetics and treatment in coinfected patients.

**Virological interaction between the two viruses**

The progression of hepatitis C mono-infection to cirrhosis and HCV-HIV co-infection is known to be slow taking decades to develop. This depends on individual variables such as duration of infection, age at time of infection, male sex, amount of alcohol consumption, metabolic disorders and HIV coinfection.\textsuperscript{41,47}

**Effects of HIV infection on the natural history of liver cirrhosis**

Multiple studies have examined the effects of HIV infection on the natural history of chronic hepatitis C infection. This is mostly studied in patients with haemophilia since HAART only became widely available eight years ago. An advantage of studying rates of progression in patients with haemophilia is that the date of HCV exposure is often known. Patients with haemophilia, coinfected with HCV and HIV, develop hepatic decompensation or liver failure more frequently than haemophiliacs with hepatitis C only (8 and 14% vs 0 and 1%, respectively).\textsuperscript{48} Graham et al.\textsuperscript{49} performed a meta-analysis of eight studies in a historical proven cirrhosis (n=4) or decompensated liver disease (n=0) or both (n=0) in both drug users and patients with haemophilia. The combined adjusted relative risk (RR) was 2.14 (95% CI 1.35-3.37) demonstrating that coinfected patients progress faster to hepatic cirrhosis. Also the risk of decompensated liver disease increased sixfold. Other authors have shown that coinfection leads to a higher rate of hepatocellular carcinoma and that progression to liver failure is shortened to six to ten years.\textsuperscript{50} One explanation for this faster progression could be the immune compromised state of these patients. Bonaccini et al.\textsuperscript{51} has shown in a summary of six previous articles that the rate of progression is inversely correlated to the CD4 count. A CD4 cell count lower than 500 cells/mm\(^3\) is associated with in an increased risk for advanced fibrosis (OR 3.2, 95% CI 1.9-5.9).\textsuperscript{52} The accelerated progression of fibrosis is more significant among patients with lower CD4 counts.\textsuperscript{53} It can also be postulated that the difference in progression rate in HCV is caused by the different HCV genotypes. However, two large studies have shown no effect of HCV genotype on fibrosis progression.\textsuperscript{54,55} A further two studies showed that genotype 1 is closely associated with more severe histological liver damage\textsuperscript{56,57} and an increase in liver-related deaths.\textsuperscript{58}

**Effects of HIV and HAART on HCV load**

It is known that HCV/HIV coinfected patients have a higher HCV-RNA concentration than HCV-monoinfected patients. Spontaneous clearance of HCV occurs in 20% of cases in monoinfected patients vs 5 to 10% for coinfected patients.\textsuperscript{59} The immune response to hepatitis C is important in clearing the virus from the blood. This is done by CD4+ T helper cells, cytotoxic T lymphocytes and production of interferon.\textsuperscript{60} With HCV infection CD4+ lymphocytes show defective proliferation and apoptosis resulting in an impaired host immune response to HCV-infected cells leading to a higher HCV-RNA concentration. As stated above, the amount of CD4 cells is a prognostic variable for progression to liver cirrhosis. Therefore the effect of highly active antiretroviral therapy (HAART) on disease progression is interesting. Given the fact that HAART increases the CD4 cell count in HCV (CD4-coinfected) patients, it can be postulated that progression to liver cirrhosis should halt. However, it is known that the total HCV-RNA load in untreated patients does not correlate with progression of liver cirrhosis. There are conflicting data on the immune response to HCV in coinfected patients. A retrospective study in France\textsuperscript{61} shows a favourable effect of protease inhibitor (PI) therapy on the progression of liver fibrosis. A total of 63 patients were treated with PIs compared with 159 PI-naïve patients. The cirrhosis rates were 2 ± 5% in PI18S and 4 ± 27% (p = 0.00065) calculated at 5, 15 and 25 years, respectively. This effect was not seen in patients on nucleoside-based regimes only. An observational study by Gushue et al.\textsuperscript{62} based on a twelve-year follow-up showed in a Kaplan-Meier analysis that patients treated with HAART had a lower liver-related mortality. Recently, Mariné-Barjoan et al.\textsuperscript{63} showed that treatment with HAART had a favourable effect on liver fibrosis in coinfected patients. These observations favour the early initiation of antiretroviral therapy in coinfected patients to stimulate immune reconstitution and thus viral suppression leading to slower progression of liver disease. Interestingly, HAART-treated patients have a significantly greater increase in HCV-RNA load than patients treated with antiretroviral therapy only monoinfected patients or untreated patients. In contrast, Martin-Carbonero et al.\textsuperscript{64} found that immune reconstitution caused by antiretroviral therapy has no effect on the accelerated progression of liver fibrosis. In the later studies HCV-RNA load was found to increase after initiation of HAART and it steadily increase over time. These observations raise questions about the possible mechanism of antiretroviral therapy halting progression of liver cirrhosis. Many questions still remain to be answered.

**Effects of HIV on HCV infection**

Conflicting results have also been reported about the effect of HIV on hepatitis C progression of the natural history of HIV infection. Together with two early studies\textsuperscript{65,66} Grebci et al.\textsuperscript{67} showed in the Swiss cohort that HCV/HIV-coinfected patients progressed faster to AIDS and death than patients with HIV infection only. The authors also noted a blunted CD4 cell response after initiation of HAART. In contrast, in a prospective study of 1995 HIV-positive patients in the USA, no difference was detected in progression to an AIDS-defining illness, progression to a CD4 cell count below 200/\(\mu\)l or survival between coinfected or HIV-negative patients.\textsuperscript{68} Moreover no difference was detected in the probability of experiencing a CD4 cell count increase of more than 50 cells/\(\mu\)l between coinfected and HCV-negative patients one, two and three years after initiation of HAART. Three recent studies, European and American, also showed no difference in increased progression to an AIDS-defining illness or death between HCV positive or negative patients.\textsuperscript{69-71} Soriano et al.\textsuperscript{70} concluded in their recent review that HCV might act as a co-factor in HIV-positive patients by immune stimulation and possibly CD4 cell depletion causing a blunt response to antiretroviral therapy. However, they observed that the evidence was really poor.

**Viral kinetics**

Lessons learned from viral kinetics in HIV have generalized to the understanding of hepatitis C and HCV. HCV has a high replication rate of 1 x 10\(^{12}\) virions/day and a half-life of only three hours.\textsuperscript{72} Viral load levels of HCV remain relatively stable over time but are higher in HIV-infected patients.\textsuperscript{73,74} The decline in HCV-RNA after initiation of interferon (INF) and ribavirin treatment on both monoinfected and coinfected patients shows a biphasic pattern (figure 1).\textsuperscript{75} The first phase is rapid and occurs within 24 to 48 hours after the start of treatment. At that time the viral production and release of HCV is blocked. This reflects the sensitivity of the virus to interferon.\textsuperscript{76} The second phase is slower and more variable in time, reflecting the rate of immune-mediated clearance of HCV-infected cells. In genotypes 2 and 3 the slope in the first and second phase is steeper than for genotypes 1 and 4 residing in a higher SVR after treatment.\textsuperscript{75} The steepness of the slope in both phases is a good predictor for achieving SVR after treatment. With conventional interferon dosing needs to be frequent because of the short serum half-life leading to large fluctuations in serum concentrations and therefore less steepness of the slope in both phases. The chemical modification of IFN by the covalent attachment of a polyethylene glycol (PEG) molecule results in a changed pharmacodynamic profile. The prolonged half-life results in a higher steady serum concentration of INF resulting in a steeper first and second phase.

In coinfected patients the second phase seems to be less steep than in hepatitis C mono-infected patients. In contrast, two studies found no biphasic pattern in the majority of patients. Talal et al.\textsuperscript{77} administered conventional interferon monotherapy to 12 coinfected patients while achieving an early virological response in only three patients and a sustained virological response in one patient. Torriani et al.\textsuperscript{78} analyzed a study of the APRICOT trial using Pegylated interferon. No biphasic pattern was seen in nine out of ten patients coinfected with HIV and HCV. Recently a triphasic model of viral kinetics has been reported by Herrmann et al.\textsuperscript{79} In 14 patients with chronic hepatitis C, they found the typical first phase, a flattened or slowed second phase and a third phase in 61% of patients. The rate of decline during this third phase was significantly faster in those patients receiving ribavirin. Therefore, Herrmann hypothesised that this third phase may be a result of the addition of ribavirin leading to an upregulation of the immune system by ribavirin. In a recent study on the antiviral action of ribavirin in hepatitis C, this effect was not noted.\textsuperscript{80} The exact role of ribavirin in the viral decay needs further study.
The treatment of coinfected patients with HCV and HIV is challenging because of the low response rates to interferon and ribavirin. Therapy with interferon-based regimes is known to cause significant side effects such as flu-like symptoms and general symptoms of fatigue, malaise and weight loss.1-3,5-8 Psychiatric disorders, particularly depression, occur with an incidence of 20 to 30% affecting treatment adherence and sometimes requiring interferon dose reduction or discontinuation.9 Also autoimmune thrombocytopenia is reported to occur with a relative risk of 4.4.10 Therefore, patients should be carefully instructed about the occurrence of the above-mentioned side effects and followed up closely by their physicians.

Clinical trials Recently two studies were published in the New England Journal of Medicine, one study in AIDS and one study in the JAMA describing the result of peginterferon alfa-2a (Pegasys) or alfa-2b (Peginteron) with ribavirin in coinfected patients with HCV and HIV. Results of sustained virological response are summarised in table 1. The first is the APRICOT study (AIDS Pegasys Ribavirin International Coinfection trial),11 a randomised multicentre placebo-controlled blinded trial with 868 patients. Patients were assigned to either IFN alfa-2a plus ribavirin, Peg-IFN plus placebo or Peg-IFN plus ribavirin 800 mg. Irrespective of the genotype all patients were treated for 48 weeks followed by a 24-week observation period. All patients were HIV positive and had a CD4 cell count >200 cells/mm3 or between 100 to 199 cells/mm3 but than with a viral load of <5000 copies per ml. HAART was followed up closely by their physicians. The occurrence of the above-mentioned side effects and required dose modification in 13% of patients with anaemia, while with thrombocytopenia and neutropenia the incidence was 9 and 3%, respectively. In both treatment arms this did not reach statistical significance. The RIBAVIC trial12 with 416 patients is a randomised controlled study of Peg-IFN alfa-2b (Peginteron) plus ribavirin 800 mg vs conventional IFN plus ribavirin 800 mg. The incidence of 4 virus drug use was 79%. Of the treated patients, 82% received antiretroviral therapy with a nucleoside reverse transcriptase inhibitor (NRTI) backbone. The overall reported SVR was 27 vs 20% and varied with genotype; genotypes 1 and 4 being 17% and genotypes 2 and 3 being 44%. In the later genotypes no significant difference was noticed between the reached SVR between peginterferon and conventional interferon. Adverse events were similar in both groups and treatment discontinuation was as high as 35%. Symptomatic mitochondrial toxicity, including symptomatic hyperlactatemia, lactic acidosis and acute pancreatitis, occurred in 11 patients (5%) nine of whom were on peginterferon. All patients received didanosine. The SVR was 12% for the conventional interferon plus ribavirin group, 20% for the peginterferon group and 40% for the peginterferon plus ribavirin group. A multiple logistic-regression model resulted in two variables independently increasing the odds of achieving SVR. Those were an HCV genotype other than 1 or 3 (OR 3.37, CI 1.56-7.34) and baseline HIV-RNA levels of less than 800,000 UI (OR 5.6, CI 1.00-6.69). Parameters related to HIV infection, such as CD4 cell count and use of HAART, were not significant. Serious adverse events were low between 5 and 10% and not statistically significant among the treatment groups. Grade 4 haematological abnormalities were more frequent in the peginterferon group. HCV treatment resulted in a slightly lower CD4 cell count but the percentage of cells was not affected.

