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Increased central venous pressure in a patient with pruritic skin lesions

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CASE REPORT

A 47-year-old man was referred because of progressive dyspnoea and eosinophilia. His symptoms started one year before, following a flu-like febrile illness of two weeks. Two months later, an effusive pericarditis was diagnosed for which the cardiologist performed drainage and prescribed diuretics. At that moment the patient had eosinophilia with counts up to 1.65 x 10^9/l with progressive pruritic skin lesions diagnosed by the dermatologist as dermatomycosis. After ruling out other apparent aetiologies for eosinophilia, including parasitic infections and allergy, the diagnosis of hypereosinophilic syndrome (HES) was made by the internist and prednisone was started. Under this therapy the eosinophil count normalised and the complaints of prurigo subsided. However, because the body weight increased more then 20 kg and dyspnoea further progressed, the patient stopped the prednisone.

On physical examination the patient appeared dyspnoeic after walking 25 meters. The central venous pressure was clearly increased (> 10 cm H_2O; *figure 1*). Blood pressure was 138/110 mmHg, with a fall of the systolic blood pressure during inspiration to 118 mmHg. Percussion, auscultation and palpation of the chest were compatible with the presence of right-sided pleural fluid. The liver was 8 cm palpable under the right costal margin. There was firm, only slightly pitting oedema of both legs, with an oedematous and erythematous aspect with pruritic papules and nodules around both knees (*figure 2*).

WHAT IS YOUR DIAGNOSIS?

See page 273 for the answers to this photo quiz.

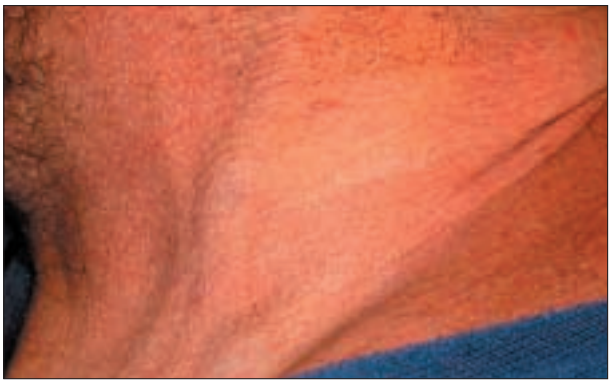

Figure 1
Distended external jugular vein as a sign of increased central venous pressure

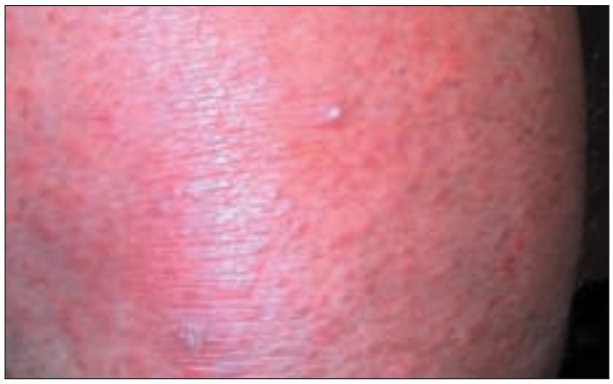

Figure 2
Oedematous eythematous skin with papulonodular lesions around the knee

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EDITORIAL

Immunomodulation by antimicrobial drugs

J.W.M. van der Meer

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ABSTRACT

Immunomodulation aims at either enforcement of host defence mechanisms or dampening of the inflammatory response of the host. Thus, immunomodulatory drugs may enhance host defence by either stimulating the inflammatory response or inhibiting the counter-regulatory, anti-inflammatory response. On the other hand, the response of the host may be down-modulated through inhibition of the inflammatory response or induction of counter-regulatory, anti-inflammatory mechanisms. Antimicrobial drugs may have such immunomodulatory effects, but so far these effects have not been exploited clinically.

Many infections are still difficult to treat, despite the availability of potent antimicrobial drugs. Obviously, this is especially the case for infections for which effective antimicrobial treatment is not available because of intrinsic or acquired resistance of the causative micro-organism. We know from animal experiments as well as from clinical studies that antibiotics, even bactericidal ones, may show limited efficacy when host defence mechanisms are defective. This is the reason that scientists have tried to find drugs that are capable of enforcing host defence. As early as in the beginning of the 20th century, George Bernard Shaw alluded to such efforts in his play 'The Doctor's Dilemma' when Sir Ralph Bloomfield Bonington says: 'There is at the bottom only one genuinely scientific treatment for all diseases, and that is to stimulate the phagocytes. Stimulate the phagocytes'.[1]

On the other side of the coin, the response of the host to infection may be deleterious; proinflammatory cytokines (such as TNF, IL-1, IL-8) and also secretory products of white blood cells (as reactive oxygen metabolites, chloramines, elastase) are able to produce serious tissue damage. Lysis of micro-organisms by host factors (complement, lysosomal enzymes, perforins) as well as by antibiotics may increase these deleterious effects. To try to cope with these effects, drugs that inhibit these effects have been searched for.

In a general sense, immunomodulatory effects of drugs fall into one of the following four categories (or combinations thereof):

1. Stimulation of the inflammatory response (e.g. by increasing the proinflammatory cytokine status or by augmenting phagocyte or T-cell function).
2. Inhibition of the counter-regulatory, anti-inflammatory response (e.g. by inhibiting anti-inflammatory cytokines as IL-10, IL-4 and TGF β).
3. Inhibition of the inflammatory response (e.g. by decreasing the proinflammatory cytokine status, by inhibiting phagocyte or T-cell function or by inducing apoptosis of inflammatory cells).
4. Promotion of the counter-regulatory, anti-inflammatory response (e.g. by increasing anti-inflammatory cytokines as IL-10, IL-4 and TGF β).

It has been known for a number of decades now that antibiotics may also exert effects other than the direct antibacterial ones. The immunomodulatory effects of

antibiotics that have been described fall into the categories mentioned above. However, at this point in time there are a series of problems if we consider the immunomodulatory effects of antibiotics.

- It is hard to delineate under which clinical circumstances we want a certain effect in addition to the antimicrobial action.
- The immunomodulatory effects of antibiotics have mainly been shown *in vitro* or in animal experiments. Many of these studies use rather artificial models, use supratherapeutic concentrations of the drug and are poorly controlled (e.g. for nonspecific effects). Often the antimicrobial effects and the immunomodulatory effects cannot be dissected.
- There is little evidence from the clinical arena that these immunomodulatory actions of antibiotics play a role in terms of outcome. The most convincing in this respect are the anti-inflammatory effects of macrolides and perhaps of tetracyclines.

In this issue of the *Netherlands Journal of Medicine,* the immunomodulatory effects of macrolide antibiotics are critically reviewed by Swords and Rubin,[2] and their paper indicates that it is important for clinicians to be informed and aware of such effects.

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REVIEW

Severe acute respiratory syndrome: lessons and uncertainties

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ABSTRACT

The outbreak of severe acute respiratory syndrome (SARS) has produced scientific and epidemiological discoveries with unprecedented speed, and this information has been spread instantaneously to the global health community through the internet. Within a few weeks, the coronavirus associated with SARS (SARS-CoV) was identified and sequenced. The source of the outbreak and the exact modes of transmission are still subjects of research. Important lessons can be learned from the SARS outbreak about both the scientific and the public health approach to emerging pathogens.

In November 2002, over 300 cases of highly contagious and severe atypical pneumonia of unknown cause had occurred in the Guangdong province in southern China. Many cases were rapidly fatal.[1] This outbreak went unnoticed until February 2003, when a physician from Guangdong became ill while staying at a hotel in Hong Kong. Twelve guests became infected, including at least seven who stayed in rooms on the same floor. These hotel guests subsequently became the index patients who spread the infection to Singapore, Vietnam, Canada and a variety of other countries. As of 9 June 2003, severe acute respiratory syndrome (SARS) has been diagnosed in more than 8400 patients in 32 countries, with a death rate of 9.3%.[2]
Starting on 13 March, 2003, the World Health Organization (WHO) coordinated an international investigation that has produced scientific and epidemiological discoveries with unprecedented speed. What is just as impressive as the speed of scientific discoveries is the instantaneous spread of information. Satellite broadcasts, webcasts and videoconferencing as well as rapid publications on the internet by the major scientific journals have supported the dissemination of emerging information to the entire global health community.
In the early 1980s, it took competing laboratories two years to identify HIV as the cause of AIDS. In 2003, an international network of 13 laboratories in ten countries was created, sharing knowledge and collaborating in an unprecedented fashion, using daily teleconferences and a secure website for sharing research data in real-time. This effort lead to identification of the coronavirus associated with SARS (now named SARS-CoV) within two weeks, and the sequencing of its entire genome in two more weeks.[3,4] Sequences were compared with those of previously characterised coronavirus strains and within days it was clear that this virus was distinct from all known human pathogens. SARS-CoV has been found in patients with SARS, using a variety of methods including tissue culture, electron microscopy, microarray technology, and polymerase chain reaction (PCR), by teams in Europe and the US.[5,6] In addition, serum was tested for antibodies to SARS-CoV, and seroconversion was documented in patients with SARS. Importantly, Osterhaus and colleagues in Rotterdam have satisfied Koch's postulates by demonstrating that monkeys develop SARS only after injection of the SARS-CoV, but not by other candidate viruses.[7]

The source of the outbreak is still a subject of speculation and research. Coronaviruses cause disease in many animals, including pigs, cattle, chickens, cats and dogs. Genetic changes occur frequently and the virus has been associated with upper respiratory infections in humans. Regions like the Chinese province of Guangdong, with its subtropical

climate and a population of 75 million living in close proximity to animals, may be the world's melting pot for recombinant animal viruses crossing species to humans. Future research, such as serological tests of wild and domestic animals and birds may identify the natural host. Likely candidates are the masked palm civet (*Paguma larvata*), the raccoon dog (*Nyctereutes procyonoides*), and the Chinese ferret badger (*Melogale moschata*). An important question is whether SARS-CoV lost its ability to infect its original host when it jumped to humans. The lack of an animal reservoir would increase the chance of containing the outbreak.

The unusually rapid transmission suggests that not only large droplets, requiring intimate or face-to-face contact with a patient or inoculation of mucous membranes, transmit the virus but that other routes of transmission may be possible. Airborne transmission through droplet nuclei could account for the extensive spread within buildings that has been observed in Hong Kong. Obviously, this mode of transmission would make containment of the outbreak more challenging. Alternatively, viral contamination of sewers or water supply systems, leading to faecal-oral transmission, has been suggested as source of the increased spread in a Hong Kong apartment complex. The detection of SARS-CoV in faecal as well as in respiratory specimens has confirmed that this virus, like many animal coronaviruses, may indeed be spread both by faecal contamination and by respiratory droplets. This dual tropism is another challenge for the management of the outbreak. Furthermore, fomite transmission could be relevant, since coronaviruses can survive on contaminated objects in the environment. It has been suggested that a few persons may be especially infectious ('super spreaders') and that most others are less likely transmit the virus, but this concept is still speculative.
Experiments with other coronaviruses have demonstrated several worrisome properties, including persistent infection, lack of protective immunity and immune enhancement, i.e. antiviral antibodies contributing to disease progression. Either these problems or co-infection with a yet unidentified virus may explain the relatively high mortality rates among SARS patients.

The infection of a large proportion of exposed medical and nursing personnel has caused considerable anxiety. While caring for the index patient in Hong Kong, 69 healthcare workers and 16 medical students, all with unremarkable medical histories, developed SARS, in turn leading to 26 tertiary cases which included family members of the infected healthcare workers.[8,9] Likewise, brief contacts by both the family physician and visitors were sufficient to transmit the infection from the index patient in Toronto.[10] Moreover, another patient was infected and died from SARS, after having been observed in the emergency department on a gurney separated by a cotton curtain from the index patient, without any direct contact. While recent research in the field of infection control is primarily directed at other topics, the SARS epidemic clearly points out the importance of basic infection control measurements.

It is still unclear whether the epidemic will disappear, level off and develop a seasonal pattern of limited upsurges in the future, or become a pandemic. If SARS transmission evolves to mimic that of influenza, containment may well be impossible without vaccination.
As has happened repeatedly in the past with other diseases for which a rapid and accurate diagnostic test is not (yet) available, national and local health authorities have been using the surveillance definition of proven and probable SARS as a basis for guidelines for recognition and isolation of possible clinical cases. However, case definitions that have been designed for surveillance aim at a high level of specificity, whereas optimal clinical care for the individual patient and prevention of secondary cases require highly sensitive case criteria. For example, whereas surveillance criteria may require the presence of fever and a pulmonary infiltrate, many patients proven to be infected with SARS in both the Hong Kong and Toronto populations did not have frank pulmonary infiltrates or had hypothermia or a normal temperature rather than fever.[8-10]

Treatment of patients with SARS is basically supportive, since no specific therapeutic agent is available. In this issue of the Journal, Van Vonderen *et al.* have reviewed the available data on treatment with the antiviral drug ribavirin or corticosteroids in severely ill patients.[11] A rationale for the use of corticosteroids derives from the similarity of the pulmonary signs to those seen in bronchiolitis obliterans with organising pneumonia (BOOP). While it appears that there is no rationale in prescribing ribavirin, the use of corticosteroids in severe cases is still a matter of debate.[11]

The emergence of SARS has represented a major challenge. Speed of scientific discovery and speed of communication are hallmarks of the response to SARS and reflect impressive achievements in science, epidemiology and international collaboration. The investigation of the SARS outbreak may serve as a template for laboratory and epidemiological response to future infectious-disease pandemics.
However, we do not know where we are currently on the epidemic curve. It is still unclear whether the epidemic will level off or will continue to move faster than our scientific and control capacities. The outcome cannot be predicted.

SARS ON THE WWW

- LCI: public health site including important protocols for healthcare institutions in the Netherlands (in Dutch), www.infectieziekten.info
- World Health Organization: WHO's information on SARS and other health information of international significance, www.who.int/en/
- The Center for Disease Control's site on SARS: info on SARS from this federal government agency (diagnosis, travel, treatment, etc.), www.cdc.gov/ncidod/sars
- Health Canada (healthcare professionals section): guidelines and all basic information, www.hc-sc.gc.ca/pphb-dgspsp/sars-sras/index.html
- Hong Kong: Hong Kong Special Administrative Region Health Department, www.info.gov.hk/info/sars/eindex.htm
- PubMed: special SARS link to all recent literature at once, www.ncbi.nlm.nih.gov.library.csuhayward.edu/entrez/query.fcgi
- SARS Reference: medical textbook with comprehensive and up-to-date overview of SARS, www.sarsreference.com/index.htm

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Ribavirin in the treatment of severe acute respiratory syndrome (SARS)

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INTRODUCTION

Severe acute respiratory syndrome (SARS) has recently been recognised as a newly emerging infectious disease with significant morbidity and mortality. It has been suggested that (early) antiviral treatment with ribavirin and high-dose glucocorticosteroids may be beneficial. We have summarised the available data on ribavirin to facilitate decision-making when confronted with (suspected) SARS.