The second trial is the ACTG 577 trial,13 which included 153 patients who were randomised to peginterferon alfa-2a (Pegasys) plus ribavirin in a dose-escalation schedule from 600 mg/day to 1000 mg/day or IFN plus dose-escalated ribavirin. As with the other trials a high percentage of genotype 1 was noted (78%). Patients had a well-controlled HIV infection with a mean CD4 count of 475 cells/mm3 and 86% received HAART. The overall SVR was 27% for the peginterferon group as 12% for the conventional interferon group. Divided by genotype, differences in SVR with peginterferon were as expected, 73% for genotypes 2 and 3 while only 14% for genotype 1. Again side effects and adverse events were similar in both arms. Premature treatment discontinuation was 12% in both groups mainly because of depression and abnormal laboratory values. One case of clinical pancreatitis was noted leading to discontinuation of treatment. This patient was receiving didanosine. Similar to the APRICOT study no effect of HCV therapy on HIV progression was noted, with even a slight increase in the percentage of CD4 cells. Laguno et al.,14 in a small single-centre study, reported their results of peginterferon alfa-2b (Peginteron) plus ribavirin compared with interferon alfa-2b plus ribavirin in 51 patients. The dose of ribavirin was adjusted to body weight with 600 mg when the body weight was <60 kg, 1000 mg when it was 60 to 75 kg and 2000 mg when it was >75 kg. Both groups were treated for 48 weeks. Twenty-one patients (42%) with genotype 2 or 3 and a HCV-RNA load below 800,000 UI were treated with peginterferon (n=4) or conventional interferon (n=7) only for 24 weeks. Of the patients, 88% received antiretroviral therapy and the mean CD4 count was 550 x 10^6/l. The SVR was 44% in the peginterferon group vs 27% in the interferon group with the SVR higher on treatment. In the peginterferon group genotypes 1 and 4 reached an SVR of 38 vs 13 and 47% for genotypes 2 and 3. No further remarks were made about the difference in duration of treatment in relation to the SVR. Altogether, 17% of the treated patients, nine in the peginterferon group and five in the interferon group, discontinued treatment because of serious adverse events such as flu-like symptoms, psychiatric disorders, lactic acidosis and severe anemia. Haematological abnormalities required dose modification in 13% of patients with anaemia, while with neutropenia and thrombocytopenia this was 9 and 3%, respectively. In both treatment arms this did not reach statistical significance.

Table 1

<table>
<thead>
<tr>
<th>Reference</th>
<th>INF + RIBAVIRIN</th>
<th>Peg-INF + RIBAVIRIN</th>
<th>Genotypes 1 and 4</th>
<th>Genotype 2 and 3</th>
<th>Side Effects/Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>APRICOT11</td>
<td>12%</td>
<td>20%</td>
<td>47%</td>
<td>53%</td>
<td>Grade 4 haematological abnormalities more frequent in the peginterferon group. AES in all groups between 5-10% CD4 cells decreased in all groups but percentage increased slightly.</td>
</tr>
<tr>
<td>ACTG13</td>
<td>12%</td>
<td>27%</td>
<td>14%</td>
<td>73%</td>
<td>Similar frequency of side effects in both groups; 12% prematurely discontinue treatment in both arms.</td>
</tr>
<tr>
<td>Laguno et al.14</td>
<td>21%</td>
<td>23%</td>
<td>38%</td>
<td>53%</td>
<td>15% prematurely discontinue treatment with 9 in Peg-INF arm and 5 in INF arm. AES not statistically significant among treatment groups.</td>
</tr>
<tr>
<td>RIBAVIC15</td>
<td>20%</td>
<td>27%</td>
<td>17%</td>
<td>44%</td>
<td>AES 35% [INF and INF + Peg] treatment discontinuation 35% [INF and 76% Peg]; no significant decrease in CD4 cells</td>
</tr>
</tbody>
</table>

What can be learned?

Comparing these four trials is difficult because of the different brands of interferon, the baseline characteristics of the participants, sample size and the dose of ribavirin. Also the duration of treatment in genotypes 2 and 3 differed with 48 weeks in the APRICOT study while only 24 weeks for patients with a low HCV-RNA load in the study by Laguno et al. One interesting observation is the wide range in reported SVR. It is not yet clearly understood why the overall SVR in the APRICOT trial and the study by Laguno is 40 to 44 vs 27 in the RIBAVIC and ACTG trials. One explanation could be the difference in black patients between the different trials (12% in the ACTG trial vs 10% in the RIBAVIC trial while no numbers are mentioned in the other two trials). The brand of interferon does not explain the differences because both the higher and the lower SVR were achieved with both peginterferons.

Currently a head-to-head study with both Pegayas and Peginteron (IDEAL study) is ongoing, but results will not become available for years. Another point is the difference in dosing regime of ribavirin. In the ACTG study a dose-escalated range is used because of fear for haematological side effects caused by ribavirin. The investigators also allowed the use of the haematological growth factors. Laguno et al.14 used much higher doses of ribavirin up to 1200 mg (weight based) without reporting more adverse haematological events but without granulocyte colony stimulating factor or erythropoietin. In chronic hepatitis C monoinfection the preferred dose of ribavirin is weight-based 1000 to 1200 mg/day.26 Recently, the PRESCO study was published by Nunez et al.15 treating coinfected patients with peginterferon alfa-2a and ribavirin to 1000 to 1200 mg for 20 or 12-18 months for genotypes 1 and 4, and 6 or 12 months for genotypes 2 and 3. An overall viral response (ITT) after 48 weeks of treatment of 63% was reported with viral response of 50 and 44% for genotypes 1 and 4, respectively. Data on the impact of extended periods of therapy on SVR are not yet available. Exclusion criteria as mentioned above were only allowed for patients with higher CD4 counts of >300 cells/l were accepted for treatment. The authors conclude that proper selection of patients, good monitoring and compliance and higher doses of ribavirin lead to a better outcome in patients approaching those of HCV monoinfected patients. Therefore, in view of the low reported haematological side effects, the optimal treatment dose of ribavirin appears to be 1000 to 1200 mg/day weight-based, especially in patients infected with genotypes 1 and 4.

The concept of an early virological response (EVR) published by Davis et al., defined as a 2 log10 decline in HCV-RNA load or undetectable levels of HCV-RNA at week 12 of therapy, safely predicts those patients who will reach SVR and those who will not.27 Patients who fail to achieve an EVR will not clear the virus and will not reach a SVR. So they are being treated with peginterferon unnecessarily, at a high cost and at risk considering the possible adverse events. Treatment is therefore stopped at week 12. In the APRICOT, ACTG and RIBAVIC trials this stopping rule is confirmed with only two out of 85 patients, none of 63 patients and one of 159 patients, respectively, not achieving an EVR at 12 weeks but reaching a sustained virological response at the end of treatment. In the four mentioned studies exclusion criteria applicable as contraindications to treatment were signs of decompensated liver cirrhosis, a major depression and signs of an autoimmune disease. Also, if patients had a CD4 count below 100 cells/mm3 and thrombocytopenia or low neutrophil counts they were not eligible for treatment.
Therefore, these patients should only be treated cautiously with peginterferon and ribavirin, and monitored closely. Another important issue is the interaction between ribavirin and antiretroviral therapy. Ribavirin, a nucleoside analogue, is known to inhibit mitochondrial polymerase gamma and to promote the intracellular conversion of didanosine to its active metabolite thereby leading to an increased and cytotoxic level of didanosine. The clinical syndrome of mitochondrial toxicity is symptomatic hyperlactataemia, lactic acidosis and pancreatitis. There is accumulating evidence warning against the concomitant use of didanosine and ribavirin. Although not reported in the APRICOT evidence warning against the concomitant use of didanosine lactic acidosis and pancreatitis. There is accumulating mitochondrial toxicity is symptomatic hyperlactataemia, lactic acidosis and pancreatitis. There is accumulating evidence warning against the concomitant use of didanosine and ribavirin. Although not reported in the APRICOT trial, the other three trials confirm that this combination leads to the clinical syndrome of mitochondrial toxicity. The same mechanism of action can account in vitro for other nucleoside analogues such as zidovudine and stavudine but this has so far not been proven to be clinically significant. In conclusion, patients with HVC genotype 1 and HIV coinfection treated with PEG-IFN plus weight-based ribavirin 1000 to 1200 mg/day can achieve an overall SVR between 27 to 44% as compared with standard IFN plus RBV. These sustained virological response rates are lower compared with the SVR in patients only infected with HCV. Although side effects are numerous and therapy is demanding for both patients and physicians, treatment with peginterferon and ribavirin is currently the best option for coinfected patients. For genotypes 2 and 3, in contrast to noninfected patients, a duration of therapy of 48 weeks is currently advised. The most common side effects of treatment are flu-like symptoms and depression, but this does not usually lead to treatment discontinuation. Adverse events are mild to moderate and can be treated with dose modification or with the use of haematological growth factors.

Where do we stand?

Where do we stand? Over the last years knowledge about viral kinetics, viral interaction and treatment in coinfected patients is accumulating rapidly. This results in a better virological insight into how these viruses interact and in how to treat this subgroup of patients safely and successfully. There is still debate about the exact impact of HCV on the natural course of HIV and about the effects of HAART on HCV RNA levels. In contrast, it is clear that coinfection with HIV leads to a faster progression of liver cirrhosis in hepatitis C infected patients. With numbers of patients increasing, it is vital that better treatment options are found. The current optimal treatment strategy is pegylated interferon in combination with ribavirin for 48 weeks. There is still debate about the optimal dose of ribavirin in view of liver toxicity. The right time to start treatment is another key question to be resolved in the near future. What is emerging from these studies is that patients are eligible for treatment when they have moderate disease meaning a CD4 cell count above 200 cells/mm³, a stable regime of HAART without didanosine and signs of portal fibrosis or more (but not decompensated liver disease) on liver biopsy. There is still debate about when to start treatment in coinfected patients with no signs of fibrosis or only showing signs of inflammation. According to the British guidelines there are two options, namely defer treatment and repeat a liver biopsy in two to three years time or start treating hepatitis C. Considering the increased progression rate to cirrhosis and fibrosis in coinfected patients some experts in the field advocate starting hepatitis C treatment in this category of patients as soon as possible preferably before starting HAART. On the other hand cure rates are low, side effects often occur and only one treatment modality is currently available. International standards are currently not available. It is generally agreed that a CD4 cell count lower than 200 cells/mm³ is a contraindication for hepatitis C treatment and that first the effect of HAART should be awaited. Also patients with decompensated liver cirrhosis are not candidates for treatment because peginterferon is contraindicated in this subgroup of patients. Treatment modalities are changing rapidly. Analogue to the antiretroviral therapy in HIV patients, new nucleoside analogues and protease inhibitors are being developed. They will be introduced into clinical practice within the coming years.

REFERENCES


Blood glucose awareness training in Dutch type 1 diabetes patients: one-year follow-up

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1Medical Psychology Section, Departments of 2Medical Statistics, 3Psychiatry and 4Endocrinology, 5Division of Clinical and Health Psychology, Leiden University Medical Centre, Leiden, the Netherlands, 6Department of Medical Psychology, Amsterdam Medical Centre, Amsterdam, the Netherlands, 7Department of Medical Psychology, Free University Medical Centre, Amsterdam, the Netherlands, corresponding author

ABSTRACT

Background: American studies have shown positive effects of Blood Glucose Awareness Training (BGAT) on the recognition of hypoglycaemia. We evaluated the effects of BGAT among Dutch patients, and compared individual training with training in the original group format.

Methods: Fifty-nine type 1 diabetes patients participated in BGAT in either a group (n=35) or an individual (n=24) setting. Before and one year after training they performed up to 70 measurements, two to four a day, at home on a handheld computer. During each measurement they estimated their blood glucose (BG), indicated whether they would be participating in traffic and raised their BG on the basis of their estimation, and then measured their BG. The incidence of severe hypoglycaemia and traffic accidents was also assessed.