RIBAVIRIN: MECHANISM OF ACTION, CLINICAL EXPERIENCE (OTHER THAN WITH SARS) AND TOXICITY

Ribavirin is a purine nucleoside analogue that was discovered by ICN Pharmaceuticals in 1970. It prevents the replication of a large number of RNA and DNA viruses *in vitro*, including myxo-, paramyxo-, arena-, bunya-, herpes-, adeno-, pox- and retroviruses. Although the antiviral mechanism of action is not fully defined, ribavirin competitively inhibits the enzyme inosine monophosphate dehydrogenase, which is required for the synthesis of guanosine, and thereby interferes with nucleic acid synthesis resulting in 'lethal mutagenesis' of the RNA genome.[1-3] The active metabolite of the drug, ribavirin triphosphate, concentrates in erythrocytes and erythrocyte levels gradually decrease with an apparent $T_{1/2}$ of 40 days. Ribavirin is primarily eliminated by renal excretion and dose reduction is required in patients with renal insufficiency. Ribavirin can be given orally (with a bioavailability of 40 to 50%), intravenously or as an aerosol.[4]

Aerolised ribavirin is approved in the Netherlands and the United States for treatment of respiratory syncytial virus (RSV) bronchiolitis and pneumonia in hospitalised children, but its use is limited by concerns regarding efficacy, risk of occupational exposure and cost. Ribavirin has a variable effect on shortening the duration of virus shedding and improves certain clinical measures relative to that of placebo in infants hospitalised with RSV pneumonia, including high-risk infants with bronchopulmonary dysplasia or congenital heart disease.[5] In infants receiving mechanical ventilation for RSV-related respiratory failure, no consistent benefits on duration of ventilatory support or mortality have been documented.[6,7] In a Cochrane meta-analysis a trend was found towards a reduction in the length of stay and days of ventilation dependence.[8] Despite these discouraging data, the American Academy of Paediatrics still advises that ribavirin is considered in severe cases of bronchiolitis, as well as in ventilated infants and infants with underlying diseases.[9]

In patients with Lassa fever, intravenous or oral ribavirin significantly reduces mortality, especially when therapy is initiated during the first six days of illness.[10] In adults with chronic hepatitis C, long-term oral ribavirin reversibly reduces serum transaminase elevations, hepatic inflammation on biopsy and fatigue without significantly affecting serum HCV-RNA concentrations.[11,12] This suggests the existence of immunomodulatory properties that may in part account for the antiviral activities *in vivo*.[3] Combination therapy with interferon-alpha-2b significantly increases the frequency of biochemical and virological response during and after cessation of therapy.[13-15]

Systemic ribavirin causes dose-related anaemia due to extravascular haemolysis and, at higher doses, suppression of bone marrow release of erythroid elements. Reversible

increases in serum bilirubin, iron and uric acid can occur, and hypocalcaemia, hypomagnesaemia, hyperammonaemia and pancreatitis have also been described. In HIV patients receiving other nucleoside analogues as part of highly active antiretroviral therapy, elevated concentrations of lactate and pyruvate have been reported. Bolus intravenous injections may cause rigors. Other side effects include pruritus, rash, nausea, depression and cough. Adverse haematological effects have not been associated with aerolised ribavirin, but this may cause mild conjunctivitis, rash, bronchospasm and reversible deterioration in pulmonary function.[1,2]

Ribavirin may affect the embryo because of its interference with DNA and RNA replication. Teratogenic effects have been found in rodent studies with relatively low doses (1-10 mg/kg), but the true risk for teratogenic effects in humans is unknown.[1,16]

RIBAVIRIN AND (SARS-ASSOCIATED) CORONAVIRUS

Animal studies and *in vitro* susceptibility testing

Ribavirin is effective for the treatment of mouse coronavirus hepatitis. Although its inhibitory activity against the mouse coronavirus is weak, it can decrease the release of proinflammatory cytokines from the macrophages of mice and also switches the Th-2 response to a Th-1 response.[17] Ribavirin may therefore serve as an immunomodulator, irrespective of its antiviral role.

In vitro susceptibility testing of ribavirin against the SARS-related coronavirus has been carried out at two institutions. Both Health Canada's National Microbiology Laboratory and the US Army Medical Research Institute of Infectious Diseases report that these tests have failed to demonstrate direct antiviral activity (inhibition of replication or cell to cell spread) of ribavirin against two isolates of the SARS-related coronavirus, at nontoxic concentrations that were effective for Lassa fever virus and other haemorrhagic fever viruses.[18,19]

Clinical reports

Reports of the use of ribavirin in cases with (suspected) SARS are limited to retrospective case series with conflicting results and numerous methodological issues.[20-26]

In a first report of 50 patients with SARS in Hong Kong, of which 49 received ribavirin, Peiris *et al.* state that a delay in starting ribavirin and corticosteroids was a risk factor for severe complicated disease.[20] In a following publication, the same authors report that they followed 75 SARS patients for three weeks who were treated with intravenous amoxicillin-clavulanate and oral azitromycin.[21] As soon as the diagnosis of SARS was established, treatment was started with 8 mg/kg intravenous ribavirin every 8 hours for 14 days and a tailing regimen of hydrocortisone (starting 200 mg iv every 8 hours) over 10 days, followed by oral prednisolone for 11 days. If patients worsened, pulses of methylprednisolone were given. In addition, patients with chronic hepatitis B were given 100 mg of oral lamivudine daily while taking corticosteroids. Fever and pneumonia initially improved but 85% of the patients developed recurrent fever after a mean of 9 days. Nine patients (12%) developed spontaneous pneumomediastinum and 20% of the patients developed acute respiratory distress syndrome (ARDS) in week 3. During the study period five patients died: two due to acute myocardial infarction, one of sepsis and two of sepsis and ARDS. Age and chronic hepatitis B infection were independent risk factors for progression to ARDS. The viral load, measured by quantitative RT-PCR, peaked at day 10. The authors concluded that the clinical progression with the inverted V viral-load profile suggested that the symptoms were initially related to the effect of viral replication and cytolysis but that the worsening in week 2 was probably related to immunopathological damage as a result of an overexuberant host-response. Because all patients in this series received ribavirin, the effect of this regimen could not be compared with standard treatment without antivirals.

In another series, 31 patients with probable SARS in Hong Kong were treated according to a treatment protocol consisting of antibacterials as first-line therapy.[22] Ribavirin and methylprednisolone were added in case of severe or prolonged illness. Of these 31 patients, one recovered on antibacterial treatment alone, 17 showed a rapid response after the addition of ribavirin and the standard corticosteroid regimen, and 13 achieved improvement only after higher dosages of corticosteroids were given. High-dose corticosteroids did not give rise to severe complications, although prophylactic antibiotics were given to patients with fever and elevated white cell counts. No side effects of ribavirin were encountered, especially no haemolysis or arrhythmia. No patients required mechanical ventilation and there was no mortality in this group.

More data that characterise the major outbreak of SARS in Hong Kong have been supplied by two other reports: first, ten cases that were treated empirically with ribavirin, eight of which were thought to have benefited from it, and, second, 138 cases with suspected SARS that received a combination therapy of ribavirin and corticosteroids if certain criteria were met.[23,24] Again, as these studies are case series, they do not address the question whether ribavirin is useful or not.

In a description of ten cases in Canada, two of three patients who did not receive ribavirin died, whereas only one of seven patients who received ribavirin died.[25]

In contrast to these reports, a larger retrospective case series involving 144 patients in Canada with suspected or probable SARS found that poor outcome was more

common in those treated with ribavirin (RR 1.9, 95% CI: 0.45-8.0, p=0.36, univariate analysis).[26] This was not statistically significant. The majority of patients in this case series (126/144, 88%) received ribavirin, of them 91% received it within the first 48 hours of hospitalisation. As it is not clear why the other patients did not receive ribavirin, this raises the suspicion of selection bias. Forty percent of patients received corticosteroids, in dosages varying between approximately 20 to 50 mg hydrocortisone for ten days. One patient received pulse corticosteroid therapy. In this case series significant toxicity of ribavirin is described: 49% of patients had a decrease in haemoglobin level of at least 2g/dl, 40% had an elevation of transaminases of at least 1.5 fold rise and 14% had bradycardia. These toxicities led to the premature discontinuation of ribavirin in 18% of patients.

ROLE OF CORTICOSTEROIDS IN THE TREATMENT OF SARS

Analogous to the treatment of severe RSV infection, corticosteroids have been advocated in the treatment of SARS. In a recent meta-analysis, a statistically significant improvement in clinical symptoms, length of stay, and duration of symptoms is suggested with the use of systemic corticosteroids for RSV bronchiolitis.[27] However, a reduction of less than half a day in the length of stay is of questionable clinical relevance. Since this meta-analysis, three additional studies have been published using systemic prednisolone or nebulised budesonide. Two of these studies did not show any beneficial effect at all.[28-30] It can be concluded that treatment with corticosteroids is not generally indicated for the treatment of RSV bronchiolitis, but that the most severely ill patients, treated with mechanical ventilation, might benefit from it.[9]

In SARS, pathological findings have shown diffuse alveolar damage. In addition, computed tomographic findings of the chest did reveal bilateral peripheral changes with ground-glass consolidation that were suggested to be similar to what is seen in bronchiolitis obliterans with organising pneumonia (BOOP), an inflammatory reaction that usually responds to corticosteroids.[24,31] In addition, avoidance of a 'cytokine storm' has been used as an argument in favour of corticosteroids.[24,32] In contrast, Oba *et al.* believe that the pathogenesis of SARS is diffuse alveolar damage with ARDS.[33] As the use of corticosteroids in ARDS is controversial[34-36] and effective antiviral agents for SARS are lacking, they believe that systemic corticosteroids should not be used.

In a recent 'perspective' in the *New England Journal of Medicine* the use of corticosteroids 'in this time of uncertainty' is only advised for 'the more ill patients' and it seems to us that this is a rational advice given today's circumstances.[37]

CONCLUSION

In vitro tests have failed to demonstrate a direct antiviral activity of ribavirin against two isolates of the SARS-related coronavirus. There are no solid clinical data to show that ribavirin is effective for the treatment of patients with SARS. Reports on side effects of ribavirin vary from no side effects to important toxicities which led to the discontinuation of ribavirin therapy in many cases. Taking this into account, Health Canada has recently stated that it will no longer provide access to ribavirin for the treatment of SARS. Similarly, we feel that the presently available data do not support the use of ribavirin in the treatment of patients with SARS. Although highly controversial, treatment with corticosteroids may be considered in severely ill patients, based upon data from RSV bronchiolitis, BOOP and preliminary reports on SARS. Whether or not corticosteroids are indeed beneficial in the treatment of SARS remains to be established.

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REVIEW

Macrolide antibiotics, bacterial populations and inflammatory airway disease

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) and other inflammatory airway conditions are major causes of morbidity and mortality worldwide. Antibiotics are used to treat acute infectious exacerbations of airway disease. However, for the macrolides, a significant and growing body of evidence indicates that anti-inflammatory effects of these antibiotics, which may be independent of their antibacterial effects, are at least partially responsible for their beneficial effect. In this review, we describe current thinking on the means whereby anti-inflammatory effects of macrolides impact chronic airway disease.

The current data indicate that some macrolides have immunomodulatory activity, mediated at least in part by effects on the activation of gene transcription mediated by NF-κβ activation that may be separable from their antimicrobial activities, and could explain their surprising efficacy in asthma and viral infections for which the role of bacteria is not established. Other, provocative work indicates that subclinical doses of macrolides may also affect signalling within and between bacterial communities, and thus impact developmental processes such as biofilm formation that are important in the establishment and persistence of chronic infections. The current data clearly suggest that activities beyond antimicrobial effects contribute significantly to the beneficial effect of macrolide therapy on inflammatory conditions.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), asthma, and chronic sinusitis are among the most common causes of morbidity and mortality worldwide.[1] Environmental and host factors play a significant role in all of these diseases, but infection by opportunistic bacterial and viral pathogens is thought to lead to a more rapid progression and worsening of disease.[2] Most of these persistent infections are caused by organisms that normally reside in the upper airways as benign commensals.[3,4] The chronically infected airway is host to an abundant microbial community.[5] This is generally asymptomatic during most of the time of carriage, although a chronic state of low-level inflammation usually occurs, and data suggest that adaptations among the bacterial population result in a modulation of the innate response to bacteria and bacterial components.[6] Periodic exacerbations of airway disease occur that are characterised by a robust inflammatory response with the production of copious amounts of mucus, and release of cytokines and other signalling molecules.[7] Inflammation is the hallmark of chronic airway disease, and treatments that eliminate or reduce the inflammatory response are beneficial.[8] Treatment with antimicrobials reduces the severity of infection and inflammatory episodes.[9] In addition, a growing body of work has clearly demonstrated that some antimicrobial agents, especially the macrolides, can also act by reducing the host inflammatory response.

MACROLIDE ANTIBIOTICS

The macrolides are a class of antimicrobials that feature one or more deoxy- or amino-sugar bound to a 14-, 15- or 16-membered macrocyclic lactone ring. Erythromycin, a 14-member macrolide, was first isolated by McGuire and

colleagues in 1952 from *Streptomyces erythreus* found in a soil sample in the Philippines. The antimicrobial activity of macrolides is due to inhibition of protein synthesis by binding to the junction of the 30S and 50S subunits of the prokaryotic ribosome, probably by means of the ribosomal L16 protein.[10] Most macrolides are bacteriostatic although they can also be bacteriocidal at higher concentrations. Bacterial resistance occurs by mutations that affect permeability and accessibility of the drug, and by alterations in ribosomal proteins. Their efficacy is typically greater for Gram-positive bacteria than for Gram-negatives.

In addition to their antimicrobial activity, macrolide antibiotics have peptide hormone (motilin receptor stimulation) activities and immunomodulatory (anti-inflammatory) activity.[11-19] These effects are independent of antibacterial properties, as the macrolide clarithromycin reduces mucin secretion and cytokine release from host cells challenged with lipopolysaccharide (LPS). Treatment with erythromycin or other macrolides significantly reduces mucus secretion and other hallmarks of inflammation independently of any antimicrobial effect, although the molecular details of the mechanism are not presently clear.[20] The mechanism for clarithromycin's anti-inflammatory activity appears to be inhibition of the activation of nuclear transcription factors NF-κβ, and AP-1 which results in diminished transcriptional activation of a host of genes associated with the inflammatory response.[19,21-25] This effect is manifested in airway epithelial cells,[19,25] as well as phagocytes.[21,22] Goswami *et al.* studied nasal mucus glycoconjugate secretion from healthy nonsmoking adults before and after treatment with erythromycin, penicillin, ampicillin, tetracycline or cephalosporins.[26] Subclinical doses of erythromycin reduced nasal secretion by 35% in both the resting state and when the nose was stimulated with methacholine or histamine. The other antibiotics had no effect on glycoconjugate secretion.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema, affects an estimated 5 to 15% of all adults in industrialised countries.[27] COPD is the fourth leading cause of death among adults in the Western world,[28,29] the sixth leading cause of death in all countries and is predicted to be among the top three causes of death around the world by 2020.[30-32] The primary risk factor for COPD is cigarette smoking, although other cofactors are certainly involved. COPD patients are heavily colonised by a variety of bacteria, including *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis.* The bacterial community extends into the lower airways, which are not usually colonised by bacteria. *H. influenzae* strains, predominantly acapsular (nontypeable) strains, account for 34% of all bacterial infections in patients with COPD.[33] The resistance of bacterial isolates to commonly used antimicrobials is increasing, as has been recognised for some time.[33]

A significant controversy regarding the progression and severity of COPD relates to the role of the colonising bacterial community in the genesis of inflammatory exacerbations. Studies using a protected-specimen brush sampling method have clearly demonstrated that bacterial counts are increased during exacerbations of COPD to levels consistent with the clinical definition of pneumonia,[34,35] but whether shifts in the bacterial population initiate the host response in an exacerbation or whether other factors are involved is a subject of intense debate.[7,36,37] The most clear evidence in support of a bacterial aetiology for inflammatory exacerbations of COPD was provided by two recent independent studies, both of which demonstrated that *H. influenzae* isolates from patients during an exacerbation are genetically and phenotypically distinct from those in asymptomatic carriage.[38,39]

Macrolides are a recommended choice for antimicrobial therapy in patients with acute exacerbations of COPD.[40] These data provide support for a bacterial aetiology for at least some exacerbations of COPD, other data have clearly demonstrated that macrolide therapy is beneficial even in exacerbations elicited by viral infection.[41] In this study, 109 patients with COPD were given prophylactic treatment with erythromycin or placebo, and the incidence of colds and number and severity of exacerbations between the two groups were compared. A majority (41/54, 76%) of the patients in the control group were diagnosed with a cold or experienced an acute exacerbation (30/54, 56%), whereas a significantly lesser number (7/55, 13%) of the patients given erythromycin had colds or exacerbations (6/55, 11%). The interpretation of this study is somewhat difficult, as the frequency and load of bacterial carriage was not evaluated. A possible interpretation is that viral infection disrupts a normally benign relationship between host and commensal bacteria.