Results: BGAT had positive effects on hypoglycaemic awareness, decisions not to drive and to raise the blood glucose during hypoglycaemia, severe hypoglycaemic episodes and traffic accidents. The accuracy of BG estimates only improved after group training, while after individual training patients tended to measure more or less frequently high BG values.

Conclusion: The training improved awareness of hypoglycaemia, and seems worthy of implementation in the Netherlands.

KEYWORDS

Awareness, driving, hypoglycaemia, handheld computers, traffic accidents, training

INTRODUCTION

In type 1 diabetes mellitus, intensive insulin therapy is effective in delaying late complications of the diabetes,1 but also increases the frequency of hypoglycaemia.2 Timely recognition and correction of hypoglycaemia is important to avoid severe hypoglycaemic episodes. A quarter of the patients with type 1 diabetes have difficulty recognising hypoglycaemia in time;4 they suffer from ‘reduced hypoglycaemic awareness’. Cox et al.5 developed ‘Blood Glucose Awareness Training’ (BGAT) to help patients recognise, correct, anticipate and prevent blood glucose (BG) values outside of the normal range. During eight group sessions, information is provided on autonomic symptoms, neuroglycopenic symptoms, mood symptoms, hyperglycaemic symptoms, and the influence of stress, food, insulin and exercise on the BG. Participants exchange experiences and do exercises, for instance to examine the effect of neuroglycopenia on cognitive and motor performance. In between the sessions, patients keep a symptom diary to examine the relationship between their personal symptoms and blood glucose levels. They estimate their BG level before measuring it, and get direct feedback on the accuracy of their estimation from a coloured grid with safe and dangerous estimation zones. In the short term, BGAT improved the ability to estimate BG levels6,7 and the detection of hypoglycaemia8 in American samples. A Dutch adaptation of BGAT improved BG estimations, the number of hypoglycaemic readings, and fear of hypoglycaemia directly after the training.6 In the longer term (12 months or more), BGAT reduced the number of road traffic accidents,4,9 while positive effects on other measures (such as hypoglycaemia detection) were maintained.4 There were no differences between the effects six months and 12 months after BGAT.10 The present study evaluated the effects of a Dutch adaptation of BGAT-III (3rd version of BGAT).11 and compared training in the original group format with individual training, which may be more easily incorporated into the hospital routine, and more tailored to an individual patient’s situation, preferences and concerns. Shortly after BGAT, only handheld computer measures were collected. We observed no significant effects on the recognition of hypoglycaemia or any other measure, with the exception of wiser decisions to raise the BG and not to drive during hypoglycaemia.12 Aims of the present study were to assess the effects of BGAT one year after training on (handheld computer) measures of BG perception, decisions not to drive and to raise the BG during hypoglycaemia; diabetes regulation; and on (questionnaire) measures of hypoglycaemia related worry, severe hypoglycaemia, and self-monitoring of the blood glucose (SMBG). We furthermore assessed possible differences between the effects of individual and group BGAT.

MATERIALS AND METHODS

Patients

Patients in the sample participated in a research project on reduced hypoglycaemic awareness.13 They were diagnosed with type 1 diabetes mellitus before the age of 40 and at least two years prior to invitation, had become insulin dependent within 18 months after diagnosis, used multiple injections a day or continuous subcutaneous insulin infusion (CSII), were under 65 years of age, and had no serious physical or psychological comorbidity. All 123 patients in the original sample were invited to participate in the training. Baseline characteristics of participants and those who declined participation are displayed in table 1.

Participants were a mean of five years older (p=0.05) and had more impaired hypoglycaemic awareness than patients who did not participate in BGAT (p=0.00-0.03).

The intervention

BGAT-III was adapted and translated into Dutch by the Dutch Psychosocial Diabetes Working Group.11 The original eight classes were reduced to six weekly sessions. The chapters on food, insulin and exercise were integrated into one chapter, as it was assumed that these topics were covered well enough by the standard diabetes education available for every patient in the Netherlands. Group BGAT was offered in the evenings, to small groups of five to nine patients, by a diabetes educator and a psychologist. The six weekly sessions lasted 1.5 to 2 hours. Individual BGAT was offered in the daytime, and consisted of up to six 30-minute sessions with a diabetes educator.

While the same manual was used for both interventions, individual training was more tailor-made: topics of specific importance to an individual patient received more attention, and appointments were scheduled in accordance with the patient.

Procedure

Patients were interviewed at the hospital, completed questionnaires, and a blood sample was sent to the laboratory for HbA1c assessment (HPLC technique).15 They then performed up to 20 handheld computer (HHC, Pixon P-250, Hoofddorp, the Netherlands) measurements at home, two to four measurements a day, over a four to six week period.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>NO TRAINING</th>
<th>GROUP BGAT</th>
<th>INDIVIDUAL BGAT</th>
<th>P TRAINING VS NO TRAINING</th>
<th>P GROUP VS INDIVIDUAL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>59.3 (8.8)</td>
<td>47.2 (6.1)</td>
<td>46.8 (5.1)</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45%</td>
<td>68%</td>
<td>50%</td>
<td>0.08</td>
<td>0.18</td>
</tr>
<tr>
<td>Female</td>
<td>55%</td>
<td>32%</td>
<td>50%</td>
<td>0.74</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td>5.1 (2.6)</td>
<td>5.6 (2.2)</td>
<td>4.8 (2.3)</td>
<td>0.26</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>Duration of DM (years)</strong></td>
<td>20.2 (10.0)</td>
<td>21.9 (8.9)</td>
<td>21.3 (12.1)</td>
<td>0.17</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td>7.9 (4.4)</td>
<td>7.5 (4.1)</td>
<td>7.5 (4.0)</td>
<td>0.11</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Neuropathy</strong></td>
<td>1.4 (0.7)</td>
<td>1.4 (0.8)</td>
<td>1.3 (0.7)</td>
<td>0.86</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>CSII</strong></td>
<td>6%</td>
<td>12%</td>
<td>5%</td>
<td>0.64</td>
<td>0.40</td>
</tr>
<tr>
<td><strong>Hypo awareness</strong> 0-10</td>
<td>6.4 (4.8)</td>
<td>4.9 (4.0)</td>
<td>5.2 (4.7)</td>
<td>0.00</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>BG level at detecting hypo</strong></td>
<td>3.7 (1.1)</td>
<td>3.0 (0.8)</td>
<td>2.7 (0.9)</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>Accuracy hypo</strong></td>
<td>0.9 (1.6)</td>
<td>1.1 (0.6)</td>
<td>1.3 (0.6)</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Recognised hypoglycaemia (%)</strong></td>
<td>45.6 (22.1)</td>
<td>51.4 (24.3)</td>
<td>52.8 (22.6)</td>
<td>0.03</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>No. of severe hypo last year</strong></td>
<td>5.0 (6.4)</td>
<td>6.6 (7.0)</td>
<td>6.6 (6.9)</td>
<td>0.03</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Participants who did not receive blood glucose awareness training (BGAT) were not included in the present study (see discussion).11 Significance of independent sample t-test, except for gender and CSII: significance of χ2-test. Educational level ranged from 1 (primary school) to 8 (university). There were no differences in mean HbA1c (BGAT vs no training) and between the groups (BGAT-III).
They were instructed to perform these HHC measurements when they habitually checked their blood glucose, and when they expected their blood glucose to be high or low. During every HHC measurement, they estimated their BG, indicated whether they would raise their BG and whether they would participate in traffic on the basis of their estimation, and then determined their blood glucose level. They were given a One Touch Profile blood glucose memory meter (Lifescan, Beersema, Belgium) to obtain uniform measurements. The study was not randomised because of practical considerations. Resources were limited, and some patients were not able to attend the group meetings during the evenings, while others were unable to attend individual sessions during the day. Therefore patients chose either group or individual BGAT, conform clinical practice. After BGAT, patients again performed HHC measurements and one year after BGAT they were asked to perform HHC measurements and to again complete questionnaires. All participants gave their written informed consent, and the Medical Ethics Committee of Leiden University Medical Centre (LUMC) approved the study.

Outcome measures

Handheld computer (HHC) measurements that were not preceded by another measurement within two hours were used to calculate the aggregated HHC measurements. Only valid HHC measurements both at baseline and one year after BGAT were considered.

Questionnaire measures

- Frequency of self-monitoring of the blood glucose (SMBG) was assessed by the open question: ‘How many times per day do you measure your BG? On these days, how often do you measure your BG?’ The mean number of measurements a day was calculated.
- Frequency of severe hypoglycaemic episodes during the preceding year was asked about episodes during the night. The numbers of episodes during the day and night were added up.
- Fear of hypoglycaemia (HFS): The Hypoglycaemia Fear Survey (HFS-95)18,19 is a validated measure of hypoglycaemia-related worry. Patients answer 15 items on a 0 (never) to 4 (always) scale. Scores range from 0 to 60, high scores reflect increased worry about hypoglycaemia.
- Traffic accidents: ‘During the previous 12 months, how many times have you been involved in a traffic accident?’ (open question)

Statistics

SPSS 6.0 was used to analyse the data. All variables were normally distributed, except for SMBG. Nonparametric tests were used for this variable. Descriptive statistics and frequencies were used to describe the sample. t-Tests (Mann-Whitney U) and χ² tests were used to assess differences between participants vs nonparticipants and patients in group vs patients in individual training. Repeated measures analysis (2 time: pre BGAT vs one year after BGAT) x 2 (treatment: group vs individual training) ANCOVA, with the baseline value as covariate was used to assess the significance of change over time and the possible differential effect of individual and group treatment. P<0.05 was considered significant. When the time x treatment interaction was significant, post hoc within-group comparisons were made, by means of paired t-tests and readings at 6.25 mmol/l progressively increasing weightings, up to 100 at a BG of 33.3 mmol/l. A higher AI reflects more frequent, or more severe, hyperglycaemia.
- Blood glucose risk index (BGRI):20-22 LBGx + HBGI The BGRI increases with the number and/or extent of extreme BG values (HHC).
- Judgement on driving during hypoglycaemia: The percentage of decisions to drive while the actual BG was below 3.6 mmol/l.
- Judgements occuring the BG during hypoglycaemia: The percentage of decisions to raise the BG (HHC) while the actual BG was below 3.5 mmol/l.

RESULTS

Fifty-nine patients participated in BGAT, 27 in a group and 22 in an individual setting. Baseline characteristics of the participants were displayed in Table 1. No baseline differences between patients in group training vs patients in individual training emerged, but there was a trend for patients in individual training to self-report higher awareness of hypoglycaemia (p=0.09). Differences between them on more objective measures of hypoglycaemia awareness did not reach significance.

Handheld computer data

Valid handheld computer measurements both at baseline and at follow-up were completed by 36 patients (61%; 24 group, 12 individual). Table 2 shows baseline and follow-up HHC data and HbA₁c, the significance of change after BGAT (time effect), and the significance of the differential effect of the two treatment conditions (interaction term).

After BGAT, the percentage of recognised hypoglycaemic episodes (p=0.02), decisions not to drive during hypoglycaemia (p=0.01) and decisions to raise the BG during hypoglycaemia (p=0.03) improved. The change in scores after group and individual BGAT differed significantly for two measures: the accuracy index (p=0.04) and the high blood glucose index (p=0.09). Post hoc comparisons showed that the accuracy index improved after group BGAT (3.5 to 8.8, p=0.005), but not after individual BGAT (11.5 to 11.7, p=0.79). The high blood glucose index tended to deteriorate after individual BGAT (HbA₁c 11.4 to 13.4, p=0.09), but not after group BGAT (10.7 to 9.9, p=0.25).