Koh gave subtherapeutic doses of roxithromycin to 25 children with chronic bronchitis, and observed decreases in sputum production and airway hyperresponsiveness.[42] In a similar study, Tsang and colleagues tested the effect of sub-bacteriocidal levels of erythromycin on lung function and mucus production in patients with COPD, and the data clearly demonstrated a beneficial effect.[43] In a more recent study, low-level roxithromycin decreased airway levels of IL-8, neutrophil elastase, and C5a, and reduced neutrophil recruitment into the lung.[44] The results of these studies provide more convincing evidence for an immunomodulatory effect, as in all cases, the level of antibiotic is significantly below the MIC.

CYSTIC FIBROSIS

Cystic fibrosis (CF) is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) protein. The primary cause of morbidity and mortality in patients with CF is opportunistic bacterial infections. There is a clear successional hierarchy in the bacterial inhabitants in the CF lung, beginning with *H. influenzae* and *Staphylococcus aureus* in infancy. These are gradually supplanted by *Pseudomonas aeruginosa* and, to a lesser extent, *Burkholderia cepacia* and other pseudomonads.[45] In general, the onset and severity of *P. aeruginosa* colonisation is a marker for worsening of CF disease. Like many organisms at mucosal surfaces, *P. aeruginosa* forms complex, differentiated bacterial communities known as biofilms. Biofilms are defined as multicellular bacterial communities that form upon a solid biotic or abiotic surface within a polysaccharide matrix. *P. aeruginosa* isolates from CF patients typically produce copious amounts of the extracellular polysaccharide alginate, which is composed of mannuronic and guluronic acids.[46] Alginate plays a role in late-stage biofilm structure and organisation,[47] but alginate-deficient mutants do form biofilms (D. Wozniak, personal communication). Biofilm formation is a complex process that involves multiple steps that are largely coordinated by quorum signalling by means of released homoserine lactone signal molecules.[48-50]
The primary defect in CF that leads to increased bacterial colonisation is a subject of intense current debate and study.[51-55] Smith and colleagues have demonstrated that the increased chloride levels found in the CF airway secretions are inhibitory for the antimicrobial activity of defensins and other peptides that are important in the innate immune defences.[51] Other work has suggested that the CFTR protein mediates bacterial uptake and killing by epithelial cells, and that mutant CFTR alleles found in CF patients are less efficient in mediating bacteriocidal uptake.[53,54] The properties of the mucus secretions in the CF lung may be different, and some have suggested that the adhesivity of mucus may have a detrimental effect on the function of the mucociliary defences.[56-62]
Antimicrobial therapy for CF has been largely credited with extending the average lifespan of CF patients during the past 20 years. The aminoglycoside antibiotics are the primary drugs used in these patients. As with the macrolides, the antimicrobial activity of the aminoglycosides is only partially responsible for their therapeutic effect. Some aminoglycosides can also diminish translational fidelity, leading to read-through of premature stop codons in mutant CFTR alleles, and thus remedy the basic defect.[63-67]
The inherent resistance of *P. aeruginosa* to most antibiotics, including the macrolides, is relatively high, and certainly is higher than the doses that are usually used in CF patients.[68] Therefore, most clinical *P. aeruginosa* strains can be considered to be effectively resistant to erythromycin and other macrolides. Equi *et al.* tested the effect of prolonged azithromycin treatment in a set of 41 patients with cystic fibrosis over the course of 15 months.[69] The lung capacity, as measured by forced expiratory volume, was significantly increased, and the presence of bacteria, IL-8 and neutrophil elastase in sputum was decreased. Wolter *et al.* reported similar results in a randomised trial comparing 60 adult patients with cystic fibrosis given azithromycin or placebo over a three-month study period.[70] In this study, forced expiratory volume (FEV) declined significantly in the control group, whereas it was unchanged in those receiving azithromycin. The levels of C-reactive protein in serum were compared as a general index of inflammation, and declined in the treatment group and remained elevated in the control group. However, Ordonez and colleagues reported no effect on FEV or sputum production in a smaller patient group given clarithromycin for a shorter period of time (six weeks).[71] The results of the former two studies suggest that long-term therapy with macrolides decreases inflammation in CF patients. Possible insights into the mechanism behind these observations were provided by work showing that sub-lethal doses of macrolides can affect *P. aeruginosa* adherence[72] and production of proteases and other virulence factors.[73] Macrolides with 14-member ring or 15-member ring structures also inhibit alginate production, whereas 16-member ring macrolides do not.[74-77]

SINUSITIS

Sinusitis is a chronic, recurrent inflammatory condition that is perhaps best viewed as a 'vicious circle' in which inflammation leads to oedema and blockage of normal sinus drainage, which allows for increased colonisation by a number of different bacterial species. Although many of the same airway symbionts that cause opportunistic infections in other chronic inflammatory conditions (pneumococcus, *H. influenzae*, *M. catarrhalis*) are often isolated from patients with sinusitis, recent work has indicated that anaerobic bacteria constitute the majority of the bacterial load from cases of chronic recurrent sinusitis as compared with facultative anaerobes or aerobes.[78]
Macrolide therapy has been recognised for some time to significantly decrease mucus secretion in patients with sinusitis, and to significantly improve outcomes.[26,79] More recent work has demonstrated that macrolide therapy significantly reduces the release of IL-8 in nasal secretions and reduces the incidence of nasal polyps.[80]

DIFFUSE PANBRONCHIOLITIS

Diffuse panbronchiolitis (DPB) is a progressive lung disorder similar to CF in clinical presentation that is found primarily

in persons from East Asia. Patients with DPB typically have chronic bronchiectasis, with coughing, excess sputum production, and a reduction in airway conductivity. Most patients also have chronic sinusitis. Unlike COPD, there is not a correlation between DPB and smoking. As in patients with CF, chronic infections with mucoid strains of *P. aeroginosa* are common in DPB.[81,82]

Macrolide therapy provides significant benefit for patients with DPB. The first evidence of this was provided by the work of Kudoh *et al.* who demonstrated that erythromycin therapy significantly improves the long-term survival of DPB patients.[83] There has been a significant body of work suggesting that clarithromycin and other macrolides significantly inhibit biofilm formation by *P. aeruginosa*, perhaps by inhibition of the production of alginate and other extracellular polysaccharides.[84-88] Because there is still significant controversy regarding the role for alginate in biofilm formation[47] relative to other potential matrix components,[89] it is not entirely certain how the inhibition of alginate production would be expected to affect bacterial biofilm formation or persistence in the lung.

ASTHMA

As in the preceding inflammatory diseases, macrolide therapy also provides benefit for patients with bronchial asthma. Some have interpreted these results as indicative of a bacterial aetiology for some asthmatic episodes. Amayasu *et al.* evaluated the effect of clarithromycin treatment on 17 patients with bronchial asthma, and demonstrated a significant reduction in inflammatory episodes and general markers of inflammation, such as blood and sputum neutrophil counts.[90] Kamoi *et al.* evaluated the impact of roxithromycin on bronchial hyperreactivity and neutrophil activation in ten asthmatic patients over the course of three months' treatment, and observed a significant reduction in both the release of superoxide and airway reactivity as compared with untreated controls. No statistical benefit was observed in this study earlier than two months into the treatment regimen. Konno *et al.* evaluated the effect of roxithromycin therapy on cytokine secretion by peripheral blood leucocytes isolated from patients with asthma, and observed lower levels of IL-3, IL-4, IL-5 and tumour necrosis factor alpha in lung lavages as compared with controls, and an overall decrease in bronchial responsiveness.[91] Shimuzu and colleagues performed two trials testing the effect of roxithromycin on the progression and severity of disease in children with asthma, and in both cases saw a significant beneficial effect.[92,93] As in the preceding sections, the exact mechanism whereby macrolides exert this effect is not presently clear.

POSSIBLE MECHANISMS FOR ANTI-INFLAMMATORY EFFECTS OF MACROLIDES: AVENUES FOR FUTURE WORK

Translational effects

As noted above, while aminoglycoside antibiotics are not generally toxic to host cells, there is some degree of modification of host translational machinery. For the CF patient, this can be of benefit by leading to production of a less defective CFTR allele. It may be worthy of note that the macrolides have a similar mode of action to the aminoglycosides, involving binding to and modulation of the prokaryotic ribosome. Therefore, an intriguing possibility for future study would be whether macrolide treatment suppresses premature stop mutations in CFTR and other host genes. Because the host defects associated with COPD and other chronic airway conditions are less defined, and probably multifactorial, it is less clear how such a translational mechanism would affect these disorders.

Bacterial signal inhibition

Signal transduction among bacterial communities mediated by homoserine and acylhomoserine lactone molecules is a common theme among many bacterial species, especially those that form biofilms. The most compelling evidence for biofilm formation by *P. aeruginosa* within the cystic fibrosis lung was provided by the work of Singh and colleagues, who demonstrated that CF isolates had quorum signalling profiles consistent with a biofilm mode of growth.[94] In the normal lung, the formation of biofilms is inhibited by a variety of factors, including the sequestering of iron by lactoferrin.[95] Some reports have indicated that low-level macrolide treatment can inhibit the formation of biofilms by *P. aeruginosa*.[84-88] The basic structure of most macrolides is similar to that of homoserine lactone and acylhomoserine lactone quorum signal molecules. Therefore, one could envisage a model in which macrolides interfere with normal bacterial population signalling, and thus eliminate a source of inflammation without killing bacteria.

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ORIGINAL ARTICLE

Compassionate use programme of irinotecan in colorectal cancer patients in the Netherlands

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ABSTRACT

Background: Irinotecan is an effective treatment for metastatic colorectal cancer. However, its use may be associated with troublesome adverse effects such as delayed diarrhoea, acute cholinergic syndrome and neutropenic infection. The manufacturer decided to release irinotecan for compassionate use in the Netherlands prior to its regulatory approval (June 1998) and first introduction for second-line treatment of metastatic colorectal cancer. In view of the drug's adverse effect profile this was done in a carefully controlled manner.

Methods: Irinotecan was made available to patients with colorectal cancer with elaborate precautions. Treating physicians requesting irinotecan for compassionate use received a protocol, providing recommendations for the proper use and the prevention/management of potentially troublesome adverse events. Limited demographic, toxicity and efficacy data were collected.

Results: Between June 1997 and September 1998, 112 patients were registered for this programme, 103 of whom actually received irinotecan. The percentage of patients experiencing grade 3-4 adverse effects was relatively low: delayed diarrhoea in 17%, nausea and vomiting 17%, acute cholinergic syndrome 6%, febrile neutropenia 4% and neutropenic infection 2%. Five partial tumour responses and a high proportion of patients with 'no change' were noted.

Conclusions: The carefully controlled release of irinotecan for compassionate use with a very detailed protocol for guidance and advice on safety precautions seems to have contributed to the relatively safe use of the drug outside the setting of a formal clinical trial.

INTRODUCTION

Irinotecan (CPT-11, trademark Campto®) is a topoisomerase I inhibitor which interferes with DNA replication and cell division.[1,2] Irinotecan has demonstrated significant antitumour activity with tolerable side effects in various phase II and III clinical trials in 5-fluorouracil (5-FU) pretreated patients with advanced colorectal cancer.[3,4] In randomised phase III studies, irinotecan has shown superior efficacy in terms of response rate, time to progression and survival in comparison with infusional 5-FU/leucovorin[5] or best supportive care.[6] The survival benefit in these trials was achieved without increasing the overall cost of medical care consumption.[7,8] Irinotecan in combination with 5-FU/leucovorin has demonstrated clinical antitumour activity in first-line chemotherapy of metastatic colorectal cancer with overall tumour response rates of 24 to 49%, prolongation of time to tumour progression and increased overall survival compared with 5-FU/leucovorin alone.[4,9,10] Based on available studies, irinotecan has been approved worldwide for both second-line treatment (after 5-FU based regimens) and, in combination with 5-FU/leucovorin, first-line treatment of advanced colorectal cancer.

One of the most common and troublesome side effects encountered during the early clinical development of irinotecan was delayed diarrhoea, which could be severe.[4] Therefore, during the later stages of development, high-dose loperamide was advocated for use in patients with first signs of liquid stools. This intervention has been shown to significantly reduce the incidence of this complication.[11,12] The recommendation to use high-dose loperamide in patients with early signs of delayed diarrhoea is therefore included in the package insert of the currently marketed product.

Another relatively frequent side effect of irinotecan was acute cholinergic syndrome, possibly due to inhibition of cholinesterase activity by irinotecan. Symptoms may occur shortly after administration and typically include diarrhoea and various other cholinergic symptoms such as diaphoresis, chills, malaise, dizziness, visual disturbances, lacrimation, salivation, bradycardia and abdominal cramps. Symptoms are usually short lasting and may be treated effectively by the subcutaneous administration of atropine.

Further common toxicities include neutropenia, alopecia, fatigue, and nausea and vomiting. Nausea and vomiting is commonly seen in association with many cytotoxic agents and is usually manageable with routine measures.[4] The combined occurrence of diarrhoea and neutropenia may lead to severe infection and poses a potential safety concern.

Irinotecan was approved for the treatment of colorectal cancer by the regulatory authorities of the Netherlands in June 1998 and was introduced in the Netherlands in September 1998. The recommended dose schedule is 350 mg/m^2, given as an intravenous infusion over 30 to 90 minutes once every three weeks. In view of the lack of an effective second-line treatment regimen for colorectal cancer at the time of introduction, the manufacturer of irinotecan (Rhône-Poulenc Rorer, currently Aventis Pharma and further referred to as Aventis Pharma) decided to make the drug available to colorectal cancer patients in the Netherlands on a compassionate use basis prior to its general introduction onto the market. In view of the specific side-effect profile, it was decided to release irinotecan to patients qualifying for compassionate use with a number of safety precautions. An important feature of this programme was the use of a 'compassionate use protocol', providing recommendations for the proper use of irinotecan and the prevention and management of possible adverse events, in particular delayed diarrhoea, febrile neutropenia and acute cholinergic syndrome.