DISCUSSION

To our knowledge, this is the first study to assess long-term effects of BGAT in a European sample. American long-term studies on the effects of BGAT reported improved detection of high and low BG readings; wiser judgments concerning BG corrections and not driving during hypoglycaemia; reduced ketonuria, severe hypoglycaemia and traffic accidents; improved quality of life and diabetes knowledge and reduced worry about hypoglycaemia one year after the training;6 few car crashes at a mean of five years after the training;4 and improved BG estimations and hypoglycaemic awareness a mean of five years after training when patients had received a booster training.6 The present study partly replicated these positive results, despite a modest sample size. We observed significant improvements in awareness and traffic accidents.

Table 2

<table>
<thead>
<tr>
<th>GROUP BGAT (N=14)</th>
<th>INDIVIDUAL BGAT (N=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BASELINE</strong></td>
<td><strong>FOLLOW-UP</strong></td>
</tr>
<tr>
<td><strong>BASELINE</strong></td>
<td><strong>FOLLOW-UP</strong></td>
</tr>
<tr>
<td>Accuracy index (%)</td>
<td>5.3 (2.4)</td>
</tr>
<tr>
<td>Recognised hypoglycaemic episodes (%)</td>
<td>27.9 (24.6)</td>
</tr>
<tr>
<td>HBGx (%)</td>
<td>15.9 (23.4)</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>5.8 (4)</td>
</tr>
<tr>
<td>High blood glucose index (%)</td>
<td>5.8 (4)</td>
</tr>
<tr>
<td>Blood glucose risk index (%)</td>
<td>6.7 (5.6)</td>
</tr>
<tr>
<td>Not driving during hypoglycaemia (%)</td>
<td>43.7 (49.7)</td>
</tr>
<tr>
<td>Basing BG during hypoglycaemia (%)</td>
<td>51.3 (39.7)</td>
</tr>
</tbody>
</table>

Significance of change after BGAT (time effect) and significance of the difference in effect of the treatment conditions (interaction term). *One patient did not measure any hypoglycaemic episodes.
positive effects on the recognition of hypoglycaemia, decisions not to drive and to raise the BG during hypoglycaemia, the frequency of severe hypoglycaemic episodes, self-monitoring of the blood glucose, and traffic accidents. The present study had no control group and was not randomised. It is therefore uncertain if the observed improvements were due to the training per se. Nonparticipants were younger and tended to be more often female than participants, but did not differ from participants in diabetes-related characteristics. Unreported data of a sample of patients who did not participate in BGAT showed that while participants improved, controls remained stable or deteriorated on most outcome measures. This strengthens our conclusion that BGAT may have had beneficial effects. Data on these control subjects were not presented here because at baseline, controls differed from participants in hypoglycaemic awareness, as was shown in table 1. They are available from the authors on request. Other studies also show that it is unlikely for patients to improve their BG estimations with the passing of time alone.7 For these reasons, we are quite confident that the observed improvements could be attributed to BGAT.

The effects of training in the original group format were compared with the effects of individual training, and two differences emerged. Group training had positive effects on the accuracy of BG estimations while individual training did not. Furthermore, after individual training, patients tended to measure more frequent, and/or more extreme, BG levels than at baseline (an undesired effect). Furthermore, after individual training, patients tended to measure more frequent, and/or more extreme, BG levels than at baseline (an undesired effect).

At follow-up, the rate of traffic accidents was reduced compared with baseline. In an American sample, reductions in traffic accidents were also reported six and 12 months after BGAT. Although traffic accidents were measured by means of retrospective self-report, in our opinion, it seems unlikely that after BGAT patients would be unable to remember accidents to a lesser degree, or that they would be more reluctant to report accidents. We think it is likely that BGAT was able to reduce the rate of traffic accidents among participants.

While the present follow-up data showed positive results of BGAT, the data directly after training did not.29 Intuitively, training effects would be expected to last (rather than increase) with time, when no follow-up booster is provided. Directly after the training, changes in outcome measures were in the right direction, but did not reach statistical significance. Maintenance of BGAT effects up to one year after the training was also reported in two American studies.4,6 We can think of two further explanations for the fact that the effects of the training were only significant at the follow-up measurement. First, directly after BGAT, after the baseline assessment and keeping the symptom diary during the training, patients were reluctant to use the handheld computers again. They were a bit ‘fed up’ with the effort of keeping note of BG readings and estimations, and answering additional questions. This may have influenced the results. Second, about a year after the training, one of the patients mentioned that right after the training, she was alert to specific symptoms that would tell her that her BG was low. At times she misjudged her BG level on the basis of these separate symptoms. After a while, however, she developed a type of ‘overall feeling’, which helped her to recognise hypoglycaemia more readily. During the year after the training, on the basis of her experience in monitoring BG symptoms, she may have developed intuitions (skilled pattern recognition, understanding without a rationality),26 which takes time to develop, and is generally considered an element of expertise.

Table 3

<table>
<thead>
<tr>
<th>GROUP BGAT</th>
<th>INDIVIDUAL BGAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASELINE</td>
<td>FOLLOW-UP</td>
</tr>
<tr>
<td>P TIME</td>
<td>P INTERACTION</td>
</tr>
<tr>
<td>HFS worrya</td>
<td>16 (9)</td>
</tr>
<tr>
<td>Severe hypoglycaemia</td>
<td>7 (5)</td>
</tr>
<tr>
<td>SMBGe</td>
<td>4.4 (8)</td>
</tr>
<tr>
<td>Trafficaccidents</td>
<td>0.3 (0.4)</td>
</tr>
</tbody>
</table>

Significance of change after BGAT (‘time’) and differential effect of the treatment conditions (‘interaction’). a49 patients returned questionnaires, smaller n ‘s are the result of missing data. bHFS = hypoglycaemia fear survey. cNumber of reported severe hypoglycaemic episodes per year. dSMBG = times a day of self-monitoring of blood glucose. eNumber of reported traffic accidents per year.

C O N C L U S I O N

We observed significant improvements in clinically relevant measures one year after BGAT, despite a modest sample size. Group training should be preferred over individual training, but individual training also improved hypoglycaemic awareness. This adapted version of BGAT seems worthy of implementation in the Netherlands.

A C K N O W L E D G E M E N T S

This study was supported by grant 95.104 of the Dutch Diabetes Research Foundation. We thank all participating patients for their time and effort, Manrique Wayenberg-Saman, diabetes educator of the LIMC, for her contributions to BGAT and the project, and R. Hoogma, MD, of the Groene Hart Hospital, Gouda, for his kind cooperation.

R E F E R E N C E S

Paroxysmal atrial fibrillation, quality of life and neuroticism

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ABSTRACT

Background: Paroxysmal atrial fibrillation (AF) is associated with significant impairment of quality of life (QoL), which is to a large extent independent of objective measures of disease severity. We sought to investigate the potential role of neuroticism in the impairment of QoL in patients with paroxysmal AF.

Methods: The study group (AF group) comprised 73 patients with paroxysmal AF (mean age 55 ± 13 years, 59 males). On average, patients had a three-year history of one symptomatic paroxysm a week lasting two hours. QoL was assessed using the Medical Outcomes Study Short Form (SF-36) and neuroticism was assessed using the short-scale Eysenck Personality Questionnaire (EPQ).

Results: The degree of neuroticism in the AF patient group did not differ from the degree of neuroticism in a group of age- and sex-matched controls (mean EPQ score 4.1 ± 3.0 and 3.9 ± 3.1, respectively; p=NS). Within the AF group, multivariate regression analyses showed that QoL in the physical domain (SF-36 physical functioning, physical role function, vitality and physical pain subscales) was not related to the degree of neuroticism.

In contrast, significant inverse relations were observed between scores on the mental health and social functioning subscales and the degree of neuroticism. Patients with paroxysmal AF had a three-year history of one symptomatic paroxysm a week lasting two hours. QoL in the physical domain (SF-36 physical functioning, physical role function, vitality and physical pain subscales) was not related to the degree of neuroticism. In contrast, significant inverse relations were observed between scores on the mental health and social functioning subscales and the degree of neuroticism.

In conclusion, the degree of neuroticism is an important predictor of psychological distress, both in the presence and the absence of stressful circumstances. More specifically, persons with a high degree of neuroticism often have vague complaints about their health, which are not readily attributable to objective somatic disease, but which may nonetheless have a negative impact on their QoL. The aim of the present study was to investigate the potential role of neuroticism in the impairment of QoL in patients with paroxysmal AF.

MATERIALS AND METHODS

Patient selection and study design

The study group consisted of patients who had participated in a previous study on QoL.1 Briefly, all consecutive patients from the outpatient clinic with paroxysmal AF, aged 18 years, were considered eligible for the study. Quality of life was defined as proposed by Gallagher and Camm.6 Paroxysmal AF had to terminate either spontaneously or after treatment with an antiarrhythmic drug. The presence of AF was based on electrocardiographic evidence, including ambulatory (Holter) monitoring. Lone AF was inferred when routine cardiac investigations (echocardiogram, ergometry) did not reveal structural heart disease. Patients with hypertension were considered to have structural heart disease. In the first study1 a set of questionnaires was administered to the patients, including questionnaires on QoL, symptomatology and personality. Data thus collected were entered into a database, and in the present study we used this database focusing on personality, that is, neuroticism. The study was performed in accordance with the Declaration of Helsinki and approved by the institutional ethics committee. Informed consent was obtained from all patients.

Quality of life and symptomatology

Details have been described previously. Briefly, QoL was measured by the SF-36,7 which is a widely used, thoroughly validated, standardised, generic health survey, consisting of eight subscales that measure physical functioning, bodily pain, role limitations due to physical or emotional problems, social functioning, as well as sense of vitality, mental health and general health. These scales together cover the three major domains of QoL, i.e. physical and social functioning, and mental health. Scores of each scale are transformed to a scale ranging from 0 to 100, with lower scores representing a lower QoL. The following symptoms were incorporated in the analysis: palpitations, dyspnoea, dizziness and chest pain. Patients were asked to rate these symptoms as they occurred during AF according to severity; none-to-mild or moderate-to-severe.

Neuroticism

Neuroticism was assessed using the revised, short-scale Eysenck Personality Questionnaire (EPQ), with a validated Dutch translation (table 6). Neuroticism is quantified using a set of 12 questions, to be answered with yes or no. The total score thus ranges from 0 to 12, a higher score signifying a higher degree of neuroticism.

Table 1. Eysenck personality questionnaire (revised, short scale)

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does your mood often go up and down?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you ever feel ‘put miserable’ for no reason?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Are you an irritable person?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Are your feelings easily hurt?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Do you often feel ‘tied-up’?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Would you call yourself a nervous person?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Are you a worrier?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Would you call yourself tense or ‘highly-strung’?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Do you worry too long after an embarrassing experience?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Do you suffer from ‘nerves’?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Do you often feel lonely?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Have you often troubled about feelings of guilt?</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

QoL is probably not surprising. On the other hand, although loss of QoL is greater in severely symptomatic patients, even mildly symptomatic AF patients have a lower overall perception of well-being (‘global life satisfaction’).1 In conclusion, the impairment of QoL in patients with AF is still partly explained, and other factors should be considered. We hypothesised that neuroticism might be implicated in the impairment of QoL in patients with AF. Neuroticism is a stable personality trait, which gives an indication of the emotional stability of a person. Persons with high scores on neuroticism scales tend to be anxious and to have more worries in general, and neuroticism has proved to be an important predictor of psychological distress, both in the presence and the absence of stressful circumstances. More specifically, persons with a high degree of neuroticism often have vague complaints about their health, which are not readily attributable to objective somatic disease, but which may nonetheless have a negative impact on their QoL. The aim of the present study was to investigate the potential role of neuroticism in the impairment of QoL in patients with paroxysmal AF.