MATERIALS AND METHODS

Programme design

A compassionate use programme, giving colorectal cancer patients access to irinotecan, was conducted under carefully controlled conditions between June 1997 and February 1999. Oncologists at hospitals throughout the Netherlands were given the opportunity to obtain irinotecan for the treatment of patients meeting the programme's entry criteria. The main motivation to initiate this programme was humanitarian in nature. The programme was aimed at patients who could not be expected to benefit from another therapy or could not enter into an ongoing clinical trial, and gave them access to a potentially beneficial drug treatment. A good benefit/risk ratio should reasonably be expected for each individual patient entering the programme according to the most up-to-date clinical data on irinotecan. A defined set of demographic, toxicity, efficacy and treatment data was collected for each course using a simple case report form (CRF). The clinical data documented in the CRF were monitored by a representative of the sponsor according to standard ICH-GCP guidelines.

Patients

Patients had to meet the following entry criteria:

- Histologically proven adenocarcinoma of colon or rectum, either metastatic or with a nonresectable loco-regional relapse;
- At least one measurable or evaluable metastatic lesion according to WHO criteria;
- Age at least 18 years;
- Having failed a prior 5-FU-containing chemotherapy regimen for metastatic disease;
- Good performance status (WHO grade 0-2) and a life expectancy of more than three months;
- No bowel obstruction or subobstruction at baseline;
- Serum bilirubin ≤1.5 times upper normal limit;
- Serum creatinine ≤150 μmol/l;
- Baseline neutrophil count ≥1.5 x 10^9/l and platelet count ≥ 100 x 10^9/l;
- No inflammatory bowel disease (Crohn's disease, ulcerative colitis);
- No known hypersensitivity to irinotecan or one of the excipients;
- Number of lines of chemotherapy ≤3 (4 if one adjuvant).

Pregnant or breastfeeding women and patients, both male and female, of reproductive potential but not using effective contraception were excluded from participation. Patients qualifying for compassionate use of irinotecan were required to sign a written informed consent stating that they were aware of the fact that irinotecan was not a registered drug and that he/she was not entering a clinical trial. Furthermore, all patients received an information leaflet from their treating physician with instructions on

the use of loperamide should delayed diarrhoea develop following treatment and other precautions against potential serious adverse effects.
At registration, the patient's date of birth, gender, date of informed consent, cancer history (primary tumour site, date of first diagnosis, metastatic spread and date of metastasis diagnosis), prior radiotherapy (yes/no, site), performance status, body weight and body surface area were noted.

Drug treatment
The recommended dose of irinotecan was 350 mg/m^2, given as a 30 to 90 minute intravenous infusion, once every three weeks. If the neutrophil count at day 22 was below 1.5 x 10^9/l, the next course was to be delayed until recovery of the neutrophil count to ≥1.5 x 10^9/l. If recovery was observed at day 35, treatment was to be discontinued.
In patients experiencing severe gastrointestinal adverse events, such as diarrhoea or nausea and vomiting, it was recommended to delay further dosing of irinotecan until full recovery of symptoms, in particular diarrhoea.
Dose adjustments for a subsequent treatment cycle were recommended as follows:

- Same dose, if lowest absolute neutrophil count (ANC) >1.5 x 10^9/l without related fever *and* <grade 4 diarrhoea without need for intravenous rehydration;
- Approximately 20% dose reduction (i.e. from 350 mg/m^2 to 300 mg/m^2, and from 300 mg/m^2 to 250 mg/m^2), if lowest ANC <0.5 x 10^9/l, *or* lowest ANC <1.0 x 10^9/l with concomitant related fever or infections, *or* severe diarrhoea;
- Patient to be withdrawn if the 250 mg/m^2 dose could not be tolerated.

Prophylactic antiemetic treatment according to local guidelines, subcutaneous atropine sulphate (in case of acute cholinergic symptoms), high-dose loperamide (with a curative intent, as soon as first liquid stool occurred), oral broad-spectrum antibiotics (in case of severe diarrhoea) and intravenous broad-spectrum antibiotics (in case of febrile neutropenia) were recommended as concomitant medication. Prophylactic loperamide, other anticancer treatment (except localised radiotherapy) and other investigational agents were prohibited.
Treating physicians were advised to make patients aware of the risk of delayed diarrhoea. Patients should be advised to inform their physician and to start appropriate therapy promptly if signs of liquid stools appeared more than 24 hours after administration of irinotecan.
Physicians were also advised to inform patients about the risks of severe diarrhoea and severe neutropenia and the significance of fever during treatment.

Follow-up
After each cycle of irinotecan, weekly blood cell counts (with differential counts) and, in patients who experienced diarrhoea, serum electrolytes and creatinine were taken. Weekly visits or phone calls were mandatory for all patients during at least the first cycle to check for adverse events and patient compliance with the recommended concomitant medication. Particular attention was to be given to higher-risk patients, i.e. patients older than 65 years, heavily pretreated patients, patients with prior abdominopelvic radiotherapy, performance status 2, or bilirubin >1 upper normal limit, patients whose performance status worsened during therapy and patients with expected poor compliance. Weekly visits were strongly recommended for these patients during the full duration of treatment.
Clinical adverse experiences were to be documented in the CRF, indicating the degree of severity according to the Netherlands Cancer Institute Common Toxicity Criteria (NCI-CTC), date of onset and cessation, outcome and relation to study medication. Serious adverse events (SAE) were to be reported to Aventis Pharma within a 24-hour working day period following their occurrence, followed by the submission of a standard SAE form.
Antitumour efficacy was evaluated according to World Health Organisation (WHO) criteria[13] by the local radiologist every second treatment cycle, using the most accurate, reliable and repeatable methods that are routinely used. Tumour responses were not independently reviewed by an external committee. Tumour responses and disease control, defined as the absence of progression for at least six cycles without deterioration in performance status, weight loss or symptom onset, were noted on the CRF. Treatment was stopped in case of progressive disease, patient's withdrawal, unacceptable adverse events irrespective the duration of treatment, or the absence of clinical benefit after six cycles.

Logistics
Drug supplies for patients meeting all requirements for participation in the programme were despatched to the pharmacy at the centre of the treating physician for two cycles at a time. Supplies for further cycles were provided if treatment was to be continued and only after communication with the supplier.

RESULTS

A total of 112 patients were registered by physicians from 40 different hospitals throughout the Netherlands. Main patient characteristics at registration are depicted in *table 1*. All patients had received prior chemotherapy, mostly a 5FU/leucovorin-based regimen or a raltitrexed (Tomudex®)-based regimen. Just over 20% of patients had also received prior radiotherapy, mostly in the pelvic region.

Treatment was initiated between June 1997 and September 1998. The last treatment course was given on 29 September 1999. Five patients did not receive irinotecan although they were registered and for another four patients largely incomplete data were obtained. The 103 patients who were actually treated with irinotecan and for whom adequate data is available received a total of 553 courses (median: 4 courses; range: 1-21 courses). These 103 patients and 553 courses were used as the denominator for the calculation of incidence and rate figures in the remainder of this paper unless otherwise indicated.

Of the courses given, 75% were within 21 days of the preceding drug administration. However, a significant number of courses had to be delayed by one to nine (22% of courses) or more than nine days (3% of courses). The median relative dose intensity was calculated at 95.5% (range: 16.7-105.2%).

Most of the common toxicities, reported in association with the use of irinotecan in clinical studies, were also reported for patients participating in the compassionate use programme. The most frequently reported clinical adverse experiences were acute cholinergic syndrome, delayed diarrhoea, and nausea/vomiting, mostly of grade 1 or 2 (*table 2*, on the next page). Grade 4 toxicity was associated with only 2.9% (16/553) of courses and included neutropenia (1.6%), delayed diarrhoea (0.7%), febrile neutropenia (0.2%), nausea/vomiting (0.2%) and other toxicities (0.2%). A 'possible' or 'probable' relationship to irinotecan treatment was reported for the majority of adverse events that are considered typical for irinotecan. The number of patients with maximum grade 3-4 was relatively small: neutropenia 21.4%, delayed diarrhoea 17.4%, nausea and vomiting 17.4%, acute cholinergic syndrome 5.8%, febrile neutropenia 3.9% and neutropenic infection 1.9% (*table 3*). Grade 4 toxicity was reported as the maximum grade in 16 patients, nine of whom suffered grade 4 neutropenia. The proportion of patients with grade 3 or 4 delayed diarrhoea was somewhat higher among those who had received prior pelvic radiotherapy (*table 4*), but no statistical significance for the association between prior pelvic radiotherapy and delayed diarrhoea was achieved (p=0.09; exact p value, Fisher's test).

Of the 103 patients, 90 were evaluable for response. Sixty-eight percent (61/90) of these evaluable patients had either a partial response (5.6%), a minor response (13.3%) or no change/stable disease (48.9%) as their best overall response (*table 5*). The median duration of response was 36.4 weeks in patients experiencing a partial response and 25.0 weeks in patients experiencing a minor response. The median duration of disease stabilisation was 23.4 weeks.

Table 1
Demographic data and patient characteristics at entry

VARIABLE	NUMBER	TOTAL (%)
Male/female	77/35	68.8/31.3
Mean age, years (range)	57.5 (25-76)	
Performance status		
0	51	45.5
1	52	46.4
2	8	7.1
3	1	0.9
Primary tumour site		
Colon	75	67.0
Rectum	29	25.9
Colorectal (not specified)	8	7.1
Metastatic tumour sites (all sites)		
Liver	71	
Abdominal lymph nodes	31	
Lung	28	
Peritoneum	17	
Other	25	
Missing data (no. of patients)	17	
Prior chemotherapy		
No	-	-
Yes	112	100
Prior radiotherapy		
No	76	67.9
Yes	25	22.3
Pelvis	19	17.0
Other	10*	8.9
Missing data	11	9.8

* *Five patients had received prior pelvic and non-pelvic radiotherapy.*

Table 3
Maximum grade toxicity per patient (n=103)

CLINICAL ADVERSE EXPERIENCE	MAXIMUM GRADE (NO. OF PATIENTS)*				
	0	1	2	3	4
Acute cholinergic syndrome	39	39	19	6	-
Delayed diarrhoea	25	35	25	14	4
Nausea/vomiting	25	30	30	17	1
Neutropenia	72	4	5	13	9
Febrile neutropenia	98	-	1	3	1
Infection with neutropenia	101	-	-	2	-
Other	10	7	47	38	1

* *Grading: 0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = life-threatening.*

Table 4
Prior radiotherapy at a pelvic site and the occurrence of delayed diarrhoea

PRIOR RADIOTHERAPY AT PELVIC SITE (N=103)	NO. OF PATIENTS WITH DELAYED DIARRHOEA GRADE 3 OR 4	
	YES	NO
Yes (n=19)	6	13
No (n=84)	12	72

Table 2
Clinical adverse experiences with grading and relation to study medication by course (n=553)

CLINICAL ADVERSE EXPERIENCE	RELATION TO STUDY MEDICATION	NO. OF COURSES WITH GRADE*					TOTAL
		0	1	2	3	4	
Acute cholinergic syndrome	No	378	-	-	-	-	378
	Possible	-	1	-	1	-	2
	Probable	-	138	30	5	-	173
	Total	*378*	*139*	*30*	*6*	-	*553*
Delayed diarrhoea	No	339	-	-	-	-	339
	Remote	-	2	3	-	-	5
	Possible	-	10	1	-	-	11
	Probable	-	123	54	16	4	197
	Not reported	-	1	-	-	-	1
	Total	*339*	*136*	*58*	*16*	*4*	*553*
Nausea/vomiting	No	324	1	2	-	-	327
	Remote	-	2	4	1	-	7
	Possible	-	14	2	-	-	16
	Probable	-	114	62	24	1	201
	Not reported	-	2	-	-	-	2
	Total	*324*	*133*	*70*	*25*	*1*	*553*
Neutropenia	No	472	-	-	-	-	472
	Remote	-	-	1	-	-	1
	Possible	-	-	-	3	1	4
	Probable	-	16	24	28	8	76
	Total	*472*	*16*	*25*	*31*	*9*	*553*
Febrile neutropenia	No	547	-	-	-	-	547
	Probable	-	-	1	4	1	6
	Total	*547*	-	*1*	*4*	*1*	*553*
Infection with neutropenia	No	551	-	-	-	-	551
	Probable	-	-	-	2	-	2
	Total	*551*	-	-	*2*	-	*553*
Other[&]	No	73	115	72	27	-	287
	Remote	-	36	23	8	-	67
	Possible	-	91	56	13	-	160
	Probable	-	209	366	45	1	621
	Not reported	-	6	11	3	-	20
	Total[#]	*73*	*457*	*528*	*96*	*1*	*1155*

[*] *Grading: 0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = life-threatening.* [&] *Other adverse clinical experiences include: abdominal pain, alopecia, anorexia, asthenia, chest pain, coughing, fatigue, febris, ileus/volvulus, leucopenia, malaise, oral mucositis, weakness (grade 3 and 4 only and in alphabetical order).*
[#] *Some patients had multiple 'other' adverse experiences; therefore, this total number does not equal the number of cycles given.*

The Kaplan-Meier curves for overall survival and progression-free survival (*figure 1*) illustrate that virtually all patients had disease progression within 15 months of enrolment in the compassionate use programme. The median time to progression was 101 (95% CI: 84-126) days. At 18 months, over 95% of patients receiving irinotecan treatment had died. Median survival was 275 (95% CI: 216-314) days and the one-year survival rate 34.9%.

Table 5
Best overall tumour response in evaluable patients (n=90) treated with irinotecan

RESPONSE	NO. OF PATIENTS	%
Complete response	-	-
Partial response	5	5.6
Minor response	12	13.3
No change/stable disease	44	48.9
Progressive disease	29	32.2
Total evaluable	90	100
Not evaluable	13	-

DISCUSSION

Given their nature, compassionate use programmes cannot substitute for prospective clinical research. Clinical trials are essential for assessing the efficacy and tolerability of a new drug before market availability. However, restrictive eligibility criteria in formal clinical trials exclude a significant proportion of advanced colorectal cancer patients with poor prognosis. Study populations with age restrictions, performance status limitations, normal major organ function, prior treatment limitations and disease measur-

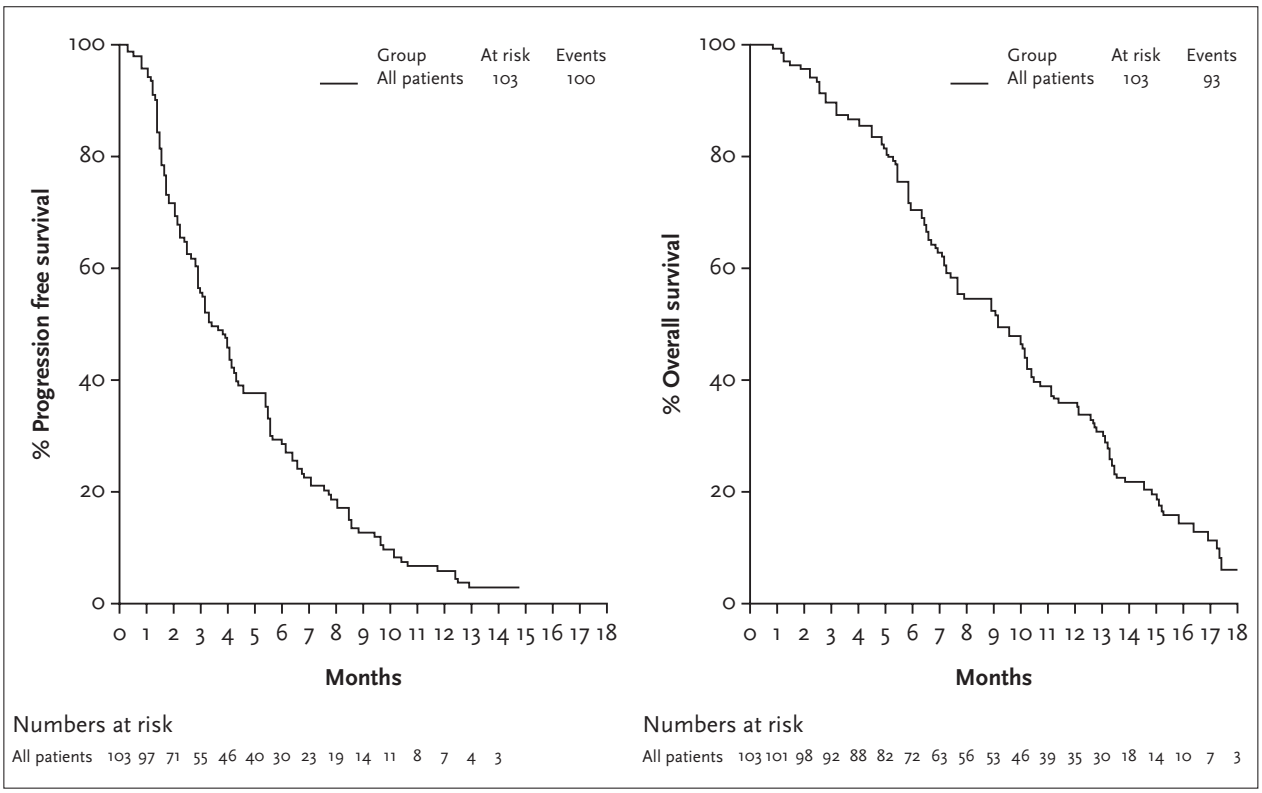

Figure 1
Kaplan-Meier curve for progression-free survival (left panel) and overall survival (right panel) among the group of patients (n=103) receiving compassionate irinotecan treatment

ability requirements allow valid data, yet are not always fully representative of the situation that prevails in routine clinical practice. Therefore, compassionate use programmes offer the opportunity to gather additional safety and efficacy data when used in unselected patients, under prescription and surveillance conditions similar to those of routine oncology practice when a new active agent is initially available to prescribing physicians.[14,15]

The carefully controlled release of irinotecan for compassionate use in patients with colorectal cancer in the Netherlands may be regarded a successful effort to make this new agent available to patients whose treatment options were exhausted. At the time this programme was launched, several large studies had already demonstrated the clinical benefits of irinotecan as second-line treatment for patients with advanced colorectal cancer.[3] However, the use of irinotecan had also been shown to be associated with several typical and troublesome side effects.[3] Delayed diarrhoea, (febrile) neutropenia, severe infection and acute cholinergic syndrome were considered to constitute significant risks of the drug in the compassionate use setting. In this setting, many treating physicians were likely to have very limited or no previous experience with the new drug. Therefore, the release of irinotecan for compassionate use occurred under the guidance of a 'protocol', which was aimed at the prevention, and adequate management of severe toxicities that might occur in association with irinotecan.

Analysis of adverse experiences as reported on the CRFs seems to confirm the success of this 'protocolised' compassionate use programme. The number of patients with maximum grade 3-4 for the most important toxicities of irinotecan (17.4% for delayed diarrhoea, 5.8% for acute cholinergic syndrome, and 3.9 and 21.4% for febrile neutropenia and neutropenia, respectively) was relatively low compared with published data from phase II and III clinical trials. A recent review of clinical studies with irinotecan[4] reported that severe cholinergic syndrome may occur in 9% of patients, grade 3 or 4 neutropenia in 23 to 44% of patients and delayed diarrhoea in up to 87% of treated patients. If managed according to recommendations very similar to those advised in the current compassionate use programme, grade 3 or 4 diarrhoea occurred in only 34% of patients, according to the same review.

A remarkable finding in the compassionate use cohort is the low incidence of severe infections with neutropenia. Only two courses with grade 3 infection and none with grade 4 infection were reported. This may be interpreted as an indication of the success of the specific precautions

that were aimed at preventing infection in a setting where neutropenia and diarrhoea are common adverse effects of treatment. Apparently, physicians treating patients in the compassionate use programme were well aware that severe neutropenia as well as other adverse effects could occur and, most likely, followed the recommendations and guidance for the proper use of irinotecan closely. Similarly, the high proportion of 'possible' and 'probable' relations in the physician-reported relation to medication for acute cholinergic syndrome, delayed diarrhoea, and nausea/vomiting suggests that physicians were well aware that these adverse events could occur in association with irinotecan treatment. Also the patients seem to have complied well with the instructions and guidelines given to them regarding delayed diarrhoea and other possible complications.

The data collected during this programme allow some further comparisons with regard to the safety and efficacy of irinotecan in clinical trials. A recently published multivariate analysis of irinotecan-induced toxicity in 416 patients has identified prior abdominopelvic radiotherapy as one of several predictive factors for a high risk of grade 3 or 4 delayed diarrhoea.[16] The data on delayed diarrhoea in the current cohort seem to show a trend for an association between prior radiotherapy at a pelvic site and an increased likelihood of delayed diarrhoea. It should be noted, however, that the total number of patients in the current cohort and the proportion of patients with prior pelvic radiotherapy are small.

In second-line chemotherapy of metastatic colorectal cancer (after prior exposure to a 5-FU-based regimen), irinotecan has demonstrated overall response rates (CR+PR) in the range of 11 to 17% at different dose schedules.[4] All patients receiving irinotecan in the current programme had received prior chemotherapy, and were likely to be heavily pretreated at the time of entry into the programme. This may be an explanation for the comparatively low overall response rate (5.6%, 5 PR) observed in the current cohort compared with the study populations usually included in first- and second-line phase II and phase III trials.

A remarkable feature of anticancer camptothecins, including irinotecan, is the high proportion of patients with long-lasting disease stabilisation, which has been observed in most clinical studies with this class of agents. In first- and second-line clinical trials of metastatic colorectal cancer, the percentage of patients with 'no change' ranged from 38 to 52%.[4] The percentage of patients with 'no change/stable disease' (48.9%) in the current compassionate use programme is at the higher end of this range and confirms the general observation of frequent disease stabilisation by camptothecins, even in a heavily pretreated patient population.

Two phase III trials of second-line treatment of metastatic colorectal cancer have shown survival benefits for irinotecan, 350 mg/m^2 as a 90-minute intravenous infusion once every three weeks, in comparison with either best supportive care or high-dose infusional 5-FU.[5,6] Median survival of irinotecan-treated patients in these trials was 9.2 and 10.8 months, respectively. One-year survival rates were 36 and 45%, respectively. Despite the relative low overall response rates observed, the comparative survival figures from the compassionate use cohort (approx. nine months median survival and 35% one-year survival) appear to be in line with the results of these trials. In one of the second-line phase III studies, best supportive care was associated with a median survival of only 6.5 months and 14% one-year survival.[6] Whether or not these data suggest a clinical benefit for irinotecan in the compassionate use setting is difficult to discern due to methodological complications such as the comparison with a historic control group and the nontrial setting in which the compassionate use data have been collected.

In conclusion, the controlled release of irinotecan in a compassionate use setting in the Netherlands prior to registration may be regarded a successful initiative, giving over 100 patients with advanced colorectal cancer access to a nonregistered drug with potential benefit for the treatment of their disease. Elaborate 'protocolised' precautions by the manufacturer of irinotecan aimed at the prevention and management of potential serious toxicities seem to have contributed to the relatively safe use of the drug outside the setting of a formal clinical trial.

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ORIGINAL ARTICLE

Nightmares, sleep and cardiac symptoms in the elderly

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ABSTRACT

Background: Sleep complaints and various sleep symptoms are common in elderly persons with cardiac diseases. Nightmares are associated with profound sleep disturbances.

Methods: The present questionnaire survey with questions on sleep symptoms, nightmares and cardiac symptoms comprised 6103 elderly subjects (39.5% men).

Results: Nightmares occurred rather often in 6.9% and very often in 2.1% of the men. The corresponding frequencies in women were 9.6 and 2.3%, respectively. Irregular heart beats were reported by 11.8% of the men and 13.1% of the women (NS). Spasmodic chest pain occurred in 12.9 and 10.6%, respectively ($p<0.01$). Irregular heart beats increased in association with increasing nightmares in both men ($p<0.01$) and women ($p<0.0001$). The percentages of men and women with both irregular heart beats and spasmodic chest pain were three times and seven times higher, respectively, among those who had nightmares very often than among those who very seldom or never had nightmares. The increase in cardiac symptoms in nightmare sufferers was not attributable to an increase in medication with cardiac drugs.

Conclusion: In this group of elderly men and women increased nightmares were associated with an increase in irregular heart beats and spasmodic chest pain.

INTRODUCTION

Sleep is important for health, and impaired sleep is a major cause of untimely death and illness.[1-3] Mortality from cardiac diseases is increased in parallel with increased sleep impairment.[4] Short sleep is associated with an increased frequency of chest pain that can be related to myocardial infarction or angina pectoris, and poor sleep is even more detrimental to cardiac health than short sleep.[5,6] Frequent waking in the night is associated with an increased risk of angina pectoris.[7] Waking up is a common consequence of nightmares. Nightmares, in turn, are common at all ages and may be insignificant in adults, but increased nightmares in the elderly often reflect somatic diseases.[8,9] Most of the nightmares occur during rapid eye movement (REM) sleep and frequent nightmares are often an expression of a disturbance in the sleep structure.[8] Nightmares may have serious consequences for health in certain conditions. They are closely related to several somatic and mental symptoms and also to impaired quality of life.[10,11] The present study was undertaken to assess the relationship between the occurrence of nightmares and cardiac symptoms in a large group of elderly persons and to determine whether this relationship, if any, remained after the possible influence of antianginal drugs and other drugs for cardiac diseases had been taken into account.

MATERIAL AND METHODS

The present study is based on an extensive questionnaire survey of sleep and health in elderly men and women in northern Sweden.[12] All 10,216 members of the pensioners' association SPF in the Swedish counties of Västerbotten and Norrbotten were asked to participate in the survey.

A further questionnaire was sent to those who did not respond within one month.

The questionnaire included questions on the general state of health, occurrence of somatic diseases and symptoms, smoking and snuffing, coffee consumption and the use of drugs. In addition there were questions about nocturnal sleep (good *vs.* poor), the ability to fall asleep after nocturnal awakenings (easy *vs.* difficult) and nightmares (very seldom, rather seldom, rather often and very often). Two statements on cardiac symptoms were analysed. 'I am troubled by spasmodic pain in the chest', referred to in the following as 'spasmodic chest pain', and 'I am troubled by a sensation of irregular heart beats', referred to in the following as 'irregular heart beats', both with the alternative answers 'yes' or 'no'. In the text these two symptoms are together named 'cardiac symptoms'.

Treatment with antianginal drugs was analysed by the statement: 'I take medication for treatment of spasmodic chest pain', and the use of other drugs for cardiac diseases by the statement 'I take other cardiac medication than antianginal drugs', both with the alternative answers 'yes' or 'no'.

Statistical methods

Standard methods were used for calculating mean values and standard deviations. Group comparisons of non-numerical data were made with the chi-square test. For simultaneous evaluation of the influence of more than one independent variable on a dependent variable, multiple logistic regression analysis (StatView 5.0 for the Macintosh) was performed. For assessing the relationship between nightmares and cardiac symptoms, two multiple logistic regression analyses were performed with sex, nightmares and sleep as independent variables and irregular heart beats and spasmodic chest pain as dependent variables. The possible influence of antianginal drugs and other drugs for cardiac diseases was assessed by a multiple logistic regression analysis with antianginal drugs and other drugs for cardiac diseases, irregular heart beats and spasmodic chest pain as independent variables and nightmares as the dependent variable.

Results

The questionnaire was initially completed by 4544 persons. In 73 persons the mailing address was wrong, 83 persons declined to participate and 42 persons had died between the time when the list of members was obtained and the questionnaire was sent. After a reminder, a further 1559 answers were received. Thus there were 6103 evaluable questionnaires, of which 39.5% were from men. The response rate was 61.3%. The ages (mean ± standard deviation) of the male and female participants were 73.0 ± 6.0 and 72.6 ± 6.7 years, respectively. Sixty-one percent of the men and 67.3% of the women lived in urban areas ($p<0.0001$). Twenty-six percent of the men and 57% of the women were living alone. Poor health was reported by 16.8% of the men and 18.7% of the women (NS). Health deterioration during the past five years was reported by 30.9% of the men and 34.6% of the women ($p< 0.01$).

Nightmares and sleep

Women were more troubled by nightmares than were men (*table 1*). In men there was no age-related difference in the occurrence of nightmares, but in women there was a slight increase in age in parallel with increasing occurrence of nightmares ($p<0.05$). Poor sleep was reported by 15.7% of the men and 33.4% of the women ($p<0.001$). Difficulty in falling asleep after nocturnal awakenings occurred in 18.0% of the men and 35.1% of the women ($p<0.001$). Sleep and the ability to fall asleep after nocturnal awakenings showed a stepwise increase in parallel with more frequent nightmares in both sexes (*table 2*).

Table 1

The percentages of elderly men and women with different frequencies of nightmares ($p<0.01$)

	MEN	WOMEN
Very seldom or never	75.9	70.9
Rather seldom	15.1	17.2
Rather often	6.9	9.6
Very often	2.1	2.3
Totals	*100.0*	*100.0*

Table 2

The percentages of men and women with poor sleep and difficulty in falling asleep after nocturnal waking in relation to the occurrence of nightmares

SEX	VERY SELDOM OR NEVER	RATHER SELDOM	RATHER OFTEN	VERY OFTEN	TOTAL	P VALUE
Poor sleep						
Men	12.8	20.4	33.8	28.0	15.7	<0.0001
Women	27.6	41.7	55.5	78.1	33.4	<0.0001
Difficulty in falling asleep after nocturnal waking						
Men	16.1	26.8	28.4	25.0	18.7	<0.001
Women	31.8	48.3	55.6	62.5	37.3	<0.0001

Frequent awakenings with a feeling of despondency was reported by 1.2% of the men and 3.7% of the women. In men there was no change in the feeling of despondency in relation to nightmares, but in women this feeling occurred in 2.2% of those who had nightmares very seldom or never, and in 4.0, 13.2 and 17.2% of those with nightmares rather seldom, rather often and very often, respectively (p<0.0001).

Nightmares, irregular heart beats and spasmodic chest pain

Irregular heart beats were reported by 11.8% of the men and 13.1% of the women (NS) and spasmodic chest pain occurred in 12.9 and 10.6%, respectively (p<0.01).

The occurrence of irregular heart beats increased in parallel with increasing nightmares in both men (p<0.01) and women (p<0.0001) (*figure 1*). Increasing nightmares were not associated with an increased occurrence of spasmodic chest pain in men, but such an association was found in women (p<0.0001) (*figure 2*). The occurrence of both irregular heart beats and spasmodic chest pain in the same patient was 3.4 (1.0 - 11.7) times more common in men and 6.4 (2.8 - 14.7) times more common in women with very frequent nightmares than in the total group of men and women, respectively.

In a multiple logistic regression analysis with sex, nightmares and sleep as independent variables, female sex, poor sleep and nightmares were all significant independent correlates of increased irregular heart beats in men. Correspondingly, poor sleep and nightmares were significant independent correlates of increased spasmodic chest pain, while female sex was associated with decreased spasmodic chest pain (*table 3*).