*Neuroticism is a stable personality trait, which gives an indication of the emotional stability of a person. Persons with high scores on neuroticism scales tend to be anxious and to have more worries in general, and neuroticism has proved to be an important predictor of psychological distress, both in the presence and the absence of stressful circumstances. More specifically, persons with a high degree of neuroticism often have vague complaints about their health, which are not readily attributable to objective somatic disease, but which may nonetheless have a negative impact on their QoL. The aim of the present study was to investigate the potential role of neuroticism in the impairment of QoL in patients with paroxysmal AF. However, the impairment of QoL in these patients, in particular regarding social functioning and mental health, seems to be related to a relatively high degree of neuroticism, independent of age and sex.

KEYWORDS

Atrial fibrillation, neuroticism, quality of life

INTRODUCTION

Atrial fibrillation (AF) is a very common arrhythmia, and its prevalence is still increasing. Two studies have recently been published with a primary focus on the impact of paroxysmal AF on quality of life (QoL).1,3 Both studies used the Medical Outcomes Study Short Form (SF-36). The two studies were consistent: patients with paroxysmal AF were characterised by rather low QoL across all domains (physical and social functioning, and mental health) compared with healthy controls. Of interest is that in both studies QoL only marginally depended on objective measures of disease severity (New York Heart Association functional class, left ventricular function) and even arrhythmia burden (frequency and duration of paroxysms, as based on the history) played a minor role. Instead, it was shown that the presence of cardiac symptoms associated with paroxysms of AF was predictive for impaired QoL.4 For instance, chest pain and dizziness were associated with a low score on the physical role function subscale, which is probably not surprising. On the other hand, although loss of QoL is greater in severely symptomatic patients, even mildly symptomatic AF patients have a lower overall perception of well-being (‘global life satisfaction’). In conclusion, the impairment of QoL in patients with AF is still partly explained, and other factors should be considered. We hypothesised that neuroticism might be implicated in the impairment of QoL in patients with AF. Neuroticism is a stable personality trait, which gives an indication of the emotional stability of a person. Persons with high scores on neuroticism scales tend to be anxious and to have more worries in general, and neuroticism has proved to be an important predictor of psychological distress, both in the presence and the absence of stressful circumstances. More specifically, persons with a high degree of neuroticism often have vague complaints about their health, which are not readily attributable to objective somatic disease, but which may nonetheless have a negative impact on their QoL. The aim of the present study was to investigate the potential role of neuroticism in the impairment of QoL in patients with paroxysmal AF.

METHODS

Patient selection and study design

The study group consisted of patients who had participated in a previous study on QoL.1 Briefly, all consecutive patients from the outpatient clinic with paroxysmal AF, aged 18 years, were considered eligible for the study. Quality of life was defined as proposed by Gallagher and Camm.6 Paroxysmal AF had to terminate either spontaneously or after treatment with an antiarrhythmic drug. The presence of AF was based on electrocardiographic evidence, including ambulatory (Holter) monitoring. Lone AF was inferred when routine cardiac investigations (echocardiogram, ergometry) did not reveal structural heart disease. Patients with hypertension were considered to have structural heart disease. In the first study1 a set of questionnaires was administered to the patients, including questionnaires on QoL, symptomatology and personality. Data thus collected were entered into a database, and in the present study we used this database focusing on personality, that is, neuroticism. The study was performed in accordance with the Declaration of Helsinki and approved by the institutional ethics committee. Informed consent was obtained from all patients.

Quality of life and symptomatology

Details have been described previously.1 Briefly, QoL was measured by the SF-36,7 which is a widely used, thoroughly validated, standardised, generic health survey, consisting of eight subscales that measure physical functioning, bodily pain, role limitations due to physical or emotional problems, social functioning, as well as sense of vitality, mental health and general health. These scales together cover the three major domains of QoL, i.e. physical and social functioning, and mental health. Scores of each scale are transformed to a scale ranging from 0 to 100, with lower scores representing a lower QoL. The following symptoms were incorporated in the analysis: palpitations, dyspnoea, dizziness and chest pain. Patients were asked to rate these symptoms as they occurred during AF according to severity; none-to-mild or moderate-to-severe.

Neuroticism

Neuroticism was assessed using the revised, short-scale Eysenck Personality Questionnaire (EPQ), with a validated Dutch translation (table 6). Neuroticism is quantified using a set of 12 questions, to be answered with yes or no. The total score thus ranges from 0 to 12, a higher score signifying a higher degree of neuroticism.
the majority no structural heart disease was apparent (AF). Almost half of the patients with structural heart disease had hypertension. None of the patients had congestive heart failure. Mean echo parameters were within the normal range. Self-reported arrhythmia burden in terms of the duration of the paroxysms ranged from 15 minutes to two days, whereas the frequency ranged from two paroxysms a year to five a week. On average, patients had a three-year history of one paroxysm a week lasting two hours. Most patients (75%) were on an antiarrhythmic agent to suppress their arrhythmia (‘rhythm control’).

### Table 2

<table>
<thead>
<tr>
<th>N</th>
<th>Age (years) ± SD</th>
<th>Sex (male)</th>
<th>Female (%)</th>
<th>Underlying heart disease (%)</th>
<th>Ischaemic heart disease (%)</th>
<th>Valvular heart disease (%)</th>
<th>Hypertension (%)</th>
<th>Lown atrial fibrillation (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>73</td>
<td>55.5 ± 13.5</td>
<td>50 (68)</td>
<td>23 (32)</td>
<td>12 (16)</td>
<td>7 (10)</td>
<td>-0.01</td>
<td>-0.74</td>
<td>-0.01</td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>Relation of QoL with symptoms and neuroticism</th>
<th>PHYSICAL FUNCTIONING</th>
<th>SOCIAL FUNCTIONING</th>
<th>PHYSICAL ROLE FUNCTION</th>
<th>EMOTIONAL ROLE FUNCTION</th>
<th>MENTAL HEALTH</th>
<th>VITALITY</th>
<th>PAIN</th>
<th>GENERAL HEALTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palpitations Neuroticism</td>
<td>-0.05</td>
<td>-0.39</td>
<td>-0.01</td>
<td>-0.07</td>
<td>-0.12</td>
<td>-0.74</td>
<td>-0.01</td>
<td>-0.04</td>
</tr>
<tr>
<td>P</td>
<td>-0.26</td>
<td>-0.01</td>
<td>-0.12</td>
<td>-0.17</td>
<td>-0.21</td>
<td>-0.35</td>
<td>-0.11</td>
<td>-0.21</td>
</tr>
</tbody>
</table>

### Discussion

Main findings

In the present study, patients with paroxysmal AF were found to have on average a degree of neuroticism similar to age- and sex-matched controls. However, within the group of AF patients, impairment of QoL, in particular regarding social functioning and mental health, was related to a higher degree of neuroticism, independent of age and sex.

Atrial fibrillation and personality

The role of personality in patients with coronary artery disease is an issue of ongoing debate.1,2 However, studies regarding personality and cardiac disorders other than coronary artery disease are scarce. In particular, to our knowledge no data are available on neuroticism in patients with AF, despite the fact that AF is rapidly becoming a major health problem associated with substantial morbidity and mortality. Perhaps based on clinical experience with individuals one might intuitively surmise that patients with paroxysmal AF have on average a higher degree of neuroticism than other persons. However, the results of our study clearly indicate that this is not the case; although the EPQ scores on neuroticism differed among the individual patients, patients with high scores, mean score in the group as a whole was similar to the mean score in the group of age- and sex-matched controls. In other words, patients with paroxysmal AF would on average appear to have a ‘normal’ degree of neuroticism.

Quality of life and neuroticism

Notwithstanding the observation that patients with paroxysmal AF have on average a normal degree of neuroticism, it would be conceivable that patients with paroxysmal AF with a higher degree of neuroticism suffer from an even lower QoL than patients with a lower degree of neuroticism. Unlike the more physical domain of QoL, in the domains of social functioning and mental health, a high degree of neuroticism was indeed found to be related to a low QoL. In more practical terms this finding implies that patients with a high degree of neuroticism experience poor social functioning and mental health, irrespective of the presence of the physical symptoms associated with their arrhythmia.

In other words, whether or not the patient suffers from palpitations (or other symptoms), social functioning and mental health are likely to be poor if the patient has a high degree of neuroticism. Extending this concept even further, it may even be surmised that the presence or absence of AF as such is irrelevant, patients with a high degree of neuroticism experience poor social functioning and mental health anyway. Our study also provides a likely explanation for the finding in a previous study on QoL in patients with AF by Paquette et al.17 By using the Barsky Somatization Amplification Scale, they investigated the tendency of AF patients to somatise, i.e. to amplify benign bodily sensations, and they showed that a high tendency to somatise predicted a poor QoL. Since the tendency to somatise is one of the established features of neuroticism, it is readily conceivable that neuroticism was the actual underlying personality disorder in these patients.

### Methodological considerations

In the present study we assessed the relation between neuroticism and QoL. The analysis was corrected for age and sex, but we did not incorporate measures on structural heart disease and arrhythmia burden. Also, medication (in particular antiarrhythmic agents) was not incorporated in the analysis. However, these factors have previously been shown to have only a minor effect (at the most) on QoL.18 Another consideration concerns the possibility that personality was affected by paroxysmal AF. In particular, it is intuitively conceivable that the degree of neuroticism would increase over time, secondary to the illness. However, as a constitutional entity, personality is stable over time, and life events (including somatic disease) do not significantly affect personality.19 Moreover, the fact that the degree of neuroticism in patients with paroxysmal AF was not higher than in controls argues against such an effect. Finally, this study was not designed to determine whether the patients were ‘neurotic’ in terms of a psychiatric disorder. Instead, the concept of neuroticism was used to describe a normal variant of human personality, and the results of our study merely indicate that the impairment of QoL in patients with paroxysmal AF is related to the relative degree of neuroticism, patients with a relatively high degree of neuroticism suffering from a lower QoL than patients with a lower degree of neuroticism.

### Possible implications

Previous studies have shown that treatment of patients with paroxysmal AF, either with medication or ablation techniques20,21 leads to improvement of QoL. However, despite significant reduction of arrhythmia burden, not all patients obtained benefit from treatment in terms of QoL. Given the results of our study, it is conceivable that differences in the degree of neuroticism between the
patients played a critical role in this connection, patients with a high degree of neuroticism benefiting less from treatment. As a practical implication, our findings suggest that when treating patients with paroxysmal AF one should take into consideration whether the patient has a high degree of neuroticism or not. If so, the goal of treatment in terms of improvement of QoL should probably be not too high, at least not regarding social functioning and mental health.

REFERENCES


Original Article

Clinical experience with venlafaxine in the treatment of hot flushes in women with a history of breast cancer

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ABSTRACT

Objective: To obtain practical experience with venlafaxine for hot flushes in breast cancer patients and incorporate this in a treatment protocol.

Method: Twenty-two women with a history of breast cancer (mean age 49.2 years, range 35-65) were referred for consideration of treatment with venlafaxine for hot flushes. Patients received extensive information on treatment with venlafaxine and were advised to self-monitor the frequency of their hot flushes.

Results: Eight women did not start venlafaxine because they had no postmenopausal complaints, were lost to follow-up, had too low a frequency of hot flushes, or refused treatment. Eventually 14 women started venlafaxine. Two of them did not tolerate venlafaxine, four reported some effect but stopped because of side effects, two women had no effect whatsoever. Six women observed a clear (50-100%) reduction in their hot flush frequency that was maintained at a median follow-up of 13 months.

Conclusion: The group of patients referred for treatment was more heterogeneous and more patients dropped out because of side effects than expected. Extensive patient education, patient selection and evaluation of the treatment effect (by self-monitoring of hot flush frequency) are mandatory to avoid useless (continuation of) treatment and to prepare patients for side effects. Under these conditions, a substantial minority of patients benefit from venlafaxine.