Medication

Antianginal medication was used by 16.6% of the men and 13.5% of the women. Use of this medication was reported by 86.6% of the men with spasmodic heart pain and 89.9% of the women with this symptom. Other cardiac drugs were used by 13.1% of the men and 10.6% of the women, and by 52.4% of the men and 43.8% of the women with irregular heart beats.

Of the men who were very seldom or never troubled by nightmares, 15.9%, were being treated with antianginal drugs; among men who rather seldom had nightmares this figure was 24.2%, rather often 28.1% and very often 33.3% (p<0.001). The corresponding frequencies in women were 13.7, 20.6, 20.5 and 34.2%, respectively (p<0.0001). The corresponding proportions of men taking other drugs for treatment of cardiac diseases were 14.3, 13.9, 20.3 and 18.5% (NS), and of women 12.1, 14.6, 16.7 and 28.9%, respectively (p<0.0001).

Table 3

Probability of suffering from irregular heart beats or spasmodic chest pain in relation to sex, sleep and nightmares

	IRREGULAR HEART BEATS	SPASMODIC CHEST PAIN
Sex (Male = 1.0)		
Female	1.3 (1.0 - 1.6)	0.8 (0.6 - 1.0)
Sleep (Good = 1.0)		
Poor	1.7 (1.4 - 2.2)	1.5 (1.1 - 1.9)
Nightmares (Very seldom = 1.0)		
Rather seldom	1.3 (1.0 - 1.7)	1.3 (0.9 - 1.7)
Rather often	2.3 (1.6 - 3.2)	1.3 (0.8 - 1.9)
Very often	2.8 (1.6 - 5.1)	3.2 (1.8 - 5.7)

Multiple logistic regression analyses with odds ratios and 95% confidence intervals.

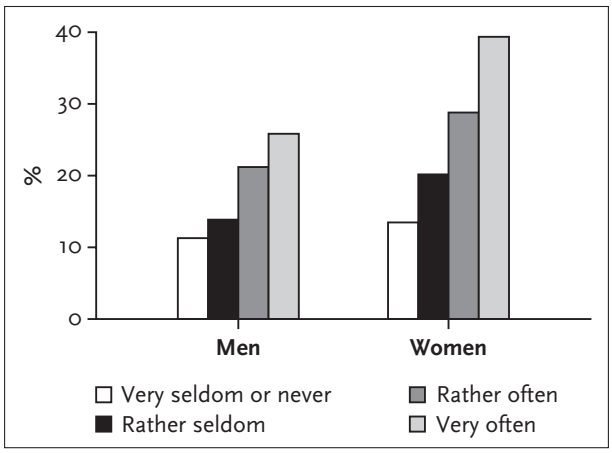

Figure 1

The occurrence of irregular heart beats (%) in men (p<0.01) and women (p<0.0001) in relation to their perception of nightmares

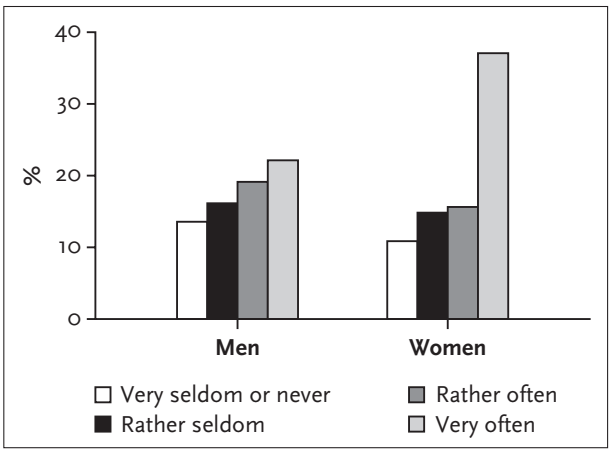

Figure 2

The occurrence of spasmodic chest pain (%) in men (NS) and women (p<0.0001) in relation to their perception of nightmares

A multiple logistic regression analysis with antianginal drugs, other drugs for cardiac diseases, irregular heart beats and spasmodic chest pain as independent variables and nightmares as the dependent variable, revealed that nightmares were increased in parallel with increased reports of irregular heart beats and spasmodic chest pain, while antianginal drugs and other drugs for cardiac diseases were deleted by the statistical model.

Sleep medication was used every night by 10.3% of the men, at least once a week by 7.5%, less than once a week by 8.8% and was never used by 73.4%. The corresponding frequencies in women were 12.2, 13.9, 16.9 and 57.0%, respectively ($p<0.0001$). In men there was no change in the occurrence of nightmares in relation to the use of sleep medication, but in women such treatment was used in 4.8% of those who very seldom or never had nightmares and in 9.3, 12.2 and 23.7% of those with nightmares rather seldom, rather often and very often, respectively ($p<0.0001$).

Coffee drinking, smoking and snuffing

Coffee drinking at least once a day was reported by 91.5% of the men and 88.5% of the women ($p<0.0001$), and 44.9% of the men and 35.1% of the women ($p<0.0001$) drank at least one cup of coffee after 6 p.m. Coffee drinking decreased with increasing age in both sexes. Daily smoking was reported by 9.7% of the men and 7.0% of the women ($p<0.001$), and daily snuff-taking by 13.5% of the men and 1.5% of the women ($p<0.0001$).

Neither coffee-drinking habits, smoking nor taking snuff showed any influence on the occurrence of nightmares.

DISCUSSION

In this study it was found that among elderly persons who were troubled by nightmares there was an increased frequency of both irregular heart beats and spasmodic chest pain.

One important question in the interpretation of these data is whether or not there is any correspondence between perceived cardiac symptoms, such as irregular heart beats or spasmodic chest pain, and objective cardiac arrhythmia or angina pectoris. One finding that supports the view that the reported symptoms correspond with cardiac arrhythmia or angina pectoris in the majority of cases is that almost 90% of the subjects who reported spasmodic chest pain were being treated with antianginal drugs and that those who suffered from irregular heart beats also reported a high consumption of drugs for cardiac diseases.

Another question in the interpretation of the findings concerns the validity of reports on nightmares and other sleep symptoms in a questionnaire. Consistent correspondence has been found between reports on poor sleep and different sleep measurements.[13,14] The correspondence between a reported propensity for nightmares, on the one hand, and increased figures for poor sleep and increased difficulties in falling asleep after nocturnal awakenings, on the other hand, would seem to allow the interpretation that there is a consistent relationship between the actual occurrence of increased nightmares and reports on nightmares. This view is also supported by the finding that increased reported awakenings with a feeling of despondency paralleled an increasing occurrence of nightmares.

In parallel with increasing nightmares, there was an increase in irregular heart beats in both men and women, while there was a significant increase in spasmodic chest pain in women but not in men. Occurrence of the two symptoms irregular heart beats and spasmodic chest pain in the same patient was increased threefold in men and sixfold in women with very frequent nightmares compared with the whole group of men and women.

An increase in the occurrence of irregular heart beats and spasmodic chest pain has also been observed in elderly people of both sexes with difficulty in falling asleep and too early awakening in the morning.[12] Indirect support for the possibility of a relationship between nightmares and the two cardiac symptoms is that antianginal drugs in both men and women showed a stepwise increase in parallel with increasing nightmares. A similar relationship between nightmares and other cardiac drugs was seen in women but not in men.

The use of antianginal drugs as well as that of other cardiac drugs showed an increase in persons with higher frequencies of nightmares. It has been reported from previous studies that the use of cardiac drugs is increased in elderly persons with insomnia.[15] One possibly confounding factor to be considered is that β-blockers are probably prescribed to some patients with angina pectoris or cardiac arrhythmia and that nightmares are well-known side effects of these drugs.[16] However, the use of cardiac drugs (including β-blockers) showed no influence on the occurrence of nightmares when the effect of irregular heart beats and spasmodic chest pain were taken into consideration in the logistic regression analysis.

Although coffee consumption was very high in this group of elderly subjects it showed no influence on the occurrence of nightmares, either as the total daily consumption or coffee drinking after 6 p.m. Smoking was rather infrequent in this group, and in men the habit of taking snuff was more prevalent than smoking. Neither smoking nor taking snuff was associated with an increased prevalence of nightmares.

In women, but not in men, the use of sleep medication was increasingly common in parallel with an increased occurrence of nightmares. This result may be a confounder of the previously reported finding that sleep medication is increased not only by sleep impairment *per se* but also in

association with impaired somatic and mental health.[17] A logistic regression analysis revealed that nightmares occurring rather often or very often, sleep and female sex were all associated with an increase in irregular heart beats. It has been shown previously that an increase in the number of nocturnal awakenings is associated with an increase in irregular heart beats and that this relationship is more pronounced in women than in men.[14] The results of the present study show that very frequent nightmares are associated with an increase in irregular heart beats independent of the detrimental effect of poor sleep.

Very frequently occurring nightmares were still associated with an increase in spasmodic chest pain after adjustment had been made for the influence of poor sleep. This finding is in line with the previous observation that there is an increase in the frequency of spasmodic chest pain in parallel with an increase in the number of nocturnal awakenings.[14] This may support the view that the increase in awakenings in elderly persons with cardiac symptoms is to some extent an expression of their more frequent nightmares. This brings us to the question of what is the cause and what is the effect with regard to nightmares and cardiac symptoms. It is known that different kinds of sleep disturbances are associated with increased cardiac symptoms. Difficulty in falling asleep[18] and increased nocturnal awakenings[7] are associated with an increased risk of spasmodic chest pain. Barry *et al.*[7] report that waking up at night mostly precedes rather than follows a nocturnal anginal attack, and Quyyumi *et al.* found that nocturnal ST depression is more often observed after than before awakening.[19] There are case reports on persons with no previously known heart disease in whom nightmares have occurred immediately before they have fallen ill with coronary artery dissection and other life-threatening cardiac events.[20] It therefore seems reasonable to assume that nightmares precede rather than succeed cardiac symptoms in the majority of cardiac events. This may indicate that nightmares and also other sleep complaints in the elderly are important health problems and should receive more attention, and that sleep-improving therapeutic measures may be one way of protecting cardiac health in the elderly. Further research is needed to elucidate this issue.

To summarise, in this group of elderly men and women increased nightmares were associated with an increase in irregular heart beats as well as in spasmodic chest pain. The use of antianginal drugs and other cardiac drugs increased in parallel with increased frequencies of the two cardiac symptoms, but the increase in nightmares could only be attributed to cardiac symptoms and not to cardiac drugs. The results indicate that in the elderly, cardiac symptoms are associated to a considerable extent with the occurrence of nightmares.

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CASE REPORT

Rituximab in the treatment of relapsing idiopathic thrombocytopenic purpura

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ABSTRACT

About 25 to 30% of patients with idiopathic thrombocytopenic purpura (ITP) are resistant to standard treatment with steroids and splenectomy. In these patients with chronic refractory ITP, there is no proven algorithm for standard care. Recently, the chimeric anti-CD20 monoclonal antibody rituximab was considered as an alternative treatment option in this patient group. We present a patient with frequently relapsing ITP after treatment with prednisone, splenectomy and high-dose dexamethasone. Since he experienced increasing side effects due to the steroids, he was treated with rituximab 375 mg/m², once weekly for four weeks, resulting in a complete long-lasting response (follow-up seven months).

INTRODUCTION

Idiopathic thrombocytopenic purpura (ITP, also known as immune thrombocytopenic purpura) is an acquired disorder, characterised by low platelet counts and mucocutaneous bleeding. The pathogenesis is presumed to be related to platelet-specific autoantibodies which, after binding to platelet antigens, cause accelerated clearance of platelets by the mononuclear phagocyte system.[1] The diagnosis of ITP remains one of exclusion of other causes of thrombocytopenia. Treatment of ITP is aimed at prevention of serious bleeding complications. Glucocorticoid treatment is the initial treatment of choice in patients with platelet counts less than 30×10^9/l.[2] The incidence of continuous remission ranges from 5 to over 30%.[1] In patients who fail to achieve a safe platelet count on prednisone, splenectomy is considered to be the next treatment. A significant number of patients fail to respond to splenectomy or suffer a relapse. The percentage of patients with this chronic refractory ITP ranges from 8 to 30-40%.[1,3] For these patients, there is no proven algorithm for standard care.[4] The advice of the American Society of Haematology is to refrain from therapy with platelet counts over 30×10^9/l and without bleeding symptoms because of the very small risk of bleeding complications in these patients.[2] In patients with platelet counts less than 30×10^9/l treatment options include removal of an accessory spleen, high-dose dexamethasone, cyclophosphamide, azathioprine, vinca alkaloids and danazol. All these agents have, at best, response rates in the range of 40 to 50%, but sustained-remission rates are usually well below 20%,[5] with frequent and often serious side effects.

Recently, the chimeric monoclonal anti-CD20 antibody rituximab (Mabthera®), which depletes B lymphocytes, was studied as an alternative treatment option in patients with chronic refractory or chronic relapsing ITP.[5-12]

In this case report, we describe a patient with chronic relapsing ITP who showed a complete remission on treatment with rituximab.

CASE REPORT

In 1994 a 50-year-old man was referred to our clinic with petechiae and easy bruising. His medical history revealed coxarthrosis since 1992. He had no other signs of haemorrhagic diathesis, such as epistaxis, haematuria or gastrointestinal blood loss. There were no systemic signs,

such as fever or weight loss. He had no history of recent infection and was not taking any medication. Physical examination revealed an obese, vital man with multiple, nonpalpable purpura on the arms and legs. Liver and spleen were not palpable, nor were there any palpable lymph nodes. He had a thrombocytopenia of 12×10^9/l with otherwise normal blood counts, a normal peripheral blood smear and bone marrow examination. Antiplatelet antibodies were detected by direct immunofluorescence testing.
The diagnosis of ITP was made and he was treated initially with prednisone (1 mg/kg), which was tapered and stopped after six weeks. He showed a rapid increase in platelet count to around 100×10^9/l, lasting ten months. He also developed diabetes mellitus for which treatment with glibenclamide was started. Then platelet counts decreased to 12×10^9/l and pulsed high-dose dexamethasone (40 mg daily for four days every month, for a period of four months) was initiated resulting in a complete response (CR) for 1.5 years (*figure 1*). In 1998 splenectomy was performed because of frequent relapses, resulting in a rapid response lasting for only three months. The presence of an accessory spleen was ruled out by CT and radionuclear scanning. The following period was characterised by multiple relapses of severe, but otherwise asymptomatic thrombocytopenia, with persistent good responses on pulsed high-dose dexamethasone. However, during this period of treatment, he suffered from weight gain, insomnia and deterioration of his diabetes mellitus. In 2001 the frequency of relapses increased. In August 2002 treatment was initiated with rituximab (375 mg/m^2 once weekly for four weeks). After the second antibody infusion, there was a rapid normalisation of the platelet count with a CR (platelet count around 200×10^9/l) up to present (*figure 1*). He did not experience any side effects. One month after the start of rituximab treatment, antiplatelet antibodies were still present.

DISCUSSION

We report here successful treatment of a 50-year-old male patient suffering from ITP with the B lymphocyte-depleting monoclonal antibody rituximab.
A significant number of patients with ITP do not respond to treatment with glucucorticoids and splenectomy. These chronic refractory patients with platelet counts less than 30×10^9/l are shown to have a significantly increased morbidity and mortality due to bleeding[3,13] and side effects of treatment.[3] In this patient group it is very important to consider both the risk of bleeding and the risk of therapy-related complications, which can be severe, especially concerning long-term immunosuppression.[14] Most bleeding complications occur with platelet counts $<10 \times 10^9$/l, so in this situation treatment is recommended.[2,4,14] For platelet counts between 10 and 30×10^9/l, the decision regarding optimal treatment, or refraining from treatment, should be based on an individual estimation of the bleeding risk, based on factors such as bleeding signs, lifestyle and age.[14] If treatment is deemed necessary, many treatment options exist, but often with disappointing results and considerable side effects.

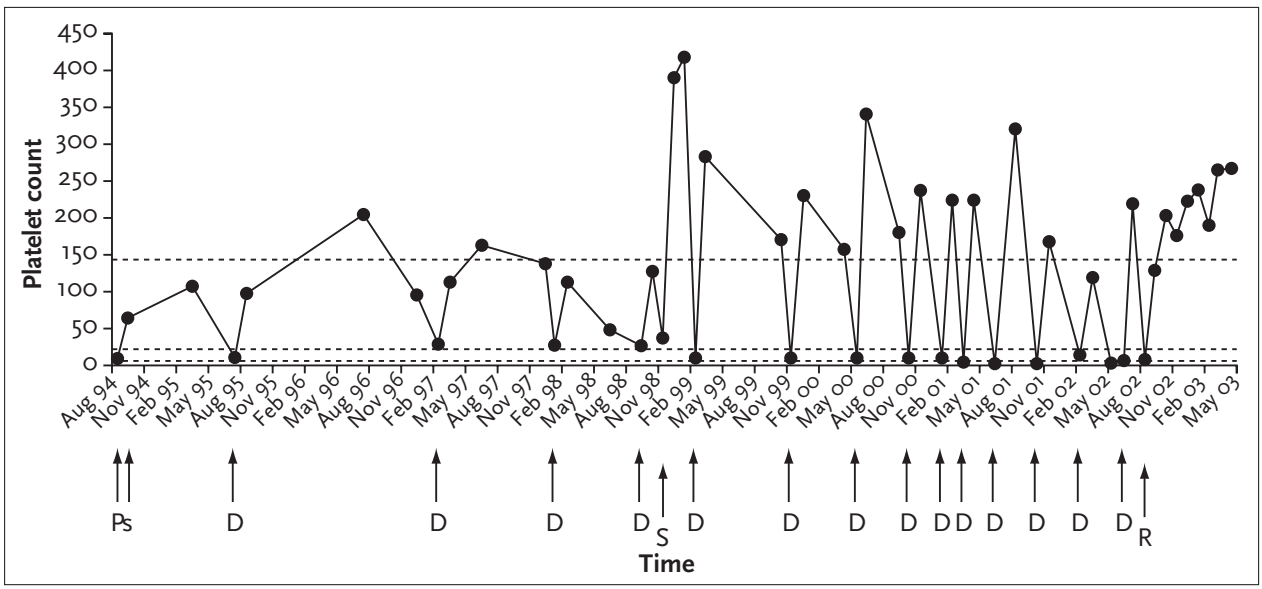

Figure 1

Schematic representation of the platelet count in the period from August 1994 until April 2003 (since August 2002 the patient is in complete remission)

P = prednisone 1 mg/kg, s = stop prednisone, D = high-dose dexamethasone, S = splenectomy, R = rituximab. Dotted horizontal lines indicate platelet counts of 10, 30 and 150 × 10^9/l.

Recently, the anti-CD20 monoclonal antibody rituximab was proposed as alternative treatment option in this patient group. Rituximab was originally used in the treatment of relapsed, low-grade B cell non-Hodgkin's lymphoma (NHL), where it showed good responses.[15] The good responses and mild toxicity recently led to the use of rituximab in ITP, with the aim of B-cell depletion and interfering with the production of autoantibodies. Stasi *et al.* administered rituximab to 25 patients with ITP previously resistant to at least two lines of treatment, with platelet counts less than 20×10^9/l or with significant bleeding. Overall response rate was 52% with five patients achieving a complete remission (CR), five a partial remission (PR) and three a minor response, with response duration ranging from 2 to 108+ weeks.[5] Recently, they added seven more patients, with four CRs and two PRs.[11] Giagounidis *et al.*[8] used rituximab in 12 patients with platelet counts less than 20×10^9/l and unsuccessful corticosteroid treatment and splenectomy. Overall response rate was 75% with 41% CRs and 17% PRs. In CR patients, response duration varied from 68 to 455+ days.[8] Perotta *et al.* treated ten patients with chronic ITP and recorded 5 CRs, with a response duration from 1 to 14+ months.[9] Saleh *et al.*, in a dose-finding study, observed a response (2 CRs, 1 PR) in three of nine patients treated with the highest dose of 375 mg/m^2.[10] In abstract form, Cooper *et al.* described 57 patients with refractory ITP treated with rituximab, with an overall response rate of 72% and complete lasting responses in 28%.[7]

In all these studies rituximab was well tolerated and side effects were typically brief and of mild intensity. As in previous studies concerning NHL, adverse events were predominantly infusion-related and generally consisted of mild (grades 1 and 2 according to the National Cancer Institute criteria), symptoms of fever, chills, rigor, rash, nausea and, rarely, mild respiratory symptoms and hypotension.[5,8,15] In our patient, no side effects were noted. The mechanism of action of rituximab in autoimmune diseases has not yet been elucidated. The rationale for its use rests on the assumption that depletion of B cells leads to a reduction in autoantibody production. Indeed, rapid depletion of circulating B cells, usually after the first gift of rituximab, is observed in all studies, with a complete recovery within 12 months.[5,8] However, despite universal B-cell depletion, some patients respond to rituximab and others do not. Platelet-associated autoantibodies decrease to normal in most, but not all patients with a long-lasting response, but normalisation is also reported in some nonresponding patients.[5,16] Two different time patterns of response to rituximab can be identified: early responders, with a rapid rise in the platelet count after the first or second antibody infusion, and late responders with a reaction between week 6 and 10.[8,11] It is speculated that the early response is mediated by a mechanism of Fc-receptor saturation of mononuclear phagocytes by opsonised B cells and that decreased antiplatelet antibody production accounts for the late response.[11]

This case report illustrates that rituximab may also be effective in steroid-responsive frequently relapsing ITP, and that rituximab might actually be a much less toxic treatment in chronic relapsing ITP than other alternatives. Follow-up in our patient is only seven months. However, because this period is at least twice as long as previous treatment intervals, and considering the serious and increasing adverse events from dexamethasone, treatment with rituximab resulted in a substantial improvement in quality of life in our patient. However, one has to be cautious with experimental treatment in patients with nonmalignant diseases. Prospective studies on long-term effectiveness and side effects of rituximab and comparison with standard treatment options for chronic ITP are warranted. In the near future, a prospective Dutch study on the role of rituximab in ITP will be commenced, most likely coordinated by the Dutch HOVON group (Huijgens and Vreugdenhil; personal communication).

NOTE

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CASE REPORT

Acute pancreatitis after a course of clarithromycin

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ABSTRACT

We present a case of acute pancreatitis after a course of clarithromycin. An 84-year-old woman died of suspected pneumonia and cardiac failure. Autopsy surprisingly revealed acute pancreatitis. Except for the use of clarithromycin no other cause for her acute pancreatitis was obvious. Pancreatitis induced by clarithromycin has been reported twice in the English literature so far. There are, however, a few reports on acute pancreatitis associated with other macrolide antibiotics, such as erythromycin and roxithromycin.

INTRODUCTION

Pancreatitis is usually caused by gallstones or excessive alcohol consumption, but may occasionally be precipitated by drugs. Among the antibiotics, tetracycline and sulphamethoxazole have been implicated most often. Acute pancreatitis is hypothesised to be due to the inappropriate intrapancreatic activation of proteases, which leads to digestion of cell membranes and further activation of other zymogens. Local effects include inflammation, oedema and ischaemia, which progress to local and regional necrosis. Mechanisms for drug-induced pancreatitis include pancreatic duct constriction; immunosuppression; cytotoxic, osmotic, pressure or metabolic effects; arteriolar thrombosis; and direct cellular toxicity.[1] Here we report a case in which clarithromycin, a macrolide antibiotic, may have induced pancreatitis.

CASE REPORT

An 84-year-old woman presented to the emergency department because of shortness of breath and loss of consciousness. A history was obtained from her daughter. She had been feeling ill for seven days prior to admission. She was short of breath and dysarthric. There was no cough or fever. She was not suffering from any pain. There were no pareses. Five days prior to admission her general practitioner prescribed clarithromycin 500 mg twice a day because of suspected respiratory tract infection. Since then her condition had worsened. She stopped eating and drinking properly and stayed in bed most of the time. The last few days her dyspnoea had increased. Urinary production came almost to a standstill. The morning of admission she lost consciousness.

Her past medical history was remarkable for transient ischaemic attacks, hypothyroidism and chronic obstructive pulmonary disease. A few months before admission she had visited our outpatient department with suspected deep vein thrombosis which was excluded by repeated ultrasound investigations. She was taking acetylsalicylic acid 80 mg, levothyroxine 125 μg, chlorthalidone 25 mg and valsartan 80 mg.

On arrival, ambulance nurses measured an oxygen saturation of 79% which improved with oxygen suppletion. In the emergency department, we saw an ill-looking woman who was talking incomprehensibly. Temperature was 36.0°C, blood pressure 150/70 mmHg and pulse 100 beats/min. Oxygen saturation was 94% with 10 litres of oxygen. There were no weaknesses. Auscultation of the heart was unremarkable and breath sounds were clear without crackles. Her abdomen was not tender and she did not seem to have any pain. Laboratory investigations revealed

a respiratory acidosis: pH 7.07, PO_2 17.1, PCO_2 14.5 and bicarbonate 29.3. Na was 134 mmol/l, K 4.8 mmol/l, glucose 7.4 mmol/l, asparate aminotransferase 819 U/l, alanine aminotransferase 658 U/l, alkaline phosphatase 109 U/l, γ-glutamyltransferase 57 U/l, lactate dehydrogenase 2066 U/l, creatinine 190 µg/l, urea nitrogen 23 mmol/l and creatinine kinase 89 U/l. No amylase determination was ordered. Haemoglobin was 8.0 mmol/l, leucocyte count 9.8 x 10^9 and platelets 187 x 10^9.
A chest x-ray showed pleural effusion on both sides. There were signs of congestive heart failure.
We considered pneumonia with an exacerbation of her chronic obstructive pulmonary disease to be the cause of her illness. Other possibilities were end-stage cardiac failure, pulmonary embolism or recent stroke. With her relatives' consent we decided not to admit her to the ICU. We lowered the oxygen supply and gave her amoxicillin/clavulanic acid. Intravenous high-dose furosemide elicited minimal urinary production. In the course of hours her saturation dropped and she became unconscious. Eventually she died the day after admission. Permission for autopsy was obtained. Surprisingly, autopsy revealed that she had severe acute pancreatitis with extensive necrosis around the pancreas. The heart was dilated and hypertrophic. The gallbladder contained multiple small stones but the common bile duct was not dilated and contained no stones.

DISCUSSION

Our patient had no history of alcohol abuse. Except for the stones in the gallbladder there were no other signs of biliary disorder. Acetylsalicylic acid is only known to cause pancreatitis in high doses. Chlorthalidone can cause pancreatitis but usually only shortly after initiation.[2] We do not know whether she was suffering from hypertriglyceridaemia. An important piece of information is that the patient had been on clarithromycin for five days. Clarithromycin is a macrolide antibiotic which is gaining popularity, especially among general practitioners, in the treatment of respiratory tract infections. At least four reports of acute pancreatitis associated with use of the older macrolide erythromycin have been published in English literature[3-7] and a few reports in French and Spanish literature. Often it is associated with high intravenous doses or intoxications. There is also one report of acute pancreatitis with roxithromycin therapy[8] and a report of a child who died from pancreatitis treated with valproic acid and azithromycin.[9]
As for clarithromycin there is one report of pancreatitis in English literature[10] and one recent report in French literature.[11] The Netherlands Pharmacovigilance Centre (LAREB) has not received any reports of a relationship between clarithromycin and pancreatitis. Direct action on the smooth muscle of the gut resulting in spasm of the sphincter of Oddi and bile reflux has been proposed as a mechanism.[1,4] Others suggest an allergic response.[1,5,7]
In this case it cannot be proven that clarithromycin was the cause of the pancreatitis, but since there was no other obvious cause, and because of the reports in literature, it is suggestive. Clarithromycin and other macrolide antibiotics are commonly used for respiratory infections. It is important to remain aware of the possible side effects.

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Why is the measurement of jugular venous pressure discredited?

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'Failure to identify the height of the jugular venous pulsations most commonly results from failure to look at it."[1]

ABSTRACT

Every doctor should be able to make a probable diagnosis of congestive heart failure by clinical examination. The most revealing clinical sign is an elevated jugular venous pressure. The measurement of this pressure was introduced by Lewis in 1930 and refined and standardised by Borst and Molhuysen in 1952. Still, this method has fallen into disuse and is thought to be not very sensitive for diagnosing congestive heart failure. A study of the methods described in the literature reveals that variations in technique are responsible for great differences in normal values. It is argued that smaller elevations of jugular venous pressure can only be measured reliably by adhering strictly to the conditions put forward by Borst and Molhuysen. In this way the sensitivity will improve considerably. A plea is made for an intensive training in this method for doctors and medical students.

Congestive heart failure (CHF) is a serious and widespread disorder. Prevalence in Western countries is estimated at 1 to 2%[2] and is increasing as a result of the ageing of the population and the improvement in short-term outcome of myocardial infarction. Early diagnosis is important, in particular in view of the newer therapeutic modalities such as the addition of ACE inhibitors, β-blockers and spironolactone.[3-5] In recent years a number of studies have been devoted to the efficiency of diagnosing CHF in a specialistic setting as well as in primary care. In general, cardiologists deem echocardiography desirable for establishing the diagnosis,[2,6,7] the left ventricular ejection fraction (LVEF) being considered as the most important parameter for the performance of the left heart. However, many patients with CHF have a normal LVEF, whereas diastolic dysfunction is prominent.[8-10] No differences in clinical signs and symptoms were found between CHF with and without a low LVEF.[10,11]

However, irrespective of the availability of specialist cardiological techniques, most patients with symptoms of CHF present to the general practitioner or the general internist. Their symptoms, e.g. dyspnoea or oedema, are not specific for heart disease. So, the doctor must be able to make a probable diagnosis of CHF by looking for clinical signs using bedside methods. This holds even stronger for doctors in developing countries, where specialist facilities may be hard to reach or even absent. It is noteworthy that in Africa cardiovascular disease is becoming a major cause of morbidity and mortality.[12]

It is common knowledge that the estimation of jugular venous pressure (JVP) is the method of choice to establish CHF at the bedside. At the end of the 19th century distinguished clinical investigators like Mackenzie and Wenckebach had already unravelled many aspects of the pathophysiology of heart disease by meticulous studies of the jugular venous pulse. Lewis was the first to use the external jugular vein as a manometer to record the pressure in the right atrium.[13] He used the sternal angle as a reference point, assuming that this point lies about 5 cm above the centre of the right atrium in all positions of the patient between lying and sitting. Borst and Molhuysen modified

and improved this method and carried out an extensive study in a more modern quantitative way, establishing normal values and interobserver variance.[14] Their most important additions to the Lewis method were:

1. The height of the blood column in the vein is measured at the lowest point of collapse during inspiration, because during atrial systole and expiration the pressure rises and does not reflect atrial filling pressure. Therefore, venous pulsations should be visible.
2. During the measurement the flow of blood in the vein is stopped by light pressure of a finger below the angle of the jaw.
3. The position of the patient is adapted so that the pulsations are visible preferably midway between the clavicle and the jaw. Patients with normal or low central venous pressure have to be positioned horizontally and it may even be necessary to raise the foot of the bed by 20 to 40 cm. The spine must be slightly over-extended and the neck must not be flexed.
4. A simple instrument containing a spirit level was introduced to measure the vertical distance between the point of venous collapse and the sternal angle. Later this instrument (depicted in *figure 1*) was replaced by an elegant device, an arched, calibrated, plastic tube containing fluid and an air bubble, that fits in a coat pocket and has been used now for many decades by doctors and medical students in the Netherlands.