KEYWORDS

Antidepressants, breast cancer, hormonal therapy, hot flushes, venlafaxine
women. The effects on hot flushes of these serotonergic drugs are thought to be mediated by an influence on a complex interaction of serotonin, noradrenaline, gonadotropin hormones and sex hormones in the thermoregulatory centres of the brain. After the publication by Loprinzi et al. in 2000, the oncology staff of our hospital decided to refer breast cancer patients with troublesome hot flushes to the psychiatric service in order to concentrate the experience with venlafaxine for this indication. At that time, we were unsure of the generalisability of the findings. In addition, the psychiatrists were familiar with venlafaxine and its side effects. The aim was to incorporate this clinical experience, finally, in a protocol or checklist.

**Table 1**

<table>
<thead>
<tr>
<th>Items to be addressed in breast cancer patients when prescribing venlafaxine for hot flushes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INFORMATION</strong></td>
</tr>
<tr>
<td>No registration for this indication; few data on long-term efficacy</td>
</tr>
<tr>
<td>Most frequently occurring side effects: agitation, anxiety, gastric symptoms, constipation, dry mouth</td>
</tr>
<tr>
<td>May influence driving ability (warning on package)</td>
</tr>
<tr>
<td>Side effects manifest first; positive effects on hot flushes later</td>
</tr>
<tr>
<td>Venlafaxine only influences hot flushes, not other menopausal complaints as vaginal dryness or osteoporosis, nor does it have a direct positive effect on joint pains, fatigue, concentration difficulties</td>
</tr>
<tr>
<td>Effect is to be expected in a reduction of 50% or more in hot flush frequency, according to literature data, intensity of flushes can also decrease</td>
</tr>
<tr>
<td>Explanations of rationale for self-monitoring of hot flush frequency: avoiding unnecessary treatment, evaluation of the effect of therapy and of the ratio of benefits over side effects</td>
</tr>
</tbody>
</table>

**INDICATION FOR PSYCHIATRIC REFERRAL, (RELATIVE) CONTRAINDICATIONS FOR VENLAFAXINE**

Previous experience (side effects) with serotonergic antidepressants (fluoxetine-Fluoxetin®, fluoxetine-Prozac®, paroxetine-Seroxat®, venlafaxine-Zoloft®, citalopram-Cipram®)

Depressed woman? Have you been consistently depressed or down, most of the day, nearly every day, for the past two weeks? In the past two weeks, have you been less interested in most things or less able to enjoy the things you used to enjoy more than most of the time? (History of manic episodes?) Have you ever had a period of time when you were feeling, *up* or *high* or so full of energy or full of yourself that you got into trouble, or that other people thought you were not your usual self? Do not count times when you were intoxicated by drugs or alcohol, or times that you had engaged in sexual or physical fights, or shoted or shoted at people outside your family? Have you or others noticed that you have been more irritable or overreacted, compared with other people, even in situations that you felt were justified?

Anxiety disorder? Easily worried and tense? Sudden attacks of anxiety? Avoidance of places and situations in which you could become anxious and that in higher doses is used for the treatment of hypertension and migraine, 10 to 20% reduction in flushes are found as compared with placebo. This is a mission and that in higher doses is used for the treatment of hypertension and migraine, 10 to 20% reduction in flushes are found as compared with placebo. This is a mission and that in higher doses is used for the treatment of hypertension and migraine, 10 to 20% reduction in flushes are found as compared with placebo. This is a mission and that in higher doses is used for the treatment of hypertension and migraine, 10 to 20% reduction in flushes are found as compared with placebo. This is a mission and that in higher doses is used for the treatment of hypertension and migraine, 10 to 20% reduction in flushes are found as compared with placebo. This is a mission and that in higher doses is used for the treatment of hypertension and migraine, 10 to 20% reduction in flushes are found as compared with placebo. This is a mission and that in higher doses is used for the treatment of hypertension and migraine, 10 to 20% reduction in flushes are found as compared with placebo. This is a mission and that in higher doses is used for the treatment of hypertension and migraine, 10 to 20% reduction in flushes are found as compared with placebo. This is a mission and that in higher doses is used for the treatment of hypertension and migraine, 10 to 20% reduction in flushes are found as compared with placebo. This is a mission and that in higher doses is used for the treatment of hypertension and migraine, 10 to 20% reduction in flushes are found as compared with placebo. This is a mission and that in higher doses is used for the treatment of hypertension and migraine, 10 to 20% reduction in flushes are found as compared with placebo. This is a mission and that in higher doses is used for the treatment of hypertension and migraine, 10 to 20% reduction in flushes are found as compared with placebo. This is a mission and that in higher doses is used for the treatment of hypertension and migraine, 10 to 20% reduction in flushes are found as compared with placebo. This is a mission and that in higher doses is used for the treatment of hypertension and migraine, 10 to 20% reduction in flushes are found as compared with placebo. This is a mission and that in higher doses is used for the treatment of hypertension and migraine, 10 to 20% reduction in flushes are found as compared with placebo. This is a mission and that in higher doses is used for the treatment of hypertension and migraine, 10 to 20% reduction in flushes are found as compared with placebo. This is a mission and that in higher doses is used for the treatment of hypertension and migraine, 10 to 20% reduction in flushes are found as compared with placebo. This is a mission and that in higher doses is used for the treatment of hypertension and migraine, 10 to 20% reduction in flushes are found as compared with placebo. This is a mission and that in higher doses is used for the treatment of hypertension and migraine, 10 to 20% reduction in flushes are found as compared with placebo. This is a mission and...
more than one third of patients appear to derive a long-term benefit from venlafaxine. The number of referrals was unexpectedly low. According to the oncology staff, women were mainly reluctant to take more drugs. In addition, a referral to a psychiatrist, for a possible treatment with a psychotropic drug, could have been an obstacle.

We realise that the procedure as presented here is relatively laborious. However, specialised oncology or psychiatry nurses could assist in patient education and self-monitoring. Moreover, most oncologists will not be confronted frequently enough with this problem to build up experience, a standardised history as shown in table 1 could be useful. In addition, it is important to obtain a short psychiatric history. For instance, in patients who went through a manic episode earlier in their life antidepressants might provoke a recurrent mania. Patients who had previously been treated with a serotonin antagonist should be asked about side effects: logically, they could experience the same side effects again. It is important to assess the presence of an ongoing mood or anxiety disorder. Questions on depression and a history of manic episodes can be asked directly or, as shown in table 1, with modules of the M.I.N.I. Screening on depression and anxiety can also be done with self-report questionnaires as the Hospital Anxiety and Depression Scale. If a mood or anxiety disorder is suspected, consulting a psychiatrist or the general practitioner is self-evident.

Finally, we believe that our clinical experience in breast cancer patients is also relevant for the treatment of hot flushes in general (as part of the physiological menopause in otherwise healthy women), especially since long-term hormone replacement therapy in women with menopausal symptoms is under debate.15 According to the literature, venlafaxine is an effective therapy for hot flushes in breast cancer patients. Our experience indicates that matters are more complex and that the best results with this drug are obtained with extensive patient information, patient selection and repeated evaluation of the effects by self-monitoring of hot flush frequency.

REFERENCES

A patient with abdominal distension

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KEYWORDS
Diagnostic imaging, intestinal obstruction, small bowel faeces sign

CASE REPORT
A 74-year-old woman was admitted to our hospital because of vomiting and abdominal pain. She had been well until 24 hours before admission, when she had had her last meal. She had not eaten anything unusual. She developed pain in the left lower abdominal quadrant, and difficulties with her bowel movements. An enema was given unsuccessfully. There was progressive distension of the abdomen. The patient started to vomit gastric and later bilious contents. No history of abdominal symptoms or weight loss was reported. She currently takes oral antidiabetic agents and an angiotensin II blocker because of hypertension. On physical examination she was not in distress and was afebrile, blood pressure 130/100 mmHg, pulse rate 88 beats/min. On auscultation increased bowel sounds with rushes of high-pitched sounds were heard. Her abdomen was distended and a large tender mass filling the whole left lower quadrant without signs of peritoneal irritation was found. There were no faeces on rectal examination. The leucocyte count was 10.2 × 10⁹/L, haemoglobin 7.2 mmol/L, C-reactive protein 560 mg/l and lactate dehydrogenase 3.55 U/L. Under suspicion of a mechanical bowel obstruction without signs of peritonitis, the patient was treated with a nasogastric tube, fasting and enemas on which she improved. An abdominal X-ray in bed taken on day two showed no bowel distension (figure 1). After removing the nasogastric tube on day two the nausea returned. Abdominal examination was unchanged. An abdominal computed tomography (CT) scan after drinking oral contrast and intravenous contrast was performed (figure 2).

Figure 1
Abdominal X-ray on day 2

Figure 2
Abdominal CT after drinking oral contrast

WHAT IS YOUR DIAGNOSIS?

See page 187 for the answer to this photo quiz.
Neurological complications following Plasmodium falciparum infection

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ABSTRACT

Several neurological complications are associated with severe falciparum malaria. Cerebral malaria is one of the most life-threatening complications. A few patients may experience a neurological syndrome after complete recovery from Plasmodium falciparum infection. In the literature especially the postmalaria neurological syndrome (PMNS), acute disseminated encephalomyelitis (ADEM), and delayed cerebellar ataxia have been reported. We describe a case of a 53-year-old woman who was re-admitted after an adequately treated P. falciparum infection with word-finding difficulties, confusion and tremor. Peripheral blood smears were repeatedly negative for malarial parasites. The clinical features best fitted a PMNS. Because of the severity of the syndrome she was treated with high-dose prednisone. She recovered completely. The possibility of ADEM is also discussed. Aetiology of these syndromes is still unknown, but it could be mediated by an immunological mechanism. PMNS or ADEM must be considered when neurological signs and symptoms occur after recovery from a P. falciparum infection.

KEYWORDS

Malaria, neurological features, Plasmodium falciparum, postmalaria neurological syndrome

INTRODUCTION

Malaria affects 300 to 500 million cases worldwide with three million deaths each year.1,2 In the Netherlands approximately 100 cases of malaria are reported annually.3 True incidence is estimated to be three times higher. Increasing incidence has been related to growing mobility, resistance of the parasite to chemoprophylaxis, resistance of the Anopheles mosquito to insecticides, changes in the climate and failing of malaria reduction programmes.3 Plasmodium falciparum is the most serious cause of malaria; it has a high mortality without treatment. P. falciparum invades erythrocytes of all ages, which can give parasitemia levels of up to 90%.4 Serious complications of P. falciparum infection include cerebral malaria, renal failure, pulmonary oedema, hypoglycaemia, anaemia, spontaneous bleeding and gastrointestinal. Cerebral malaria, an acute encephalopathy, is the most serious neurological disorder related to a P. falciparum infection. Symptoms are cerebral oedema and diffuse petechial bleedings with fever, severe headache, delirium and also stupor or coma with generalised seizures. Mortality is up to 20% and 10% of survivors still have neurological symptoms after discharge from the hospital. Malaria or quinine-induced hypoglycaemia can also lead to coma.5

A few patients may experience a neurological syndrome after complete recovery from P. falciparum infection. In the literature especially the postmalaria neurological syndrome (PMNS), acute disseminated encephalomyelitis (ADEM) and delayed cerebellar ataxia have been reported.1-4 We present a case of PMNS and will also discuss other possible causes of neurological complications following malaria, such as ADEM.

CASE REPORT

A 53-year-old woman was admitted to our hospital because of fever (body temperature up to 39°C), chills, headache and myalgia. She also mentioned severe tiredness, nausea, vomiting and nonbloody diarrhoea. Eleven days previously she had returned from a seven-day city tour in Kenya. She had not taken any chemoprophylaxis for malaria. Her fellow travellers were all healthy. A peripheral blood smear showed 6% parasitemia with P. falciparum. Physical examination revealed a seriously ill woman. Blood pressure was 105/70 mmHg, pulse rate 120 beats/minute and body temperature 41°C. Except for right upper abdominal pain, there were no other lightments, and in particular no hepatosplenomegaly. Neurological examination was normal. Immediately after admission, her blood pressure dropped to 85/50 mmHg with a good reaction to fluid challenge.