The importance of measuring JVP has been stressed by authoritative clinicians and most textbooks on cardiology, internal medicine and physical examination.[15-20] It has been stated more than once that the examination of the jugular veins should be an integral part of every physical examination.[1,15] The independent prognostic significance of elevated JVP in CHF has been shown in a large retrospective study.[21] In a study relating clinical signs with right heart catheterisation[22] it was found that an elevated JVP had the highest predictive accuracy for elevation of the pulmonary capillary wedge pressure. This comes close to the statement by Lewis that 'there is a perfectly clear relation, constant within narrow limits, between the degree of breathlessness and the pressure in the (jugular) veins'.[13]

So, there seems to be little doubt concerning the value of JVP measurement. However, there is a general impression among experienced clinicians that the exact measurement is practised less and less. The same idea has been expressed in the United States: 'Once a cardinal aspect of the clinical cardiovascular examination, jugular venous pulsations are unlikely to be sought by contemporary physicians'.[1] This is not just an idea, it also appears from the literature in case reports and scientific papers. When it is stated that 'JVP was normal', 'not elevated', 'neck veins not distended', one knows that no exact measurement took place. In recent studies into the efficiency of diagnosing CHF the JVP was not even mentioned among the clinical signs.[23-27]

Why is JVP discredited? One can think of some obvious reasons. The availability of the modern noninvasive tools, such as echocardiography, brings about a boundless trust in technology rather than in using one's own eyes and hands at the bedside. Besides, there is nothing stylish and flashy about standing for five minutes next to a patient, carefully moving his head to and fro, looking for venous pulsations. The task forces on heart failure of the European

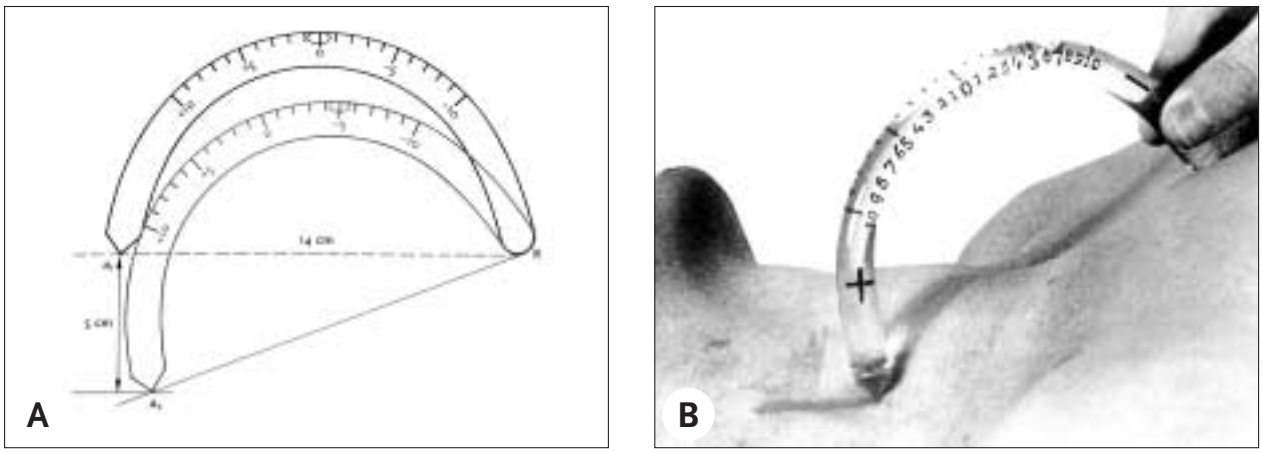

Figure 1

A. The 'venous arch', a plastic, calibrated, arched tube, filled with fluid and an air bubble, to measure the vertical distance between two levels, in this example 5 cm.

B. Application of this instrument for measuring jugular venous pressure, in this case R-6 cm, a normal value.

and Dutch societies of cardiology[2,6] do not attach much value to the measurement of JVP. Their arguments are in the first place that the method is difficult because training and experience are necessary. This is a peculiar argument, suggesting that other procedures, e.g. the determination of LVEF, are easy without the need for training and experience. Performing a physical examination properly is not easy and therefore doctors have to be well-trained professionals. The second argument is that only a minority of patients with CHF have an elevated JVP. The study most cited in this respect, by Stevenson and Perloff,[28] concerned 50 patients with chronic CHF: an elevated JVP was only found in 25 of them. However, most patients were already being treated with digoxin and diuretics and the ten patients who still had oedema also had an elevated JVP, just as the patients with a right atrium pressure above 10 mmHg. Moreover, their method of measurement can be criticised (vide infra).

The crucial question remains: what is the value, in terms of specificity and sensitivity, of an elevated JVP for diagnosing CHF?
Little doubt exists concerning the specificity.[2,22] As to sensitivity a close look at the technique of measurement is necessary. A striking difference appears to exist regarding normal values. With the carefully standardised method of Borst and Molhuysen[14] in a large normal population, 90% of the results were between -4.5 and -8.5 cm relative to the reference point, equivalent to a right atrium pressure of +0.5 and -3.5 cm H_2O. (As the measurement is in fact taken relative to the reference point (R) it seems appropriate to present the results in that way: R -4.5 and R -8.5, as is customary in the Netherlands.) In 12 patients there was a close match between JVP and right atrial pressure measured by catheterisation.[14] In the literature usually only the upper limit of the normal range is given: R + 3,[15,18,19,29] R + 4,[16,20,30] R + 5[17] or R + 6.[8,23] These upper limits are at least 7 to 10 cm higher than with the method of Borst and Molhuysen. Most authors advise positioning the patient with head and thorax elevated between 30 and 45° above the horizontal plane. In patients with markedly elevated JVP the blood column will then be visible above the clavicle, but smaller elevations will be missed. Although some mention that it may be necessary to lay the patient flatter to see pulsations, they keep their upper limit at the high level. McGee[29] even remarked: 'It is difficult to conceive how the clinician could ever distinguish low and normal CVP during examination, ... , levels that actually make the jugular veins invisible to the examinator'. The sternal angle is almost universally used as the point of reference. In the above-mentioned study by Stevenson and Perloff, JVP was determined relative to the clavicle with the patient in an elevation of 30 to 45°.[28] The pressure was defined as normal when the blood column was not visible. So, slight elevations of JVP were probably missed.

It can be concluded that the alleged low sensitivity of elevated JVP for diagnosing CHF[2,6,28] is probably caused by the use of methods that can only establish strongly elevated pressures. Moreover, by not trying to measure lower and normal pressures the medical student will never learn to measure JVP properly. In this respect it is regrettable that an outstanding textbook of physical examination[20] states that in patients with JVP below the reference point the pressure is not elevated and thus there is no need to measure it.
Of course there are patients with a borderline JVP, which makes a definite conclusion not possible. In these cases use may be made of the abdominojugular reflux sign, which is rather well founded.[31-33]
It seems justified to state that the best way to measure JVP is by adhering strictly to the stringent conditions put forward by Borst and Molhuysen.[14] In the international literature this method is seldom mentioned. In the Netherlands it has been described twice in great detail in recent years.[34,35]

Some minor points of disagreement remain to be discussed.
The assumption that the reference point is always 5 cm above the centre of the right atrium has been open to criticism.[14,29] In a recent study using computed tomography in 160 patients the median vertical distance between the sternal angle and the mid-right atrium was found to be 5.4 cm.[36] There was a considerable variation between individuals and between positions of the patient. The distance tended to increase with more upright positions. So, in patients with markedly elevated JVP, the pressure tends to be underestimated a little, which is not a serious drawback.

Some authors prefer the internal jugular vein to measure JVP, others prefer the external vein. In one textbook[19] it is stated that use of the external vein is unreliable because of interfering valves that should not exist in the internal jugular vein. However, recent investigations with modern visualising methods demonstrated, without a doubt, valves in the internal jugular vein, although they were often incompetent.[37,38] Moreover, if the pressure is measured at the lowest point of collapse of the vein, interference by valves is not possible. There is enough evidence to claim that pressures in the external and the internal vein are not different.[39,40] The external vein is visible, which makes measurement easier. So, in line with the publications of Lewis[13] and Borst[14] the external vein is to be preferred, provided pulsations can be seen. If not, the internal jugular vein should be tried.

So far, we have discussed JVP measurement regarding the diagnosis of CHF. However, there is also a role for this method in monitoring therapy of CHF and in assessing

the volume status of patients with other diseases.[1,14] Especially in patients presenting with oedema or dyspnoea it is an essential method to rule out CHF as the cause. Apart from measuring JVP, the study of the jugular venous pulsations may disclose abnormalities, such as tricuspid valve insufficiency and atrioventricular dissociation. Making discoveries like these at the bedside is a gratifying experience.

It is clear that every doctor should be able to measure JVP properly. This applies in particular to those who wish to care for patients in less affluent surroundings, but also to all physicians in primary care and internists. How to achieve this? In the first place, the responsibility lies with clinical teachers in medical schools. They must have mastered the method themselves. Secondly, all doctors must be convinced by logical and scientifically sound arguments that the measurement of JVP in the proper way, as outlined above, is a valuable method that should be practised frequently.

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Van 't Laar. Why is the measurement of jugular venous pressure discredited?

ANSWER TO PHOTO QUIZ (ON PAGE 232)

INCREASED CENTRAL VENOUS PRESSURE IN A PATIENT WITH PRURITIC SKIN LESIONS

Laboratory analysis showed eosinophilia (1.16 x 10^9/l) with an increased plasma IgE concentration (3450 U/ml). The skin lesions on both legs, macroscopically resembling Well's syndrome,[1] showed neutrophilic and eosinophilic infiltration on biopsy, compatible with an eosinophilic folliculitis. These findings (and others, see below) confirm the diagnosis hypercosinophilic syndrome. The chest x-ray showed right-sided pleural fluid with a normal heart size and no pericardial calcifications. Analysis of the pleural fluid showed a low albumin concentration and lactate dehydrogenase activity, with 0.7 x 10^9/l leucocytes and 29% eosinophils. The ECG had microvoltages and T-top inversion on leads II, III, aVF and V_4-V_6.
The finding of increased CVP, narrow pulse pressure and pulsus paradoxus indicate an impeded filling of the heart. Although these features are occasionally encountered in emphysema and pulmonary embolism, the presentation in this case suggests one of the three following diagnoses:

- Relapse of effusive pericarditis (eventually with tamponade);
- Restrictive cardiomyopathy due to eosinophilic infiltration and/or myocardial fibrosis;[2,3]
- Constrictive pericarditis.[3,4]

Sonographic evaluation of the heart revealed only minute amounts of pericardial effusion with normal myocardial contractility. In the myocardial muscle biopsy, eosinophilic infiltrates and endomyocardial fibrosis were absent. The pressure curve of the right ventricle had the form of a 'square-root' characteristic of pericardial constriction, further supported by the thickened pericardium on the CT scan (*figure 3*).

DIAGNOSIS

Constrictive pericarditis in hypereosinophilic syndrome initially presenting with effusive pericarditis.[5]

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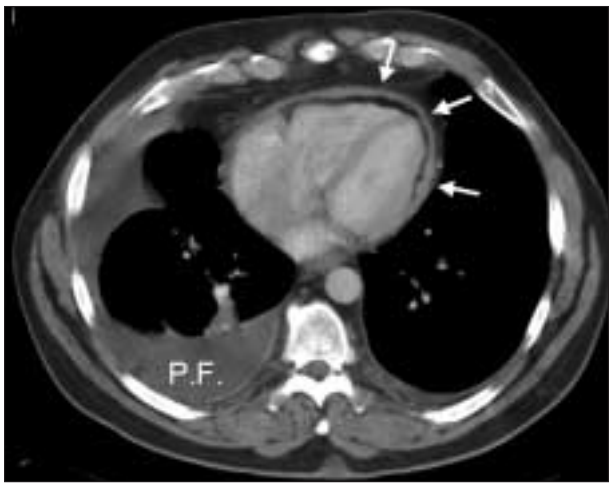
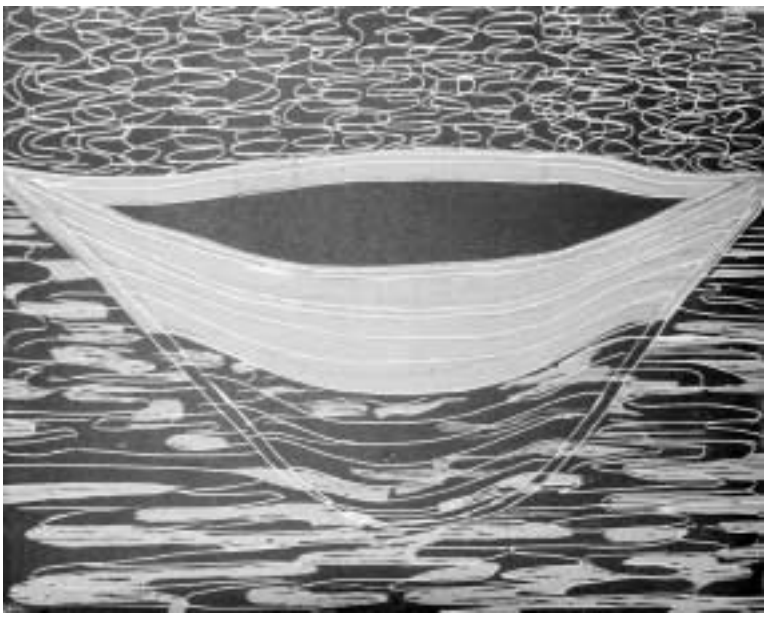


Figure 3
CT scan of the chest with right-sided pleural fluid (P.F.) and thick pericardium (arrows)

Netherlands
The Journal of Medicine

'Oeverloos'

Marina J.H. Rupert



This month's cover shows a wood print entitled 'Oeverloos'.
Graphic artist Marina J.H. Rupert lives and works in Amsterdam. Besides graphic art she creates paintings and drawings. Her prints are usually a search for associations of imagination. These imaginations are visualised in her graphic art by a special technique in which the pictures are printed in layers, leading to a stratified composition.

Marina likes to experiment with different printing techniques on top of each other to give an extra dimension to her work and to see how sharp contours of a dry-point needle reflect on flat print of wood carving. Graphic art is exciting and it surprises the artist because of the several ways in which the same print technique can be used.

She used to expose regularly in group exhibitions but since 2000 she has mainly been exhibiting her work at the Zuid-Hollandse Grafiekmanifestatie in The Hague and in the SBK Centre in Amsterdam. This year her work can also be seen in PILAT in Twijzel, Friesland.

A limited edition (6) of the original print (size 90-70 cm) is available at a price of € 350. You can order the print at Galerie Unita, Rijksstraatweg 109, 6573 CK Beek-Ubbergen, the Netherlands or by e-mail: galerie-unita@planet.nl.

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[2.] Kaplan NM. Clinical Hypertension. 7th Edition. Baltimore: Williams & Wilkins; 1998.

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