Laboratory investigations (table 1) showed raised liver enzymes, mild renal dysfunction which recovered within two days and diffuse intravascular coagulation. Electrocardiography revealed a sinus rhythm with right bundle block and elevated T tropes in leads III, AVF and V5. Chest X-ray was normal. She was treated for seven days with quinine 600 mg three times a day by intravenous infusion. Peripheral blood smear became negative on day 4 and blood cultures were all negative. Because of consolidation of the middle and lower segment of the right lung on the chest X-ray cefazolin (1 g three times a day) and ciprofloxacin (200 mg twice daily) were given for seven days. Abdominal echography revealed splenomegaly and some pleural effusion on the right side.

On day 5 she became afebrile. After 13 days she was discharged from the hospital in a good clinical condition. Five days later she was readmitted because of arthralgia and a body temperature of 38°C. She was tired, had diffuse pain in her body and a nonproductive cough. Physical examination revealed some crackles on inspiration, painful abdominal palpation and normal joints. Laboratory investigations (table 1) showed anaemia, mild transaminase elevations and negative peripheral blood smear for malaria. Chest X-ray was normal and she was readmitted for observation.

Table 1

<table>
<thead>
<tr>
<th>Key Laboratory investigations</th>
<th>DAY 5</th>
<th>DAY 18</th>
<th>DAY 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (mmol/l)</td>
<td>9.8</td>
<td>6.3</td>
<td>5.8</td>
</tr>
<tr>
<td>Leucocytes (10⁹/l)</td>
<td>9.1</td>
<td>3.5</td>
<td>2.8</td>
</tr>
<tr>
<td>Thrombocytes (10⁹/l)</td>
<td>22</td>
<td>376</td>
<td>166</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>184</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Sodium (mmol/l)</td>
<td>128</td>
<td>159</td>
<td>137</td>
</tr>
<tr>
<td>Potassium (mmol/l)</td>
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<td>4.5</td>
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<tr>
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<tr>
<td>Alanine phosphate (U/l)</td>
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<tr>
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<td>934</td>
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<tr>
<td>γ-GT (U/l)</td>
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<td>APTT (sec)</td>
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<tr>
<td>D-dimer (mg/l)</td>
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<tr>
<td>Blood smear (%)</td>
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*Number of infected erythrocytes

Three days after readmittance, she became confused and had progressive difficulty in finding words. Her blood pressure was 90/60 mmHg, pulse rate 100 beats/minute and body temperature 37°C. Physical examination showed shortness of breath. The neurological examination revealed a mixed aphasia, a position tremor, general restlessness and wide open eyes with mydriasis; pupil reactions to light and convergence were normal. Neck stiffness, paresis or abnormal reflexes were absent. The differential diagnosis included a parasitic infection (malaria, bolelliosis or trypanosomiasis), bacterial infection (enteric fever), viral encephalitis, acute disseminated encephalomyelitis (ADEM), a postmalaria neurological syndrome (PMNS) or a drug-related disorder (quinine or ciprofloxacin). Laboratory investigations showed normocytic anaemia, leucopenia and decreasing liver enzymes levels (table 1). Peripheral blood smears were repeatedly negative for parasites. Examination of the cerebrospinal fluid (CSF) showed 5 x 10⁹/l leucocytes (24% lymphocytes and 60% monocytes) and a protein level of 0.67 g/l. Results of extensive serological studies and cultures, both of serum and CSF, were negative except for Rickettsia conori (IgM 1:128, IgG 1:64) and Rickettsia tsutsugamushi (IgM 1:32, IgG 1:728) in the serum. Brain computer tomography (CT) was normal. Magnetic resonance imaging (MRI) of the brain failed because of anxiety and dyspnoea. Electroencephalography showed diffuse slowing of the background activity with intermittent dysrhythmic discharges consistent with a diffuse encephalopathy.

On suspicion of severe PMNS prednisone was given intravenously (75 mg/24 hours for three days, and then tapered with 10 mg/day). We also started doxycycline 200 mg per day for a possible rickettsiosis, although clinical course, the absence of a rash or any other skin appearance and the negative investigation of CSF and negative blood pressure dropped to 85/50 mmHg with a good reaction to fluid challenge.

Blood pressure was 105/70 mmHg, pulse rate 120 beats/minute and body temperature 37°C. Physical examination showed shortness of breath. The neurological examination revealed a mixed aphasia, a position tremor, general restlessness and wide open eyes with mydriasis; pupil reactions to light and convergence were normal. Neck stiffness, paresis or abnormal reflexes were absent. The differential diagnosis included a parasitic infection (malaria, bolelliosis or trypanosomiasis), bacterial infection (enteric fever), viral encephalitis, acute disseminated encephalomyelitis (ADEM), a postmalaria neurological syndrome (PMNS) or a drug-related disorder (quinine or ciprofloxacin). Laboratory investigations showed normocytic anaemia, leucopenia and decreasing liver enzymes levels (table 1). Peripheral blood smears were repeatedly negative for parasites. Examination of the cerebrospinal fluid (CSF) showed 5 x 10⁹/l leucocytes (24% lymphocytes and 60% monocytes) and a protein level of 0.67 g/l. Results of extensive serological studies and cultures, both of serum and CSF, were negative except for Rickettsia conori (IgM 1:128, IgG 1:64) and Rickettsia tsutsugamushi (IgM 1:32, IgG 1:728) in the serum. Brain computer tomography (CT) was normal. Magnetic resonance imaging (MRI) of the brain failed because of anxiety and dyspnoea. Electroencephalography showed diffuse slowing of the background activity with intermittent dysrhythmic discharges consistent with a diffuse encephalopathy.

On suspicion of severe PMNS prednisone was given intravenously (75 mg/24 hours for three days, and then tapered with 10 mg/day). We also started doxycycline 200 mg per day for a possible rickettsiosis, although clinical course, the absence of a rash or any other skin appearance and the long incubation period made this diagnosis improbable.16 Rapid recovery was seen within 24 hours. On day 13 she left the hospital. One month later she had recovered completely.

DISCUSSION

Our patient had neurological signs and symptoms that seemed to be related to the prior P. falciparum infection. We excluded cerebral malaria by negative peripheral blood smear and also other causes of infectious meningocerebrovascular disease as trypanosomiasis, viral or bacterial infections. Although Salmonella typhi infection can cause neuropsychiatric symptoms such as confusion, ataxia, meningitis, myelitis and acute psychosis,1-4 this diagnosis was thought to be less likely because of the relatively long incubation period, and the negative investigation of CSF and negative cultures of blood and faeces.

We did find positive Rickettsia serology suggesting a possible infection with R. conori. R. conori infections are frequently reported from Africa and are known in Europe.
as Mediterranean spotted fever and in Kenya as Kenyan tick typhus. This rickettsial infection can cause cerebral symptoms and severe myalgia. However, our patient developed her symptoms more than a month after returning from Kenya and did not show any signs of a rash or eschar. A rickettsial infection was therefore less likely to be the cause of the symptoms present during her second admission to the hospital. Another explanation for the neurological symptoms of our patient could have been the earlier prescribed medication. Neurological symptoms induced by quinoline (such as ciprofloxacin) develop during the first days of treatment and disappear within 24 to 48 hours after discontinuation. So the time interval excludes a side effect of ciprofloxacin. A quinoline intoxication was another option in our differential diagnosis. Calculated creatinine clearance on admission was 34 ml/min, which needed readjustment of the dosage of quinine. After rehydration creatinine clearance was 66 ml/min within two days, which justifies normal dosage. Quinoline intoxication results in hypokalaemia, hypoglycaemia, cardiac toxicity, visual symptoms (also blindness) and neurological features as convulsions, coma and ataxia. Except for the neurological symptoms our patient did not have any of the symptoms mentioned above. Normally these symptoms develop during or shortly after the usage of quinoline. In our case the symptoms developed 14 days after the last gift of quinine, and therefore a quinoline intoxication was less likely.

It was most likely that she had PMNS or ADEM. Both syndromes have been reported showing complete recovery of P. falciparum infection. In general, the inclusion criteria for PMNS are recent syndromes have been reported following complete recovery after the last gift of quinine, and therefore a quinine intoxication was less likely.

The time of the diagnosis all patients were afebrile. The median time from parasite clearance to the onset of neurological symptoms was four days (range 6 hours to 60 days). In our patient neurological symptoms were found 17 days after the first negative peripheral blood smear. In PMNS acute confusion or psychosis was seen in 15 cases, seizures in eight and a fine tremor of the extremities in one. Serum and CSF investigations showed no other cause such as metabolic disorders or infections that explains these features. A minor increase in the CSF protein level was found in 13 patients described by Mai et al. Both patients described by Schnorf et al., the case of Mohsen et al. and in our patient. All patients described by Mai et al. recovered spontaneously within ten days. They suggested a relation with the use of mefloquine. Mefloquine may cause neuropsychiatric symptoms and seems to be a risk factor for developing PMNS, although five of 22 patients with PMNS were not taking mefloquine. In the randomised trial by Mai et al. ten patients out of 22 who were on mefloquine developed PMNS and one out of 20 treated with quinine developed PMNS. Both patients reported by Schnorf et al. were taking quinine as was our patient.

The clinical spectrum of PMNS was expanded by Schnorf et al. They classified PMNS according to the severity of symptoms: 1. Mild or localised form characterised by isolated cerebellar ataxia or ptosis. 2. Diffuse, but relatively mild self-limiting encephalopathy characterised by acute confusion or epileptic seizures. 3. Severe, progressive corticosteroid-resistant encephalopathy, characterised by motor aphasia, generalised myoclonus, postural tremor, and cerebellar ataxia. This classification includes cerebellar ataxia occurring after P. falciparum neurological complications, which was first described in Sri Lanka by Senanayake in 1984. Senanayake and de Silva reported 74 patients with cerebellar ataxia after P. falciparum infection. All these patients were fully conscious and alert without any signs of cerebral involvement. They all had gait ataxia. One third of these patients still had a parasitaemia at the time the ataxia occurred in contrast to the patients with PMNS. Ataxia started 3 to 41 days (median 13 days) after the last febrile period and there was no response on antimalarial therapy, which suggests that the P. falciparum infection was not the cause of the cerebellar ataxia.

Our patient had a progressive process of confusion, drowsiness, intention tremor and word-finding difficulties had developed a severe PMA syndrome according to the classification by Schnorf et al. Rapid recovery was seen after starting prednisone 75 mg/day for three days, followed by tapering by 10 mg/day. Both patients described by Schnorf et al. were treated with prednisone 9 and 12 days respectively after development of neurological symptoms. Treatment with prednisone (60 mg/day for seven days, than tapered was given to three of 79 patients with cerebellar ataxia in the studies of Senanayake and de Silva. One patient recovered within seven days, while the symptoms of the others remained for two to 30 days. In summary, treatment with prednisone is suggested when there is a severe and progressive course of PMNS.

Aetiology of PMNS remains unclear. As in cerebellar ataxia and ADEM, it seems to have an immunological origin. The delay between the onset of the P. falciparum infection and the PMNS could also be an immunological mechanism, just as the rapid response to prednisone treatment.

Schnorf et al. and Mohsen et al. found normal brain CT scans, while MRI in two patients showed several discrete white matter lesions, which have also been described in mild ADEM. However, white matter lesions are far more prominent in most cases with ADEM including those with minor signs and symptoms. The hallmark lesions of ADEM are perivenular inflammation and surrounding demyelination which may be minimal or widespread, with coalescence of the multiple lesions. ADEM is characterized by the presence of hypertensive lesions in brain MRI or diffuse or scattered low-density lesions in the white matter. Recovery can begin within days, with complete resolution occasionally noted within a few days, but more often over the course of weeks or months. In postmalarial cerebellar ataxia demyelinating lesions have been described in the pons and cerebellar peduncles which disappeared after resolution of symptoms, but in two other cases MRI was normal.

Unfortunately, in our patient MRI scanning was not possible. CT scanning did not show any abnormalities. From the evolution of signs and symptoms we concluded that our patient was suffering from PMNS, but a relation between PMNS and ADEM remains possible.

CONCLUSION

The aim of this case report was to draw attention to neurological syndromes after P. falciparum infection, especially the postmalaria neurological syndrome, which has not been described before in the Netherlands. Patients with a severe P. falciparum infection can develop a neurological syndrome which is related to a prior adequately treated P. falciparum infection after an initial good and rapid recovery. What is important is that the fact no parasites can be found in the blood when these symptoms emerge. It can be difficult to distinguish between these syndromes and other neurological syndromes. Treatment with steroids may be considered when the features are severe and the course is progressive. Aetiology remains unclear, but an immune mechanism seems probable.

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Treatment of postoperative bleeding after fondaparinux with rFVIIa and tranexamic acid

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ABSTRACT

Treatment of a haemorrhagic shock after just a single dose of fondaparinux in an orthopaedic patient with reduced renal clearance is presented. Since all routine haematostatic parameters were nearly normal, single doses of rFVIIa (50 µg/kg) and of tranexamic acid (15 mg/kg) were administered to improve thrombin generation and reduce fibrinolysis. This case is the first showing the effectiveness of combining single doses of rFVIIa and tranexamic acid in controlling severe postoperative bleeding after fondaparinux.

KEYWORDS

Activated, clearance, factor VII, female, fibrinolysis, fondaparinux, haemorrhagic, orthopaedic, pentasaccharide, postoperative bleeding, recombinant, renal, shock, surgery, tranexamic acid

INTRODUCTION

Venous thromboembolism (VTE) develops in about 15% of orthopaedic patients after total hip replacement, despite the use of the current thromboprophylactic treatment, particularly low-molecular-weight heparins (LMWHs). Recent studies suggest a superior efficacy of the new pentasaccharide fondaparinux over LMWHs in major orthopaedic surgery, resulting in no increase in the risk of fatal bleeding and need for reintervention, despite a higher nonfatal bleeding rate. The present case is the first report of a patient developing severe postoperative bleeding after 2.5 mg of fondaparinux, which was successfully terminated after the administration of 6 mg recombinant activated factor VII (rFVIIa), combined with tranexamic acid.

CASE REPORT

A hip prosthesis was revised in a 79-year-old female patient. The patient had documented hypertension, and had previously undergone a subtotal thyroidectomy, and total hip replacement on both sides. There was no patient or family history of bleeding tendency. Perioperative medical treatment (jainmetocostophine as necessary, onoprazol 20 mg, calcium citrate 500 mg, ranolafine 60 mg, indapamine 2.5 mg, all once daily) was interrupted eight hours prior to surgery. During the surgical procedure the femur was extended substantially. Perioperative blood loss (1500 ml) was replaced by crystalloids. Postoperative blood management was according to the hospital’s transfusion algorithm developed to reduce allogeneic red blood cell transfusions for major orthopaedic surgery, restricting red cell transfusion to patients over 60 years of age and with Hb levels <5.0 mmol/l, and to patients with cardiac disease and with Hb levels <5.5 mmol/l. In order to prevent deep venous thrombosis the first dose of fondaparinux (2.5 mg) was administered subcutaneously six hours postoperatively (t=6 h). At that time the haemoglobin level was 6.5 mmol/l, blood pressure 135/60 mmHg, heart rate 60 beats/min, and blood loss per drain 75 ml/h. At t=7 hours the patient had received just one single dose of fondaparinux and haemorrhagic shock developed due to a severe bleed from the operative site as monitored by wound drains: haemoglobin (Hb) 3.7 mmol/l, blood pressure 90/40 mm Hg, heart rate 102 beats/min. Three units of red blood cell concentrates were transfused resulting in a clear rise in haemoglobin level (3.8 mmol/l) and blood pressure (110/50 mmHg). However, in the following hours blood loss persisted at an average drain rate of 13 ml/h, with deterioration of the anaemia (Hb 3.5 mmol/l), and development of atrial fibrillation. At t = 20 hours three additional units of red blood cell concentrates were transfused resulting in an increased Hb level (5.4 mmol/l). Coagulation parameters were checked as bleeding persisted for 35 hours after a single dose of 2.5 mg fondaparinux. Since the platelet count was 69 x 10⁹/l, and all routine coagulation parameters (INR 1.5, prothrombin time (PT) 11 seconds, activated partial thromboplastin time (APTT) 38 seconds, and Ca++ 2.39 mmol/l) were nearly normal, plasma concentrates and platelets were not administered.

However, rFVIIa, being the only known antidote for severe bleeding after fondaparinux, was administered intravenously. Simultaneously, intravenous tranexamic acid therapy (5 g three times a day) was started to stop fibrinolysis. Within one hour, blood loss diminished from 75 to an average of 2 ml/h by drain, which did not increase during the following 24 hours. Arterial blood pressure and Hb level rose after one final unit of red blood cell concentrate RR 160/60 mmHg, heart rate 80 beats/min, Hb 5.9 mmol/l. The coagulation parameters (INR 0.9, PT 9 sec, APTT 38 sec) and platelet count (107 x 10⁹/l) remained stable.

DISCUSSION

This case shows the risk of severe postoperative bleeding even after a single dose of fondaparinux in orthopaedic patients with reduced renal clearance. Furthermore, it is the first case showing the effectiveness of a single dose of rFVIIa in combination with tranexamic acid in controlling severe bleeding after postoperative thromboprophylactic treatment with fondaparinux in elective orthopaedic surgery. Fondaparinux, the first of a new class of synthetic pentasaccharides, binds to antithrombin (AT-III), thereby increasing its activity towards inactivation of factor Xa by about 300 times, and delaying tissue factor-induced clot formation. Furthermore, fondaparinux accelerates fibrinolysis due to downregulation of the activation of thrombin-activatable fibrinolysis inhibitor (TAFI). However, it has no direct effect on thrombin, nor on platelets. Fondaparinux has improved antithrombotic effectiveness after both total knee and hip replacement in combination with low-molecular-weight heparins. In a meta-analysis of four trials, patients receiving fondaparinux had a 25% reduction in the relative risk of VTE at day 35 compared with LMWHs, but more postoperative bleeding.

Fondaparinux is completely reabsorbed two hours after subcutaneous injection and has a variable half-life depending on kidney function and age: T½ is 17 hours in young healthy adults, 21 hours in the elderly, 29 hours at creatinine clearance 30 to 50 ml/min, and 72 hours when creatinine clearance <30 ml/min and is registered for once-daily usage. Consequently, the drug must still be active after two half-lives. In this case report the patient’s creatinine clearance was 45 ml/min according to the Cockcroft formula, which resulted in an estimated fondaparinux T½ of 29 hours at minimum, suggesting the drug was effective for up to 58 hours. Since the classical coagulation parameters (INR, APTT and PT) were (near) normal and the platelet count was adequate at the time of the haemorrhagic shock, administration of coagulation factors and suppletion of platelets was not necessary. According to some studies severe bleeding after fondaparinux in the presence of sufficient coagulation factors is best stopped by recombinant FVIIa. Factor VIII activates factor X, which initiates the conversion of prothrombin into thrombin, also partially improves thrombin-activatable fibrinolysis inhibitor (TAFI)-mediated inhibition of fibrinolysis. The potential clinical use of rFVIIa as haemostatic treatment of major bleedings related to fondaparinux has not been evaluated, but its ex-vivo effectiveness has been proven. FVIIa is capable of normalising coagulation times and thrombin generation during fondaparinux treatment in healthy subjects. Accordingly, both 90 µg/kg rFVIIa and 15 µg/kg tranexamic acid, an antifibrinolytic agent with active serum plasma levels for seven to eight hours, were administered intravenously. Within one hour bleeding stopped and blood pressure normalised. Despite rFVIIa’s short T½, no additional doses were needed, possibly because of the additional antifibrinolytic activity of the tranexamic acid. Since the direct cost of rFVIIa was € 5900 and of tranexamic acid was just € 21, it is suggested from the present case to use combined treatment of just a single dose of rFVIIa and an antifibrinolytic agent to resolve bleeding problems after the use of fondaparinux in orthopaedic surgery and in the presence of normal coagulation parameters. Otherwise, in case of a prolonged prothrombin time and APTT, the coagulation should be first normalised using human plasma.

REFERENCES


DIAGNOSIS

Clinical presentation suggested mechanical bowel obstruction, although conventional radiographs did not support this. Because no signs of peritonitis were present, initially a more conservative treatment was started. We were surprised by the abdominal mass, which was also present on the CT, showing the small bowel feces sign which is usually caused by partial mechanical obstruction of the small bowel. The proximal part of the small intestine was filled with contrast, followed by distended loops filled with fecal-like material. More distally, no intraluminal contrast or fluids were seen. Partial small bowel obstruction causes slow transit time leading to reabsorbing fluid. Once thickened only liquids will pass. Bacterial overgrowth causes gas bubbles as we normally see in the colon. An abdominal radiograph taken 12 hours after CT scanning showed contrast in the rectosigmoid (figure 3).

REFERENCE


‘Untitled’

Carole Witteveen

About the Cover

This month’s cover shows a graphic art, mixed technique/silk-screen printing by Carole Witteveen. Carole works in Nijmegen, the Netherlands. She attended the Academy of Art in Arnhem and the Jan van Eijk Academy in Maastricht. She teaches at the Academy of Art in Arnhem, and has exhibited her work at numerous individual and group exhibitions in the Netherlands (Villa Sonsbeek and De Gele Rijders in Arnhem, Galerie Magenta in Nijmegen, Museum Waterland in Hoorn, Purmarn Gryafik in Purmerend, Kunst in de AA Kerk in Groningen and Kunst Rai Amsterdam 2003) and abroad at Kunstverein in Basel, Switzerland, Zentrum Artoll in Bedburg-Hau, Germany, Centro La Luz in Santander, Spain, Les Images in Kasteel Brasschaat, Belgium, Kunstraum in Wuppertal, Germany, and Solas Sillas, Spain). She has served on a number of committees for advice and selection of art and participated in the Dutch television programme Kunst te Kijk (Viewing Art). In her work, she wants to depict beauty and desire, metamorphosis and changes, myth and reality; things around us that we see but do not observe. A limited edition (5) of original print of this month’s cover (size 30 x 40) is available at a price of € 275. You can order the print at Galerie Unita, Rijksstraatweg 109, 6731 CK Beek-Ubbergen, the Netherlands or by e-mail to galerie-unita@planet.nl. Galerie Unita is online at www.galerie-unita.com.

Based on the findings of the CT, the patient underwent abdominal surgery. The small intestine was partially fixated probably due to abdominal trauma during a car accident eight years before. Thickened feces-like material was manually pushed towards the colon after adhesiolysis took place. There were no signs of peritonitis or malignancy. The small bowel feces sign suggests a slowly developing partial mechanical obstruction leading to a slow transit state, such as adhesions, hernias or tumours. Once clinical presentation of small bowel obstruction is protracted, CT imaging can lead the clinician in making treatment decisions.

REFERENCE

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The language of the Journal is English. English idiom and spelling is used in accordance with the Oxford dictionary. Thus: Centre and not Center, Tumour and not Tumor, Haematology and not Hematology.

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Subheadings should not exceed 55 characters, including spaces.

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The Results should be presented precisely without discussion.

The Discussion should directly relate to the study being reported. Do not include a general review of the topic, but discuss the pertinent literature.

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